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World Psychiatry

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The promise of evolutionary psychiatry

In this issue of the journal[1], R.M. Nesse – one of evolutionary psychiatry's most intellectually fertile theorists – provides a primer of the field's accomplishments and makes a compelling argument for evolutionary psychiatry as a foundational science for psychiatry. He portrays a rapidly maturing field bursting with fresh insights and provocative hypotheses. Using innovative methodologies – ranging from genetic analysis of natural-selection histories of specific alleles to studies of nomadic human groups living in conditions similar to our human evolutionary environment – evolutionary psychiatry has moved from heuristic speculation to scientifically fruitful empirical testing of rival hypotheses. Nonetheless, the promise of this field has thus far largely lain dormant.

This is a good time to examine the strengths and limitations of evolutionary psychiatry. Psychiatric nosologists are currently grappling with the failed aspirations of the DSM-III revolution and disputing what, if anything, should replace it, whether symptom dimensionalization (e.g., Hierarchical Taxonomy of Psychopathology, HiTOP)[2], network theory[3], biologicalism (e.g., Research Domain Criteria, RDoC)[4], or something else. Each competitor for psychiatry's nosological mantle characterizes itself as a "paradigm shift". How does evolutionary psychiatry fit into this dispute about psychiatry's future?

The most fundamental contribution of evolutionary psychiatry is that, by studying distal natural-selective processes that explain the existence and functional architecture of psychological mechanisms, it illuminates evolved human biological design and thus the nature of normality. It provides the functions relative to which we can identify the "dysfunctions" referred to in DSM's and ICD's definitions of mental disorder[5]. It can thereby help us to refine disorder categories to be more valid. For example, evolutionary psychiatry can clarify why social deviance and other problematic mismatches between individuals' natures and current social demands are not necessarily mental disorders, and reveal the importance of context in recognizing normal emotional functioning.

The "smoke detector" explanatory heuristic mentioned by Nesse illustrates such novel insights into normality. It reminds us that the organism's defense systems are often designed to react vigorously even to modestly probable threats, because failing to defend when the threat is real (a "false negative") can be fatal or highly costly, whereas an overreaction (a "false positive") is not too costly. Thus, many biologically designed defensive responses, from fever to anxiety, sometimes occur at levels disproportionate to actual threat.

Evolutionary psychiatry usefully resists the tendency to reify superficial symptom syndromes into disorders with presumed single etiologies. There are multiple reasons why a function may fail, and what seem like disorders may be normal reactions to extreme environmental conditions. To extend an analogy used by Nesse, if one's automobile does not start, a trouble-shooting manual will provide a dozen possible breakdown etiologies, but also note that you may simply be out of gas. From an evolutionary perspective, some current DSM symptom syndromes are best construed as entries in a "trouble shooting guide" for the mind that point to sets of potential explanations, both normal and pathological, for the problematic condition. Throughout his review, Nesse emphasizes that natural selection explains *vulnerability* to disorder (because by definition disorder is not naturally selected). Vulnerability is risk, and risk for disorder may transform into disorder for multiple reasons.

The importance of the normal/disorder demarcation is not only conceptual/nosological (distinguishing disorder from problems in living) or sociopolitical (answering anti-psychiatric critics who argue that psychiatry is about social control). It also underlies a distinctive and powerful medical strategy of discovery. Biological design's extraordinary complexity often eludes full understanding at the causal-mechanism level. However, shared intuitions about biologically designed functioning offer a background explanatory framework that allows identification of manifest design failures, and etiological or curative factors can then be sought despite gross ignorance of internal mechanisms. I call this the "wrench in the gears" strategy because, as with the gears of a machine, one can see that there is a failure of designed functioning and find a way to fix it without ever understanding what a machine does or how it works. This strategy worked well in physical medicine. Evolutionary psychiatric insights could translate into more powerful use of traditional medical strategies of disorder identification and treatment discovery.

A major contribution of evolutionary psychiatry is that it can help to resolve the current impasse between dimensional and categorical views of mental disorder. Sometimes problematic extremes on symptom dimensions are due to mutations that constitute clear categorical dysfunctions. For example, many known mutations cause intelligence to fall within the disorder of intellectual disability. Recent research suggests that mutational dysfunctions define normal/disordered boundaries on continuous symptomatic dimensions between premenstrual syndrome and premenstrual dysphoric disorder[6], and between morning sickness during pregnancy and the disorder of hyperemesis gravidarum[7].

Moreover, independent of mutations, evolutionary psychiatry can provide normal/disordered boundaries based on the presence or absence of natural selective pressure – what I call the "overshoot" problem. The distribution of alleles across genetic loci contributing to a multigenic selected trait commonly forms a normal curve with regard to strength of the trait, with the mean and some interval around it being naturally selected. However, one or both tails of the distribution may not confer the trait at a naturally selected level. Some instances of intellectual disability appear to be due not to mutations but to non-selected distributions of alleles at intelligence-relevant genetic loci. For emotions, one can imagine that both tails, too little and too much, might be non-selected.

Another example of discontinuity along dimensions is the "cliff-edge" phenomenon noted by Nesse. This occurs when selective

forces have pushed us to a genetic sweet spot regarding a certain trait that does not tail off gradually but, with relatively minor changes in the allele distribution, suddenly transforms into disorder. Many psychological traits may need to stay within narrow bounds to enable adaptive social interaction, so small variations may yield cliff-edge disorder vulnerability.

Emergent properties of specific allele combinations may exist for other unexpected reasons. For example, a recent study found that certain combinations of positively selected alleles yielding cognitive advantage increased risk for autism spectrum disorder[8]. Moreover, beyond alleles, at the trait level, there can be dysfunction-causing combinations of individually selected positive traits (e.g., certain combinations of individually selected personality traits can yield personality disorders such as psychopathy). All of this goes to show that it is not dimensionality *per se* but the way selective processes operated on various elements on a dimension that determines normality and disorder.

Evolutionary psychiatry's role thus transcends the current dispute over psychiatry's nosological future. Whichever proposal triumphs, psychiatry's status as a medical discipline requires distinguishing normal variation from mental disorder, which rests on understanding human psychobiological design. Symptom networks, extremes on symptom dimensions, and intense brain circuitry activations can be normal or abnormal depending on context. These proposals, whatever their merits, rearrange the symptomatic deck chairs on our nosological Titanic without addressing the root problem: i.e., that DSM psychiatric nosology is sinking due to lack of attention to the evolved nature of human normality, yielding invalid normal/disorder demarcations[9]. Only evolutionary psychiatry provides a scientifically defensible answer to the fundamental nosological normal/disorder "demarcation" problem.

Because the way people are biologically designed does not always fit social values and ideals, evolutionary psychiatry treads on potentially controversial ground. There is a tension between social idealizations – what we want to believe about ourselves and demand of our society's members – versus the scientific reality of human nature. M. Foucault correctly observed that a society's view of human nature tends to be distorted and permeated by its values and biases, rationalizing its efforts at social control. If psychiatry is to make scientific progress, it must understand the truth of human nature that lies beyond cultural preconceptions as a basis for valid diagnostic concepts that support psychiatric science. The promise of evolutionary psychiatry is that it is the one subdiscipline of psychiatry devoted to realizing this foundational goal.

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Biomarkers in psychiatric disorders: status quo, impediments and facilitators

As probes of the beating heart of a disorder, few research domains match both the promise and complexity of biomarkers. From monoamines to cortisol, inflammatory markers, neuroimaging and cognition, serial waves of enthusiasm have broken concerning biological markers in psychiatry only to dissipate feebly on the shores of research validation, but research is still very active in this area. Biomarkers have diverse potential roles: there may be biomarkers of risk, of diagnosis/trait, of state or acuity, of stage, of treatment response, and of prognosis[1]. This classification is not arcane; a marker might succeed in one domain but fail in others – there are multiple examples in general medicine that this is indeed the case.

In this issue of the journal, Abi-Dargham et al[2] explore the most promising candidate biomarkers in major mental disorders. They highlight an electroencephalographic event-related brain potential, the N170 signal, for autism spectrum disorder; striatal resting-state functional magnetic resonance imaging (fMRI) measures for schizophrenia; an electrophysiological metric, error-related negativity, for predicting the onset of generalized anxiety disorder; and resting-state and structural brain connectomics for social anxiety disorder. All of these candidate biomarkers await confirmation by definitive and replicated studies.

There are multiple hurdles to be cleared in the race to the finishing line of clinical translation of biomarkers. One of the most significant ones is related to current diagnostic classifications. It is implausible that symptom-based classifications can cleave the biology of nature at its joints, yet they remain the reference point against which biomarkers are indexed. Most psychiatric disorders are extremely heterogeneous and at the same time overlap extensively with other disorders. Comorbidity, with other psychiatric disorders and with non-communicable physical disorders, is the rule, and both can influence any exploratory marker. There are also extensive interactions between any potential marker and a plethora of variables, including early life experiences, genetics and epigenetics, current stressors, medications and other therapies, environmental and lifestyle risk factors, stage of illness trajectory, age, as well as secondary biological adaptations to these variables.

A frequent stumbling block is power, with most biomarker

studies of relatively small sample size confounding the efforts to detect influences which generally are of similarly small effect size. Aggravating this is the selection of controls: many studies compare healthy "supernormal" controls with clinical populations, amplifying perceived differences.

Methodological problems are also legion. Even within a singular disorder such as schizophrenia, there are large differences driven by stage, comorbidity, inpatient or community setting, background treatment, and many more. Several markers, such as cytokines, are highly sensitive to collection variables – including phase of menstrual cycle, fasting status, concomitant medications, and diurnal rhythms – and to environmental factors such as smoking, physical activity, nutritional status, as well as substance and alcohol abuse. Also, most biomarker studies use stored samples, and many analytes deteriorate significantly with storage. Most biomarker studies are cross-sectional in nature, a design which does not disentangle state and trait effects and cannot inform causal associations. Even if a biomarker is found, it may reflect another factor: for example, low vitamin D appears to be a marker of a sedentary lifestyle – a consequence rather than a cause. Additionally, there are huge commercial and personal interests in this area, with biotech companies and individuals incentivized to be overly optimistic and amplify promise.

Against all these challenges, the bar for adoption by clinicians and funders remains extremely high: to achieve clinical utility, any marker needs to have very high sensitivity and specificity, as well as low complexity, low cost and easy integration into clinical care.

The limitations of single marker studies, alongside the availability and increasing capacity of omics technologies, have catalyzed a series of studies using these latter technologies. Platforms exist for metabolomics, transcriptomics, genomics, proteomics and lipidomics amongst others[3]. This facilitates simultaneous dynamic assessment of multiple metabolites and can capitalize on systems biology approaches that appreciate the tight interconnection between multiple processes, including inflammation, oxidative biology, cell signalling pathways, lipid biology and cellular metabolism. Meta-analyses of omics studies have found several lipidomic abnormalities in mood disorders[4]. Multimodal neuroimaging approaches combining clinical and imaging data might predict treatment outcomes[5]. Combinations of different omics modalities among themselves and with data sources such as neuroimaging and cognition offer promise. Such large-scale data allow artificial intelligence analysis.

The stratified medicine approach also provides a template to bypass the lack of gold standard pathophysiology. As an example, even though the pathophysiology of breast cancer is only partly understood, recognition of the overexpression of human epidermal growth factor receptor subtype 2 (HER2) in breast cancer facilitated enhanced prognostic models and the development of monoclonal antibodies against this receptor subtype. Similarly, even though the cause of colorectal cancer is unknown, the characterization of KRAS mutations enabled stratification and detection of those who may respond to epidermal growth factor receptor (EGFR) inhibitors such as cetuximab. In psychiatry, pharmacogenomics targeting P450 enzymes offers the possibility of detecting individuals who might need higher or lower doses of medication, which can increase the likelihood of response to therapy.

It is critical to be mindful that failure or success in one domain – such as diagnosis or trait, state or stage, response or prognosis – does not imply outcomes in another domain. As an example, structural neuroimaging has not proved so helpful in informing the differential diagnosis of depression. But a multimodal imaging approach was more promising in predicting the clinical course and outcome of this condition[6].

While a definitive Google map to the destination is not available, the following road signs are likely to be useful. First, it needs to be emphasized that the bar for biomarker research should not be based on p values or effect sizes, but on sensitivity and specificity, or positive and negative predictive value in a clinical context. Any clinically impactful test must be both cost-effective and simple to implement. As the field moves from singular to aggregate and more complex markers, this barrier increases in height. Second, the field needs to adopt a consistent terminology of the different biomarker domains. Third, like clinical trials, biomarker studies need rigorous *a priori* power calculations and concomitantly adequate sample sizes. To increase methodological rigour, biomarker studies should ideally be pre-registered, with pre-specified primary outcomes, criteria for multiplicity, and assessment criteria. Fourth, rigorous guidelines for methodological standardization, for example guidelines for the collection and preparation of biological samples[7], are needed. Finally, consistent reporting standards, such as the STARD (Standards for Reporting of Diagnostic Accuracy) framework, will enhance the field[8].

Notwithstanding the necessity of hypothesis-generating studies, markers with a plausible link to known pathophysiology should be prioritized. Complementing top-down disorder-based approaches, bottom-up symptom- and symptom cluster-based approaches might add value; exemplars include biomarker stratification based on typical vs. atypical symptoms in depression. Automated collection of selected measures by remote sensing using digital technologies offers promise, and such large-scale data are amenable to artificial intelligence methodologies. Large-scale and long-duration international longitudinal cohort studies with repeated multiple biomarkers that span peripheral blood measures, electrophysiology, neuroimaging and cognitive neuroscience, mirrored by deep clinical phenotyping, are likely to be a path forward – the planned BD^2 Integrated Network for Bipolar Disorder is an exemplar[9].

In conclusion, considerable progress has been made in identifying a diverse suite of candidate biomarkers in psychiatry, but substantial challenges remain. Fortunately, multiple promising approaches are on the horizon. But, mindful of the road travelled so far, and the obstacles ahead, T. Bayes may still have the last word.

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Evolutionary psychiatry: foundations, progress and challenges

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Evolutionary biology provides a crucial foundation for medicine and behavioral science that has been missing from psychiatry. Its absence helps to explain slow progress; its advent promises major advances. Instead of offering a new kind of treatment, evolutionary psychiatry provides a scientific foundation useful for all kinds of treatment. It expands the search for causes from mechanistic explanations for disease in some individuals to evolutionary explanations for traits that make all members of a species vulnerable to disease. For instance, capacities for symptoms such as pain, cough, anxiety and low mood are universal because they are useful in certain situations. Failing to recognize the utility of anxiety and low mood is at the root of many problems in psychiatry. Determining if an emotion is normal and if it is useful requires understanding an individual's life situation. Conducting a review of social systems, parallel to the review of systems in the rest of medicine, can help achieve that understanding. Coping with substance abuse is advanced by acknowledging how substances available in modern environments hijack chemically mediated learning mechanisms. Understanding why eating spirals out of control in modern environments is aided by recognizing the motivations for caloric restriction and how it arouses famine protection mechanisms that induce binge eating. Finally, explaining the persistence of alleles that cause serious mental disorders requires evolutionary explanations of why some systems are intrinsically vulnerable to failure. The thrill of finding functions for apparent diseases is evolutionary psychiatry's greatest strength and weakness. Recognizing bad feelings as evolved adaptations corrects psychiatry's pervasive mistake of viewing all symptoms as if they were disease manifestations. However, viewing diseases such as panic disorder, melancholia and schizophrenia as if they are adaptations is an equally serious mistake in evolutionary psychiatry. Progress will come from framing and testing specific hypotheses about why natural selection left us vulnerable to mental disorders. The efforts of many people over many years will be needed before we will know if evolutionary biology can provide a new paradigm for understanding and treating mental disorders.

Key words: Evolutionary psychiatry, natural selection, vulnerability to diseases, evolutionary medicine, depression, anxiety, substance use disorders, eating disorders, schizophrenia

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Calls for new directions in psychiatry have echoed for decades, but only now is recognition growing that the field has been hobbled by using only one half of biology. Almost all effort has gone into research on mechanisms, while the rest of medicine and behavioral science have long also investigated the evolutionary origins and functions of those mechanisms. Evolutionary medicine goes further to ask why natural selection left some traits vulnerable to malfunction. Evolutionary psychiatry answers that question for mental disorders.

Research on animal behavior was transformed when it adopted an evolutionary foundation in the final decades of the 20th century[1-4]. Recognition that brains are shaped by natural selection to maximize gene transmission expanded ethology from a descriptive science to one grounded in theory that predicts behavior. For instance, the assumption that birds lay as many eggs as possible was replaced when theoretically inspired studies showed that birds adjust egg laying in ways that maximize the number of surviving fledglings in the current environment[5]. Animal behavior textbooks are now all grounded on evolutionary biology.

Medicine has long relied on knowledge about adaptive functions as well as mechanisms. Knowing the functions of the pancreas, the mitral valve, and the cough reflex is crucial for understanding their malfunctions. Internal medicine textbooks describe pathology in the context of normal physiological functions. Psychiatry textbooks, instead, describe pathology with little reference to normal functions.

Explaining traits that leave a species vulnerable to a disease poses special challenges, because most evolutionary explanations describe how traits give advantages. Webbed feet make ducks paddle faster. Sweating stabilizes body temperature. Cough clears foreign matter from the airways. So, it seems natural to try to explain mental disorders by proposing ways they could offer advantages. That approach is essential for negative emotions, to correct the pervasive error of viewing adaptations as if they were diseases. However, viewing true diseases as if they were adaptations is an even more serious error that is common in evolutionary psychiatry. It is tempting to try to explain schizophrenia, anorexia nervosa or autism by proposing ways that they might offer advantages, but such hypotheses are almost always wrong. Diseases are not adaptations shaped by natural selection. They are not universal traits. They harm fitness. Trying to explain diseases as if they were somehow useful gives rise to a conceptual fog, which will be dispelled, not by global debates about adaptationism, but by systematically considering specific hypotheses in the light of rigorous evolutionary theory.

Evolutionary medicine does not explain diseases; it explains traits that make bodies vulnerable to disease. Examples include the narrow birth canal, the windpipe opening into the pharynx, and the tendency for immune responses to attack the body's own tissues. The usual explanation for disease vulnerability has been that natural selection cannot prevent all mutations. That is an important explanation, but several others are equally important[6-10]. Natural selection is too slow to keep up with rapid environmental change or fast-evolving pathogens. It can't start fresh to correct a suboptimal design. It increases the performance of traits at the cost of reduced robustness. It maximizes gene transmission, at the expense of health and happiness. And it shapes useful defenses such as pain and anxiety that feel awful and are prone to excessive expression. Evolutionary medicine frames and tests hypotheses based on these explanations.

Evolutionary psychiatry is the subfield of evolutionary medicine that addresses mental disorders[11-16]. The term invites misunderstandings, because it sounds like a new treatment method, perhaps one that is alternative or somehow radical. But evolutionary psychiatry is simply the field that uses the principles of evolutionary biology to better understand, prevent and treat mental disorders. It brings in a missing basic science, that joins genetics, physiology, learning theory, cognitive science, neuroscience and psychodynamics, to better understand and treat mental disorders.

Evolutionary biology is, however, different from the other basic sciences. The others describe mechanisms, each one emphasizing a subset of causes and associated treatments. Learning theory looks to conditioning for causes and to behavior therapy for treatment. Cognitive science attributes problems to distorted thinking and encourages cognitive therapy. Psychodynamic theory looks for the effects of early life events and unconscious processes and recommends psychotherapy. Neuroscience attributes disorders to brain abnormalities and advocates medication treatment. Evolutionary psychiatry does not emphasize one kind of explanation for why some individuals get sick, nor does it advocate for one kind of treatment or some new kind of treatment. It instead provides a framework that can integrate knowledge from other basic sciences. It asks new questions whose answers provide new kinds of explanations for mental disorders. Instead of asking why some individuals get a disorder, it asks why natural selection left all humans vulnerable to the disorder.

This paper has two aims. The first is to provide an overview of evolutionary psychiatry encouraging interest and work in the area. The second is to provide readers with tools to assess evolutionary hypotheses. To that end, discussion of specific disorders is preceded by four brief sections on basic principles. The first summarizes some evolutionary principles and their appropriate and inappropriate applications to mental disorders. The second outlines how evolutionary medicine frames and tests hypotheses. The third provides a brief history of evolutionary applications in psychiatry. Finally, an overview of normal emotion functions sets the stage for examining their dysfunctions. Applying these principles to anxiety, depression, substance abuse, eating disorders, and schizophrenia illustrates the current utility and future promise of evolutionary psychiatry.

WHAT EVOLUTION CAN AND CAN'T EXPLAIN

Finding evolutionary explanations for traits that make a species vulnerable to disease is an onerous task. A brief overview of natural selection can encourage critical assessment of proposals that are unlikely to be correct, especially those that suggest that a disease is somehow useful or that traits that harm individual fitness can persist because they give benefits to a group.

Textbook examples describe natural selection adapting a species to a changed environment. In the classic example, as Victorian soot darkened tree trunks, lighter colored moths became easier prey for birds, so darker moths had more offspring and became more common over the generations[17]. Such examples correctly emphasize that traits are adaptive or maladaptive only in relation to a specific environment, but they give the misimpression that natural selection is mostly about change. Far more often, instead, natural selection keeps things the same. Birds with wings too long or too short are more likely to die in storms, so selection stabilizes the average length at an intermediate value[18].

Natural selection also shapes physiological and behavioral systems that adapt organisms to cope with changing environments [19-21]. These range from simple reflexes like sweating to mechanisms that mediate decisions of all kinds, from what to have for lunch to whether to continue a marriage. How many control systems are shaped by natural selection? Tens of thousands; they control the expression of every gene, the processes that regulate metabolism and replication in 200+ different kinds of cells, the development of tissues and organs, and, of course, every physiological parameter. Perhaps most important of all, they control behavior.

Behaviors themselves are not shaped by natural selection, but genetic variations cause brain variations that interact with environments to give rise to behavior variations that influence fitness. This process shapes brains that induce behavior maximizing transmission of genes to future generations. This simple principle is the foundation for behavioral science. It does not mean that all behavior by all individuals maximizes genetic fitness in all environments; it applies only on average, in the natural environment, if the mechanisms are intact. However, recognizing that normal behavior has evolved to maximize the number of offspring who survive and reproduce is an essential foundation for evolutionary psychiatry.

Maximizing the number of surviving offspring requires subtle allocation of effort among several tasks: getting food and shelter, staying alive, finding mates and social partners, and mating and investing in offspring. The field of behavioral ecology studies how organisms allocate effort in ways that maximize reproductive success[3,4]. Diseases of aging are an example. Genes that cause aging and death are selected for if they increase reproduction[22,23].

The group selection mistake

Until the 1960s it was assumed that natural selection shapes behaviors which benefit groups and species. Vivid confirmation seemed to be offered by a 1958 Walt Disney film of lemmings jumping into a fjord so that a few other lemmings could survive late winter food shortages to perpetuate the species. However, in 1966, G.C. Williams pointed out that the individuals who sacrifice the most will reproduce the least, so genetic variations that induce tendencies to sacrifice individual fitness will be selected out even if they benefit the group[24-30]. This insight revolutionized the study of social behavior[1,25,31]. As for the Disney video, it was faked[32]; the film crew could not find lemmings jumping to their deaths, so they paid local residents to trap them and used brooms off-camera to sweep them into the sea, a fine example of manufacturing evidence to support a false but attractive hypothesis.

If selection acts only to maximize gene transmission, how can

it explain traits such as honeybees suicidally stinging intruders? W.D. Hamilton recognized in 1964 that behaviors which decrease individual reproduction in bees can increase the fitness of other bees who have some of the same genes[33]. More exactly, a trait that reduces individual fitness will be selected for if the genetic costs to the individual are less than the genetic benefits to kin in the group. This principle of kin selection is often illustrated by W.B. Haldane's apocryphal reply to a question about whether he would sacrifice his life for his brother: "No, not for one brother. But I would for two. Or for eight cousins". Kin selection is an essential foundation for psychiatry. The term "inclusive fitness" describes the combined effects of direct selection that gives benefits to the individual and indirect selection that benefits kin[28,34-38].

The cooperation of cells in a body illustrates the power of the principle. They cooperate so well because they all start off as identical twins. That is no accident; natural selection has shaped mechanisms that keep germ and somatic cells separate, and the process of meiosis and recombination minimizes the risk of selfish elements replicating at the expense of other genes and the host, although they can still sneak in, especially at the centromere[39-42]. Infected cells eliminate themselves by the process of apoptosis. This sacrifice can be viewed as a benefit to the host, but it increases transmission of the cell's genes.

The principle that social traits can evolve only if they increase the representation of an individual's genes in future generations is still widely misunderstood. The idea that helping tendencies are shaped by benefits to the individual's genes can be morally disorienting in ways that arouse passionate objections[43]. However, the conclusion is inescapable. As summarized in K. Boomsma's recent book on the topic, "No field study has proved that group selection can produce important adaptive change without being challenged by a simpler alternative explanation based on individual kin selection"[25, p.83]. Explanations for mental disorders based on benefits to a group should be viewed with suspicion.

Realizing that selection works at the level of individuals and their genes has led some scientists to argue that all normal behavior is ultimately selfish[44]. However, selfish genes can increase their representation in future generations by motivating generously cooperative behavior even with non-kin. Individuals who trade help or resources can both get advantages, but any delay in the exchange arouses the risk that one party will defect. The resulting complications arouse intense emotions. Hundreds of studies and publications describe how such exchange relationships work, and the special roles of reputation and culture[45-63].

People in the close personal relationships that are especially relevant for mental health avoid calling attention to costs and benefits; they attribute instead their relationships to attachment, caring and emotional commitments. Kin selection is the most powerful explanation, but friendships with non-kin also have special value. Psychologists J. Tooby and L. Cosmides note that bankers are eager to lend when you have a collateral to guarantee a loan, but, when you are really in a jam, bankers are useless and friends are invaluable[61].

The capacities for friendship and morality that are so relevant for psychiatry are shaped by natural selection in kin networks and cultural contexts that make the process extremely complex, but partner choice seems to be important[64-67]. Individuals preferred as partners get relationships with other superior partners to their mutual advantages, so characteristics that make individuals valuable as social partners are selected for, possibly even in a runaway process[65,68-70]. Those characteristics include having abundant resources and tendencies to share them generously but selectively. This process of social selection shapes competitive altruism[71,72] and extreme attempts to please others, helping to explain problems involving self-esteem, guilt, and social anxiety[16].

Complex social traits are sometimes attributed to learning or culture, as if these were alternatives to evolutionary explanations, but the capacities for learning and culture are themselves products of natural selection. They create new selection forces that shape subtle mechanisms which regulate complex emotional and behavioral responses, and those mechanisms give rise to the amazing diversity of human behaviors. Instead of suggesting an alternative to evolutionary explanations, that diversity reflects the flexibility of behavior arising from evolved mechanisms. How natural selection shaped human prosocial capacities may turn out to be the most important contribution of evolution to psychiatry, but there is no room here to elaborate on this large, subtle and controversial topic.

Sexual selection

Sexual selection shapes traits that increase gene transmission at a cost to host's health and welfare[73,74]. The lovely long tails on peacocks and majestic antlers on deer are expensive hindrances for the individual, but they increase matings, so they are selected for despite their costs. Debate continues about the extent to which they are honest signals of vigor vs. products of a runaway process of signaling and preference for extreme signals; both seem to be relevant. The implication for human problems is profound. Competing for mates accounts for a substantial fraction of human behavior and a high proportion of violence and personal misery[75,76]. A study that quantifies the proportion of clinical problems that can be attributed to mate competition and sexual problems would be welcome.

Individual differences

Natural selection works because individuals with some genetic variants will have more offspring than others. Can natural selection maintain genetic subgroups within a species that thrive in specialized niches? Yes, but only in specialized cases that are unlikely to be relevant for mental disorders. In general, whatever alleles and traits maximize fitness tend to become universal, so explaining the persistence of variation remains a central issue for evolutionary biology[77-79]. The global possibilities are subgroups that evolved in different environments, stochastic variations, balancing selection, trade-offs, and morphs or behavioral types adapted to different niches. All have been proposed to explain

mental disorders, so a brief mention of each is warranted.

Subpopulations evolving in different environments can experience different selection force. For instance, high solar intensity shaped increased skin pigmentation that protects equatorial populations from damage to skin and folic acid deficiency, and low solar intensity shaped decreased pigmentation that protects populations in cold cloudy regions from vitamin D deficiency and rickets[80,81]. Differences between populations that evolved in different locations are unlikely to be important for psychiatry.

Stochastic variations account for most individual differences[82]. Deleterious mutations arise inevitably, and natural selection purges them only slowly. Does natural selection maintain some optimal low level of mutation to ensure that variations are available when needed? No, it minimizes mutation rates within the limits of genetic drift and the costs of repair mechanisms[83]. Higher mutation rates might benefit a species, but mutator genes do not persist, because they decrease the fitness of individuals who have them[84,85]. Systems that increase mutation rates temporarily in bacteria in stressful situations are intriguing[86], but unlikely to be relevant for humans.

Balancing selection can maintain variation at a genetic locus if different alleles are superior across different external or genetic environments[87,88]. The persistence of the allele for sickle cell hemoglobin is the classic example of balancing selection by heterozygote advantage[89]. When rare, sickle cell hemoglobin alleles are likely to be paired with an allele for normal hemoglobin, creating heterozygote individuals who are protected from both malaria and the severe disease experienced by individuals with two sickle cell alleles. Most other confirmed examples of heterozygote advantage are also hemoglobinopathies[89,90]. Heterozygote advantage is relevant here mainly when variation at a single locus has major phenotypic effects, so it is unlikely to explain the persistence of the alleles with tiny effects that influence the risk of mental disorders.

Frequency dependent selection can maintain variation for complex traits as well as the genes that code for them. The classic example is polymorphic shells in a ground snail; predators form a search image for the most common shell pattern, giving an advantage to less common patterns[91]. It has been suggested that sociopathy could similarly give higher than average fitness when its rarity in a population makes others gullible, and reduced fitness when it becomes more common[92], but the idea is controversial, to say the least.

Balancing selection in shifting environments can also maintain genetic variations[87,93]. For instance, an allele that increases anxiety will be selected for when dangers are rife and against when environments are safer. This kind of balancing selection can maintain genetic variation that influences the risk of a disorder, but it does not directly explain why systems are vulnerable to failure.

Trade-offs maintain variations that are sometimes attributed to balancing selection[94,95]. Individuals with values away from the mean will have lower than average fitness, but they will have benefits as well. For instance, higher than average stomach acid levels increase the risk of ulcers, but protect against infection. Individuals with high levels of social anxiety are less likely to win social competitions, but also less likely to be attacked. Individuals at the extremes of the systematizing-empathizing dimension will have lower fitness than those at the mean, but individuals at both extremes will also have advantages that can enhance reproductive success under some conditions[96]. The advantages experienced by individuals with trait values away from the mean have been of special interest for autism, schizophrenia and attention-deficit/hyperactivity disorder (ADHD)[97-101]. The advantages experienced by individuals with values away from a trait mean deserve close attention to understand the relevant trade-offs, and they may help to explain a wide trait distribution. However, fitness is highest at the mean for most traits, so explanations for mental disorders based on benefits at trait extremes should not be accepted without critical assessment.

Specialized morphs that can exploit ecological niches are sometimes proposed to explain a mental disorder. Natural selection can shape multiple phenotypes in a species, such as different mating types in fish, turkeys and orangutans[102]. But most can persist only if their mean morph-specific fitness is the same, and that usually requires negative frequency dependent selection that gives greater advantages to a morph when it becomes less common[103,104]. For instance, when they are rare, smaller fish that sneak in to fertilize eggs have higher fitness than larger male fish guarding the nests, but their fitness falls when they are common. Morphs that increase adaptation to social niches may turn out to be relevant. However, mental disorders are not morphs with equal fitness maintained by frequency dependent selection.

The possibility that different personalities may get advantages in different social niches is spurring interest and controversy[105-113]. Variations arising from adaptive plasticity mechanisms that detect and respond to environmental cues are more likely than genetic morphs, but it is difficult to distinguish functionally adaptive responses from epiphenomena[114-117]. Increased stress sensitivity in individuals exposed to early adversity is an example relevant in psychiatry[118]. Work in this area is interesting, but unlikely to explain variations that harm fitness.

To summarize, attempts to explain a trait that harms inclusive fitness by benefits to a group are inconsistent with evolutionary theory. Most individual differences are products of stochastic genetic variations that have small or inconsistent effects on fitness, but frequency dependent selection can also maintain variations, and research on morphs could be relevant. However, most adaptive individual variations are produced by universal facultative adaptations or adaptive plasticity[116,119-121]. In the natural environment, most such adaptations maximize fitness at the population mean, but, because they involve trade-offs, individuals with values away from the mean will have advantages along with net disadvantages; those advantages can increase disease vulnerability by spreading the trait distribution, but they do not make the disease an adaptation.

The above brief discussions caution against uncritical acceptance of hypotheses that are likely to be inconsistent with evolutionary theory, but they should also enhance respect for the many areas of active research and discourse in basic evolutionary biol-

ogy that are relevant for mental disorders. No mental health professional can know enough to avoid mistakes, so collaborations with evolutionary biologists will be essential. In the meanwhile, many sources are available to provide guidance[2,4,10,24,25,122-129]. Reading them is fascinating for anyone, and a prerequisite for those proposing potentially controversial evolutionary explanations for mental disorders.

EVOLUTIONARY MEDICINE: EXPLAINING DISEASE VULNERABILITY

My early efforts to use evolutionary principles to explain vulnerability to mental disorders[130] quickly made it clear that explaining vulnerability to disease in general had to come first. The crucial advance came from working with G.C. Williams to frame the core question: Why does natural selection leave a species with traits that make it vulnerable to disease?[131,132]. Table 1 summarizes some categories of explanations for disease vulnerability. Each deserves brief comment.

Individual variations are the predominant explanation for disease vulnerability. They result mainly from mutations and developmental stochasticity that natural selection cannot eliminate. They are akin to limitations on quality control in a manufacturing process.

Multiple deleterious mutations arise in each individual in every generation. They are selected out with a speed proportional to how much they decrease fitness. The result is a few rare variations with large effect sizes, fewer with moderate effects, and thousands with tiny effects. This is exactly what genome wide association studies (GWAS) are showing for major mental disorders[133]. Most alleles that increase the risk of mental disorders persist because their rate of elimination by natural selection is balanced by the rate of new mutations[87,134].

Developmental variation is also unavoidable, and it increases the risk of disorders such as schizophrenia and autism. Could natural selection maintain a low level of developmental instability because that creates phenotype variations that increase reproduction for a few individuals in specialized niches despite lowering the average fitness for individuals? The possibility should not be accepted uncritically, but it is theoretically intriguing and potentially relevant[135-137].

Table 1 Evolutionary explanations for disease vulnerability

1. Individual variations resulting from mutations and developmental instability
2. Species-wide vulnerabilities resulting from genetic drift and path dependence
3. Parasites that evolve much faster than hosts
4. Mismatch between bodies and novel environments
5. Trade-offs that increase the fitness of individuals
6. Traits that increase gene transmission at a cost to robustness
7. Defensive responses that are vulnerable to excess expression and dysregulation

Species-wide vulnerabilities make many traits suboptimal. Genetic drift and path dependence are both important. Genetic drift can leave a whole species vulnerable, as illustrated by our inability to synthesize vitamin C. Mildly deleterious mutations can become more common, especially in a small population, simply from the stochasticity of evolution[83]. Path dependence leaves some traits suboptimal because natural selection cannot redesign a trait from scratch. An automotive engineer can reroute a fuel line that is prone to cause fires, but the path of the urethra through the prostate gland cannot be changed, despite all the trouble it causes. The constraints on brain design are vastly larger, so an allele that gives an advantage by slightly altering one circuit will likely create problems for others.

Parasites that evolve faster than hosts are more important for the rest of medicine, but they are also relevant for psychiatry. Antibodies against streptococci with antigenic coats similar to human proteins can attack heart valves, causing rheumatic fever, as well as cells in the caudate nucleus, causing some cases of obsessive-compulsive disorder (OCD).

Mismatch with modern environments explains many woes[131,138-140]. Natural selection is too slow to keep up with rapid social and environmental changes. Fat, salt and sugar were in short supply in the African savannah, so we have preferences for them and little protection against the diseases that result when they become readily available. Sanitation, immunizations and antibiotics have decreased the burden of infectious diseases, but rates of autoimmune diseases are escalating[141,142]. Myopia is rare in hunter gatherers, but common and increasing rapidly in modern societies; whether the cause is close work, lack of sun, working in closed spaces, or some combinations of factors remains unknown[143].

The above four factors all result from the limitations of natural selection. It cannot prevent all mutations and developmental variations, and it is too slow to protect against fast-evolving pathogens and fast-changing environments. However, some vulnerabilities result from systems optimized by natural selection.

Trade-offs that benefit individuals leave many traits less robust than they might be. High blood pressure causes atherosclerosis, low pressure causes fainting, so natural selection stabilizes the average at an intermediate level, with control systems that adjust the pressure to the situation. The risks of infections and autoimmune diseases stabilize the aggressiveness of immune responses at an intermediate level that nonetheless results in both infections and autoimmune diseases.

Traits that increase reproduction are selected for even if they reduce health and happiness. Competing for mates requires huge investments in appearance, wealth and social status[144]. The dieting that sets off eating disorders is usually in the service of competition for mates[145]. Reproductive competition helps to account for mortality rates three times higher in men than women in early adulthood in modern countries[146]. The tendency for orgasm to occur sooner for males than females maximizes fitness at the cost of mutual sexual satisfaction[130]. Pregnancy has obvious costs, and parturition is risky[147]. Then there are all the efforts, sacrifices and worries required to raise children. Freud's emphasis on the importance of sex was along the right lines, but no one in his time

recognized that selection shapes organisms to maximize gene transmission.

Defenses such as pain, cough, anxiety and low mood are useful responses shaped by natural selection[148,149]. Their aversiveness is essential to their utility, but the resulting suffering is the bane of our lives. The mild unpleasantness of sweating and shivering motivates moving to someplace where heat generated by the body just matches heat radiated, about 20°C. The greater unpleasantness of nausea and vomiting protects against eating toxic things again. Physical pain is not some abstract signal which gently suggests stopping actions that cause tissue damage; it is an excruciating conscious feeling that motivates escaping the situation and avoiding it in the future. Anxiety and low mood provide similar protection against other dangers. These adaptive responses evolved because they protect against harm. They are aversive for good reasons, and their regulation systems are shaped to benefit our genes, sometimes at a cost to ourselves.

The above summary of evolutionary medicine is brief to the point of being telegraphic, and it does not discuss phylogenetic approaches to infectious diseases and cancer that are proving very useful. Several articles put the current field in a historical context that includes many applications before the 1990s[150-152]. Since then, evolutionary medicine has grown into a substantial field, with many textbooks[6,10,12,153] and edited volumes[147,154-156]. The International Society for Evolution Medicine and Public Health has annual meetings, and sponsors an open-access journal and other online resources. Courses on evolutionary medicine are now offered in most research universities in the US[157]. However, despite many pleas[157-159], medical schools still provide little or no coverage of evolutionary biology as a basic science for medicine[160].

THE DEVELOPMENT OF EVOLUTIONARY PSYCHIATRY

The many books and papers about evolutionary approaches to mental disorders have had little influence on psychiatry. Historical context provides part of an explanation. C. Darwin said little about mental disorders, despite his connection with psychiatrist J. Crichton-Browne to get illustrations for his book on emotions[161]. For the rest of the 19th and early 20th century, psychiatry was, along with the rest of medicine, enamored with vague notions about the degeneration of families or the species that had little to do with evolutionary biology[162-164]. Subsequent evolutionary contributions to psychiatry came in three phases: first ethology, then sociobiology and evolutionary psychology, then evolutionary medicine.

Applications of ethology to psychiatry initially made little use of evolutionary biology. Everything changed in the mid-1960s. Recognition that capacities for social behaviors are shaped by kin selection and benefits from trading favors provided one foundation. The other was recognition that a full explanation for a trait requires an evolutionary explanation of its origins and functions as well as a proximate explanation of its mechanisms. E. Mayr advocated for this distinction effectively[165-167], but it became more useful as a part of Tinbergen's four questions[25,168-172]: What is the mechanism? How does it develop? What is its phylogeny? What is its adaptive significance? The first two questions are about proximate mechanisms, the other two are about evolution[171]. Recognition that all four questions deserve answers is now an established foundation for behavioral biology that continues to inspire commentary[168,170,173-177].

The significance of these advances was widely recognized only after the publication of *Sociobiology* by E.O. Wilson[178] in 1975 and *The Selfish Gene* by R. Dawkins[179] in 1976. They inspired the first applications of evolutionary ethology to psychiatry. Especially influential were a series of papers by M.T. McGuire[180-182] and related articles that he welcomed as Editor of *Ethology and Sociobiology* (now *Evolution and Human Behavior*). Other early explorations of the implications for psychiatry came in books by M. Konner[183], and B. Wenegrat's *Sociobiology and Mental Disorder*[184]. The term "evolutionary psychiatry" was first used by P.D. MacLean in an article on how a phylogenetic view of the "triune brain" could counter reductionism[185].

Studies by J. Bowlby and M.D. Ainsworth on the adaptive significance of infant attachment, and mental problems resulting from its disruption, were foundational for evolutionary psychiatry and have inspired continuing research[186-191]. Recent reassessments have proposed that anxious and ambivalent attachment styles are not necessarily pathological; they can be strategies that infants use to get resources from mothers who might not otherwise be forthcoming[192-195]. Especially clinically relevant is a recent proposal that considers how understanding maternal neglect in the light of its evolutionary origins and functions can be helpful for patients[196].

L. Sloman and J.S. Price also conducted early important research, first with chickens, then with vervet monkeys, to test the theory that depression can be understood as "involuntary yielding behavior" that prevents attacks after losing a status battle[197,198]. An early paper envisioning a wide range of evolutionary applications in psychiatry[130] inspired a farsighted but sadly ignored plea to avoid speculating about how diseases might be useful to a species[199].

Evolutionary medicine emphasized mental disorders from its origins[131,132]. In 1998, psychiatrists M.T. McGuire and A. Troisi published *Darwinian Psychiatry*, the first book using evolutionary medicine principles to understand mental disorders[200]. Since then, a steady stream of books and papers have further developed the field, now called "evolutionary psychiatry" to expand acceptance by those put off by anything "Darwinian"[201-215]. Progress has been especially fast in the UK, where the Special Interest Group on Evolutionary Psychiatry of the Royal College of Psychiatrists has now over 2,000 members[216]. Two leaders of that group, R.T. Abed and P. St. John-Smith, recently edited the first multiauthor overview of evolutionary psychiatry[11].

The field of evolutionary psychology has grown in parallel, making major contributions for understanding psychopathology. This field initially emphasized research on mating strategies, because they influence reproduction so directly[76,144,217-221]. A 1988

meeting established the Human Behavior and Evolution Society[222], and encouraged development of evolutionary psychology as a broad field that inspired many papers, books[223-230], courses and controversies, many of which had a political flavor[231-234]. Several major publications from evolutionary psychology focus on mental disorders[208,227,235-239].

The fifty years of advances in understanding behavior and mental disorders summarized above have had little influence on psychiatric research and practice. Identifying the obstacles that have slowed adoption of evolutionary biology as a basic science for psychiatry may help to overcome them. The education gap is a major impediment. Few psychiatrists get a chance to learn how evolutionary principles explain behavior. Many do not even know that evolutionary explanations are needed, and few know how to frame and test evolutionary hypotheses[8]. Elementary errors result, even in books on the topic. For instance, many who are curious about evolutionary psychiatry are likely to turn to a book by that title[240], which presented some intriguing Jungian ideas in a mishmash of speculation about diseases as if they were adaptations evolving because they benefit groups. The book aroused justified skepticism[241].

Wariness about evolution in general is also an obstacle, especially in the US, where some religious groups deny that evolution has had any role in shaping humans. Hesitation among scientists arises from perceptions that evolutionary psychology is somehow controversial[242,243]. While work in all fields deserves critique, sensible scientists all recognize that natural selection shaped the brain, and the importance of understanding the adaptive significance of behavior is increasingly acknowledged across the breadth of psychology[232,244,245].

The largest obstacle, however, is uncertainty about what evolutionary biology has to offer. Mental health clinicians need better ways to help their patients now. So, advances in basic behavioral biology can seem abstract. However, evolutionary psychiatry can improve clinical care now by providing sensible explanations that support all kinds of therapy, as well as new ways to frame disorders that patients can understand and appreciate. Each section below emphasizes such practical applications.

EMOTIONS AND THEIR DISORDERS

Negative emotions are, like pain and cough, symptoms that exist because they have given selective advantages. They have evolved in conjunction with control systems that express them in the situations where they are useful. Those systems express false alarms even when functioning normally, and they are prone to malfunctions that cause disorders. Usually, however, anxiety and low mood are symptoms that indicate a problem, not disorders produced by malfunctioning control systems.

Psychiatry textbooks have long chapters about emotional disorders, but little or nothing about normal emotions. How we can regulate our emotions is the topic of many books and papers, but how our emotions regulate us gets little attention. Controversies about the nature of mood and anxiety disorders persist despite the efforts of expert committees[246-252]. Decades of research have not found the expected specific brain or genetic abnormalities. Medication treatments are somewhat effective, but when to use them is the topic of vigorous public debate[253,254]. News articles suggest that tsunamis of emotional problems are sweeping over whole populations. And, while mental health clinicians and researchers do what they can to stem the tide, it will never be enough. The situation arouses appropriate emotions: confusion and frustration.

The standard approach asks why some people have emotional problems and others do not. The responsible factors have been studied in exhaustive detail: individual differences in genetic make-up, early experiences, drug use, cognitive biases, relationships, family dynamics, and larger social factors. Thousands of papers and textbooks describe why some individuals experience emotional disorders and others do not.

An evolutionary medicine approach asks different questions [12,16,200,255,256]: Why do we all have capacities for negative emotions? How are they useful? How is their expression regulated? Why are their control systems vulnerable to malfunction? Answers to these questions provide a biological foundation for understanding and treating emotional disorders in the context of normal emotions.

Recent research progress has led to a consensus that emotions are adaptive states shaped by natural selection[229,257-266]. However, this progress is obstructed by a tendency to tacit creationism that describes emotions as if they were distinct products of a designer's vision, each with a specific mechanism that carries out a specific function[267,268]. For instance, anger is said to serve the function of signaling an imminent attack. Or threatening the end of a relationship. Or expressing dominance. Emotions do serve functions, but one emotion can serve many functions, and one function is advanced by many emotions. So, trying to map specific emotions to specific functions generates complexity and controversies.

The obstacle can be overcome by a definition of emotions based on the situations that shaped them. Emotions are special states that adjust physiology, arousal, cognition, facial expression, motivation, memory, behavior, and subjective experience in ways that gave selective advantages when expressed in situations that recurred and influenced reproductive success over the evolutionary history of a species[229,256,264]. Control systems process information from multiple internal and external sources to express emotions in the form and to the degree that maximizes fitness in the current situation. On average. In the natural environment. In response to always insufficient information. If the control system is intact. With variations induced by cultural and individual experiences[269].

Mapping emotions to situations instead of functions helps to quell some persistent controversies: How many emotions are basic and how many are secondary? Which aspects of an emotion are primary, and which are secondary? Does subjective feeling initiate physiological changes, or does perception of bodily changes give rise to the feeling? An evolutionary perspective suggests that these questions do not have specific answers. Instead, multiple aspects of an emotion are expressed somewhat concordantly, influenced by details of the situation, by each other, by expectations, by cultural learning, and by recursive feedback loops.

The driving modes of modern cars offer a useful but imperfect analogy. Setting a car for sport, normal, eco or snow mode adjusts engine timing, gear ratios, suspension firmness, torque distribution, and dashboard appearance in ways that increase the ability to cope with different situations. The analogy is imperfect, because cars come off the assembly line as identical as quality control can make them, while minds are products of slightly different genomes interacting with varying environments. Furthermore, and more importantly, organic control systems are both more jury-rigged and more adaptable, so variations in a situation can arouse different aspects of an emotion to different degrees. For instance, different kinds of unpropitious situations arouse different symptoms of low mood[270].

The algorithms that detect the presence of situations in which emotions would be useful are nothing like an engineer's decision tree. They are products of a process that is like machine learning, steadily improving fitness by successively changing different parameters at different levels, and keeping whatever works[271]. The resulting organic complexity makes reverse engineering extremely difficult. Further complexity arises because multiple overlapping situations may be present; conflicting goals may be pursued simultaneously; and individuals have different values, goals, resources, strategies, relationships, and prior experience. Emotion control systems generally work, but describing the brain mechanisms that mediate them is an onerous task.

It is easier to describe the situations that an organism encounters. Situations that influence fitness can be categorized on three dimensions: kind of resource (physical or social), valence (opportunity or threat), and the situations that arise routinely during goal pursuit. Table 2 shows 24 situations that arise in goal pursuit and their corresponding emotions. The need to deal with opportunities and threats specific to more specific kinds of resources further differentiates the states. For instance, situations that arise in getting and keeping or losing a mate have shaped capacities for romantic love, sexual arousal, caring, commitment, guilt, jealousy, and grief.

Any approach to emotional symptoms which assumes that all individuals are the same loses the most important information. General checklists of life events and levels of stress do not measure the situations that arouse emotions. Information about the individual's life situation provides a starting point for distinguishing four categories of emotions: useful for the individual; harmful for the individual, but useful for increasing gene transmission; harmful for the individual and for fitness, but arising from normal mechanisms; and harmful products of an abnormal regulation mechanism.

Appraisal theories of emotions are especially helpful in understanding individuals. Emotions are usually aroused not directly, but by an individual's appraisal of what new information means for his/her ability to make progress towards personal goals[272-274]. Those goals can differ dramatically between individuals and even within an individual at different times. The emotional impact of a positive pregnancy test depends on whether the woman was eager to conceive or considering a divorce. One patient insisted that she should not be depressed now because she had just started a job at a brokerage firm that tripled her previous salary; she was reluctant to talk about having to give up her previous career as a struggling artist.

The implications for psychiatry are profound. General measures of stress and checklists of life events ignore many factors that influence an individual's emotions. Diagnostic criteria based only on the number, severity and duration of symptoms are necessary to get the reliability required for epidemiology, but they are not grounded in biology. Determining if an emotion is normal requires assessing the presence or absence of a situation in the context of an individual's values, goals, strategies, expectations and psychodynamics. Determining if an emotion is useful for the individual is a separate question. An evolutionary framework for understanding the origins, functions and regulation of normal emotions provides a foundation for understanding abnormal emotions, starting with anxiety and mood disorders.

ANXIETY AND ITS DISORDERS

Almost all research on anxiety has focused on why some people have too much of it. An evolutionary perspective brings in the other half of biology to ask how natural selection shaped subtypes of anxiety, why normal control systems may sometimes express so much excess anxiety, and why some people have too little anxiety [275-280]. This reframing of anxiety disorders can improve clinical outcomes.

The smoke detector principle

Normal regulation mechanisms express anxiety when the ben-

Table 2 Situations that arise in goal pursuit and corresponding emotions

	Domain	Before	Usual progress	Fast progress	Success	Slow progress	Failure
Opportunity	Physical	Desire Hope	Engagement	Flow	Pleasure	Frustration	Hunger Privation
	Social	Excitement	Friendship	Pride	Happiness	Anger Low mood	Sadness Loneliness
Threat	Physical	Fear	Coping	Confidence	Relief	Despair	Pain Sadness
	Social	Anxiety	Defensive arousal	Confidence	Pride	Anger	Shame Grief

efits are greater than the costs. The presence of real danger is often uncertain, and the costs of a false alarm are often low compared to the costs of no or too little anxiety. So, false alarms are normal and expected in any optimized system. Regulation of the panic response offers a relevant example. If a panic attack false alarm costs 100 calories, but not having a panic response when a predator is present costs 100,000 calories, then the panic response is worthwhile whenever the chance of a predator being present is greater than one in 1000. Therefore, 999 out of 1000 responses from an optimized control system will be false alarms that are normal and necessary for maximizing fitness. This is called "the smoke detector principle", because everyone knows that it is worth putting up with occasional annoying false alarms to ensure protection from a real fire[131,149].

The smoke detector principle is equally useful in the rest of medicine. Most treatments do not cure, but relieve distressing symptoms such as pain, cough or nausea. That is usually safe, because optimized control systems tend to express defenses when they are not essential and because the body has backup systems. Sometimes, however, a defensive response is necessary: giving a cough suppressant to a patient with pneumonia may be fatal. Recognizing the smoke detector principle is fundamental for making wise medical decisions.

The related concept of "error management" describes the benefits of tendencies to cognitive distortions[281-283]. An example is given by the decisions that men make about whether a woman is sexually interested. The benefits of assuming "yes" are large compared to the costs of assuming "no". So, overestimating a woman's interest gives a selective advantage, as well as obviously causing many social problems. This example also illustrates the more general principle that natural selection shapes the mind to maximize fitness at the cost of objectivity.

Hypophobia

An evolutionary perspective calls attention to the neglected disorder of hypophobia[277,278,284]. While many people experience too much anxiety, some experience little or none, even when it would provide vital protection. Individuals with hypophobia do not request treatment. They instead come to attention in the accident ward, unemployment lines, and court proceedings.

Hypophobia is a serious and potentially fatal condition that deserves study even though the victims do not request treatment.

Panic disorder and agoraphobia

The consistent symptoms of panic attacks and their obvious adaptive utility make evolutionary analysis relatively straightforward[285]. Panic is an emergency response that can be lifesaving in the face of acute danger. As recognized by W.B. Cannon over a hundred years ago[286], the rapid heart rate, fast breathing, and shunting of blood from the skin and gut to muscles all make sense as part of a fight-flight reaction. Learning that these symptoms can be useful helps patients to recognize that they are experiencing a false alarm in a normal system, instead of a possible heart attack or stroke.

Panic attacks escalate into panic disorder due to positive feedback loops, often initiated by the tempered reassurance of an emergency room physician who says: "It doesn't seem to be a heart attack or a pulmonary embolus, but, if it happens again, come back right away". The patient starts monitoring, and the next experience of shortness of breath or rapid heart rate arouses anxiety that further increases heart rate and shortness of breath, causing more anxiety that spirals into a full panic episode. Fear of fear produced by the possibility that symptoms could be from a dire medical illness is a common route to full-blown panic disorder[287-289].

The self-adjusting nature of defense control systems further increases vulnerability. Repeated arousal adaptively increases the sensitivity of many defensive responses. Repeated tissue damage indicates that nociception has been insufficient, making a reduced pain threshold adaptive[290,291]. Such self-adjusting control systems are intrinsically vulnerable to vicious positive feedback cycles. If the pain threshold gets low enough to cause spontaneous pain, that can initiate the terrible feedback cycle of chronic pain. Repeated panic attacks signal a dangerous environment in which a faster more intense response to smaller cues of danger will be worth it, initiating a second kind of positive feedback cycle that makes panic disorder worse.

Most cases of agoraphobia are initiated by repeated panic attacks. Many publications consider possible psychological and neurological explanations, but the coexistence of agoraphobia and panic disorder is predicted by an evolutionary perspective. Repeated experiences of life-threatening danger indicate a dangerous environment in which venturing far from home may be fatal. If you encountered a lion at the watering hole two nights in a row, it is best to stay home. If getting water is essential, it will be wise to go with friends, make the trip short, and be on alert and ready to flee at the least hint of danger.

Learning about these general pathways to panic disorder and agoraphobia helps many patients. Instead of viewing themselves as disease victims, they can instead recognize that their symptoms exist for a reason and that they give advantages as well as disadvantages. Explicitly integrating this perspective with behavior therapy and medication treatment helps even more. Patients often wonder why panic attacks continue to be precipitated in grocery stores despite repeated visits without encountering actual danger. The smoke detector principle, adaptive sensitization, and positive feedback loops all provide partial answers. But because fear of fear is often central, extended exposure to the panic symptoms themselves is often essential to effective behavior therapy, which means staying in the situation until panic symptoms fade.

Many patients are reluctant to take medication for panic disorder. Concerns about dependence and rebound are justified for benzodiazepines, but antidepressants can often stop panic attacks without such problems. Patients nonetheless often worry that the medication will "just cover over the symptoms". Such concerns can be relieved by explaining that using medications to stop panic attacks for several months resets the system to a

sensitivity appropriate for a safe environment, making symptom return less likely when medications are stopped. Discussing these factors increases the likelihood that prescriptions are filled, pills are taken as prescribed, and side effects and minor breakthrough attacks are appropriately ignored.

Phobias

Specific phobias have long been a focus for evolutionary thinking about anxiety disorders, because snakes, spiders and storms pose risks that make anxiety responses seem innate. However, framing such symptoms as "innate" or "learned" is too simple; many are products of "prepared learning". Studies by S. Mineka and colleagues found that young monkeys raised in a laboratory showed no fear of snakes, but a single observation of another monkey showing fear while looking at a snake was sufficient to create enduring avoidance[292,293]. Observing another monkey showing fear of a flower did not create avoidance. Other seminal studies conducted by A. Öhman and colleagues showed physiological responses to subliminal images of spiders and other dangerous cues[294].

The nature of the response to different dangers reflects the actions of natural selection[278]. Fear of heights creates freezing, enclosed spaces motivate escape, and social dangers arouse displays of submission or confrontation.

The challenge of behavior therapy is to convince patients to do the exercises. Helping patients to recognize that their anxiety is decreasing even a little during exposure therapy, from subjective units of distress of 90 to 85 for instance, helps to motivate continuing with difficult exercises[295]. Reframing phobic fears as exaggerations of normal useful responses, and describing how desensitization works, helps many patients to engage actively in treatment, especially if they can be convinced that their exercises are influencing a mechanism that exists to reduce anxiety levels as a function of experience.

Generalized anxiety disorder

Psychologists study two global motivational states: promotion in situations that offer opportunities and prevention in situations that pose risks[296]. Most people shift back and forth depending on the situation, but people with generalized anxiety disorder (GAD) put almost all their life's energies into prevention. The human gift of foresight[297] is turned entirely to anticipating possible harms and losses. If someone does not come home exactly on time, visions of tragic accidents arise. A possible job layoff sets off fears of having to live on the street. The mechanism that allocates effort to pursuing opportunities is blocked by constant attention to possible risks[298]. The human tendency to generalize amplifies the problem: the one time in 100 that the fear proves grounded seems to justify fear for the next 99 times.

It is fascinating that the alleles that increase the risk of GAD are the same as those that increase the risk of major depression[299-301]. Both states protect against losses, and the high genetic correlation suggests that they evolved from a common precursor.

Treatment of GAD is difficult. Sometimes antidepressants are effective and cognitive therapy can help, but the tendency to allocate effort to prevention runs deep in many people. Describing the need to seek a balance between prevention and promotion can help, but systematic cognitive therapy is more effective.

Social anxiety disorder

Attending a party seems less dangerous than balancing on a cliff or deciding if a sound was made by a lion or a monkey, but the anxiety can be just as intense[302-304]. What can be lost? Everything. Human success depends on social resources – friends, allies, and membership and status in a group[305]. They can be lost in an instant by sharing an unpopular opinion, siding with the wrong party in a dispute, or even smiling when sadness is expected. The delicacy of the matter is magnified by the need to inhibit selfish, sexual and aggressive impulses. Social anxiety is also aroused by fear of failing, or fear of being attacked by a competitor or a moralist who detects a possible deviation. The risks are higher now that events can be captured on media for posterity.

The human tendency to extreme social sensitivity is a product of cultural mores and social selection that increases fitness for those who are preferred partners[65]. The clinical implications are the same as for other anxiety disorders: discussing the utility of social sensitivity and the costs of too little social anxiety helps patients to recognize that they have advantages as well as disadvantages, but that their concern is excessive. As with performance anxiety, the fear is of making mistakes, so the best exercises require actually making mistakes.

Obsessive-compulsive disorder

OCD has been now removed from the diagnostic group of anxiety disorders, but its symptoms include fear of contamination, fear that some small misstep will harm others, fear that an aggressive impulse will be acted on, and rituals to prevent those outcomes[306-308]. Some patients report driving around a block again and again to check if they might have hit someone, then calling the police later to check again. Others drive home from work to see if a hair curler is still plugged in, not just once but several times.

OCD anxiety is distinctive because fear of harming others is often more extreme than fear of being harmed. This feature has suggested that OCD may represent an extreme of a psychological immune system[309], or an extreme of the human ability to represent future consequences of actions[306]. It may also reflect a dysfunction that is not related to a defense[307,310-312]. Of course, these are not mutually exclusive possibilities.

Behavior control systems in OCD are disrupted in a peculiar way. The system that normally turns off protective behaviors fails. For most people, when a protective behavior is judged sufficient, thinking turns sharply elsewhere. Decision-making is assisted

by the useful irrationality of concluding that the decision made was the right one. Social psychological studies demonstrate the endowment effect: people value an item more as soon as they have chosen it[313]. It would be interesting to study the endowment effect in people with OCD.

However, the problem is not just an absent stop signal. Attempts to disengage from washing or other protection behavior arouse more anxiety, creating a positive feedback cycle. It is as if the ability to inhibit conscious awareness of impulses to harm has failed. Presumed strong natural selection for such inhibitions in the past 100,000 years may be relevant[16]. Or it may simply be that OCD is the syndrome that arises from damage in a specific locus in the caudate nucleus, the same way that aphasia results from damage to Wernicke's area. Different explanations may apply to different cases.

DEPRESSION AND LOW MOOD

It is hard to see anything useful about depression. Pessimism, hopelessness, lethargy, low self-esteem, and ruminating about death or suicide are worse than useless, so depression is usually assumed to be abnormal. But, like physical pain, ordinary low mood is a potentially useful response to a bad situation. Both can be expressed excessively or when they are not needed, resulting in the vast suffering. Treatments are somewhat effective, but, as is the case for anxiety, the search for causes of depression has come up short: plenty of statistically significant results, but no specific common genes, neurotransmitters or brain abnormalities have been found. Controversies and calls for new directions abound.

An evolutionary perspective suggests taking a medical approach. Not the crude "medical model" which assumes that symptoms are products of a specific abnormal mechanism, but an approach like that in the rest of medicine, where some symptoms are recognized as useful responses aroused by disease or disadvantageous situations. Progress in understanding mood disorders will come from discerning the origins, functions and regulation of normal mood. That means identifying the situations in which low mood is useful, how it is useful, how it is normally controlled, and why mood control systems are so vulnerable to malfunction.

Scores of papers propose evolutionary explanations for depression, but reading them can be frustrating. Sadness, low mood, depression symptoms, and depression syndromes are not always clearly delineated. Some articles aim to explain the capacity for ordinary mood variations, others for the symptoms of depression, some more for the syndromes of major depression, melancholia or bipolar disorder. Many proposed explanations are framed as "the function of depression", often arguing for the importance of that function over alternatives proposed by other authors. Table 3 lists some examples. All deserve consideration, but, in full evolutionary context, they are not competitors. They are varying ways that a group of related states can be useful if expressed in a cluster of overlapping untoward situations that have recurred over the course of evolutionary history.

Considering the evolutionary origins of the capacity for mood frames a different question. In what kinds of situations would the characteristics of low and high mood increase inclusive fitness? Low mood can be useful in unpropitious situations in which efforts are likely to be wasted or cause losses. The intense effort and risk-taking characteristic of high mood can likewise be useful in propitious situations that offer big payoffs for small investments. It is interesting to consider that time-limited situations are likely to arouse more intense emotions; if good times are likely to end soon, intense activity and risk taking will be worth it; if bad times are likely to end soon, it is best to just wait.

Table 3 Functions proposed for depression

Soliciting help (Lewis, Klerman, Hamburg)[314-316]
Involuntary yielding (Price, Sloman, Gilbert)[197,198,318]
Sickness behavior (Hart)[319-322]
Conservation of resources (Engel, Beck)[323,324]
Extortion of resources (Hagen)[325]
Social navigation (Watson and Andrews)[326]
Disengagement (Klinger, Brickman)[327-329]
Withdrawal to consider options (Gut, Andrews and Thompson)[330,331]
Adjusting effort intensity and goals (Klinger, Nesse)[328,329,332-334]
Motivating behaviors to gain group acceptance (Allen, Leary)[335,336]

Natural selection has differentiated the global states of low mood into overlapping subtypes whose utility depends on the resource involved and why effort is likely to pay off[270,337]. Table 4 lists some kinds of situations in which aspects of low mood can be useful and how they can have increased fitness in past generations.

This approach frames depression as extreme versions of overlapping states shaped to cope with different unpropitious situations. It provides a framework for considering them together instead of emphasizing one explanation or viewing subtypes as distinctly separate. As is the case for anxiety disorders, the wish for simplicity is undermined by the messiness of organic complexity. Notions that all situational causes for depression can be collapsed into "stress", whose effects are mediated by the hypothalamic-pituitary-adrenal (HPA) axis, are inconsistent with an evolutionary view. The mood system is not nearly that crude. Mood symptoms are differentiated to deal with different kinds of unpropitious situations[337-341]. However, that does not mean that different patterns of low mood are distinct modules; they are overlapping suites of responses whose structure is very different from anything an engineer would design.

The wish for simplicity helps to explain the prevalence of black or white opinions that depression is usually a product of brain abnormalities or usually a normal response. A more encompassing evolutionary view encourages recognition that some episodes of depression are aroused by current situations, while others are excessive or distorted responses, and others are unrelated to any current situation. In his case series from 1934, A. Lewis concluded that each group comprised about a third of his patients[316]. My experience has been similar, but controlled studies of population samples would be valuable. Clinicians in different settings see

Table 4 Some situations in which low mood can increase fitness

Situation	How low mood can increase fitness
Infection	Sickness behavior conserves energy for fighting infection and avoids dangers while incapacitated
Loss of a resource	Sadness stops actions that resulted in loss, and motivates trying to recover or replace the lost resource, warning others about danger, and protective actions to reduce future losses
Loss of a loved one	Grief motivates trying to prevent similar future losses
A season of scarcity	Seasonal low mood conserves energy when foraging is likely to be unsuccessful or dangerous
Failing efforts to reach a goal	Low mood reduces wasted effort and motivates waiting, considering other strategies, or pursuing other goals
Loss of a status contest	Depression signals submission, thus avoiding attacks by more powerful others
Threat of exclusion from a group or relationship	Low self-esteem motivates doing things valued by others
Lack of crucial resources	Depression signals a need for help
Unable to meet all commitments	Stress activates increased effort but also withdraws effort from some activities

different proportions of patients in each group, thus explaining some differences of opinion about the causes of depression.

The above summary of current thinking about evolution and depression is telegraphic in its brevity. Many reviews and books are also available for those interested[210,329,342-355]. Research to test specific proposals is needed, but difficult to carry out. It will be some years until work in this area settles down to the extent that a summary can become a routine part of psychiatric education. In the meanwhile, work in the clinic and the laboratory continues, where some applications of evolutionary thinking can be useful even now.

Mood disorders are manifestations of failed control systems, so control systems theory is needed for a full explanation[356-358]. Several observers have noted the tendency for depression to induce behaviors that perpetuate and escalate symptoms in a positive feedback cycle[359,360], and new research on metacognitive therapy provides ways to disrupt the cycles[361]. Pessimism decreases initiative that could lead to success. Low self-worth inhibits social contacts. Lethargy decreases exercise. In modern societies, people can retreat to a room alone and shut off contact with others, a perfect recipe for making depression worse. Activation therapy can break the cycle[362].

As noted already, the self-adjusting nature of defense control systems makes them especially prone to positive feedback cycles that cause disorders. Much depression is like chronic pain that persists because repeated arousal adjusts the response threshold to a lower level[290,291]. Depression is recognized to be vulnerable to "kindling", in which repeated episodes make further episodes more likely[363,364]. Brain mechanisms are being explored, but the question of whether kindling is a defect, an epiphenomenon, or an adaptation to an unfavorable environment remains to be fully addressed.

An evolutionary control system perspective helps to make sense of the repeated finding that many people with depression have the tendency to mood fluctuations, even if they do not meet criteria for bipolar or cyclothymic disorder[365,366]. All control systems are compromised by the trade-off between high gain and stability. Bipolar disorder has the characteristics of a control system with excessively high gain[367]. The early stages of mania often ramp up as enthusiasm generates success, making the environment appear extremely propitious, so that even higher energy and investments seem justified, in a runaway vicious cycle. Most people, after a great success, experience a letdown that often seems mysterious. That tendency, a reflection of what psychologists call opponent process[368], is just the ticket for preventing mood from escalating out of control, and it seems to be missing in people with bipolar disorder.

Why did natural selection leave mood control systems vulnerable to dysregulation? The standard explanations from evolutionary medicine all apply.

Individual genetic and developmental variations leave some individuals more vulnerable than others. The set point for mood seems to be as stable as that for body mass. An individual's mood responsiveness also tends to stay consistent over time. Both are influenced by genetic variations. There is no reason to assume that the responsible alleles are deleterious mutations. Most are probably just variations whose tiny effects would not influence fitness much, at least in ancestral environments.

Mismatch with modern environments may or may not be important; we lack adequate data to be sure and drawing firm conclusions will be difficult. Some evidence suggests that mood disorders are more common now than they were in the past[369]. However, the belief that the incidence of mood disorders has been increasing in recent decades is distorted by the salience of current problems and the tendency to forget bad times in the past[370]. Epidemiological studies that followed the same population over time have not consistently found substantial increases[371]. Even the presumed increased incidence of anxiety and depression related to the COVID-19 pandemic is not confirmed by systematic epidemiological assessment[372].

Nonetheless, substantially different rates of mood disorders in different countries[373] imply strong socio-cultural influences, perhaps partially mediated by physical factors as well. Concern about the influence of social media is certainly justified, even if hard to confirm[374]. We know that mood is influenced by social comparisons, and that people display especially positive views of their lives on social media, making observers feel inadequate by comparison[375]. However, some anthropological reports found

depression in populations far removed from such modern influences[376,377]. While small group sizes and rapid cultural changes make definitive studies difficult, the question is important enough to justify a major investment.

Trade-offs are important in shaping mood regulation systems. The inherent trade-off between high gain and stability has already been mentioned. The smoke detector principle may also be relevant. Large costs are likely to be incurred by foraging when no food is available or by engaging in status competitions with more powerful others. The costs of waiting, conserving resources and avoiding initiative are likely to be low. So, like other defensive responses, low mood is expressed more readily and intensely than seems sensible. This has important treatment implications. Most of medicine consists of relieving painful normal responses. Recognizing that low mood can be useful does not suggest that it should not be treated. However, it does encourage careful assessment of the situation to try to identify unpropitious situations that can be changed.

Other trade-offs arise because natural selection shapes organisms to maximize reproduction at the expense of individual health and welfare. A night spent in any busy psychiatric emergency room includes plenty of cases precipitated by infidelity, divorce, abandonment, or the dilemma of whether to leave a relationship. Such relationships are so close to the center of human lives that it can seem heartless to observe that these intense feelings are in the service of reproduction at the expense of individual welfare.

How are these principles useful in the clinic? Changes in the approach to four aspects of care are useful: the clinical evaluation, how to talk with patients about depression, how to describe treatment, and how to look for new treatments.

The review of SOCIAL systems and its implications

The standard clinical evaluation asks about recent life events, but sometimes lumps them into the general concept of stress. An evolutionarily informed clinician can instead conduct a review of social systems, following the model of the medical review of systems, to identify situations that might be arousing symptoms. Behavioral ecologists use several categories of effort to study decision trade-offs: somatic effort is to stay alive and healthy and to get external resources like food and shelter; reproductive effort goes towards finding mates, mating, and parenting; social efforts go towards getting allies, group membership and status in a group. Closely related categories of human resources can be summarized using the acronym SOCIAL: Social resources, including friends, groups and social status; Occupation and other valued social roles; Children, family and relatives; Income, savings and material resources; Abilities, appearance, health, skills and other personal resources; and Love and sex.

A full clinical assessment asks about how things are going in each area: what the person has, wants, hopes for, fears, is trying to do; and obstacles, opportunities, dilemmas and pending decisions about activities in that domain. This requires clinical sensitivity. Calling attention to things a person wants but does not have can arouse useless bad feelings. But taking time to discuss the situation in each domain often reveals problems that never come up in general discussions about stressful events: a child on drugs; an obese spouse addicted to sodas; a phone call from a previous lover; a job opportunity passed up to stay with the family; a medical problem calling attention to the brevity of life; an arrest warrant that prevents socializing.

Such problems rarely have easy solutions; if they did, the person would have solved them. Many can be characterized as social traps[378]. People make big investments to create occupations, marriages, relationships with other people, memberships in groups, and status in certain domains. When rewards fade, consideration of making a change grows, but it is unwise to impulsively give up on a major life enterprise; pessimism about options could conceivably be useful to prevent turning too quickly to look for a different job or partner[339]. So, people stew, dealing with dissatisfaction and difficult decisions in their own ways. Clinicians who learn about such dilemmas can work with a patient to gradually try to understand why the person is trapped in the dilemma, and the costs, risks and opportunities of alternatives.

It is especially important to find out if the individual is trapped pursuing an unreachable goal, because that is the perfect depressogenic situation[339,378,379]. Normal low mood withdraws effort from the domain and motivates waiting or considering alternatives. If no alternatives are possible, or they have been tried and failed, the system further withdraws motivation, and pessimism encourages turning effort to a more productive enterprise. However, alternatives are not always available. When the likelihood of success fades after years in trying to get a degree, become a sports professional, start a restaurant, find a better job, or convince a partner to marry, giving up too quickly is unwise. But continuing to persist in pursuing an unreachable goal escalates ordinary low mood to clinical depression, which then itself interferes with pursuing the goal[328,329,333,380-382]. Studies of this phenomenon show that depression often fades when a major goal is truly given up[383], and that people capable of giving up major goals are protected against depression[384]. It is also clear that mood is influenced not by success or failure, but by rate of progress towards a valued goal[385-390].

If the above framework is found to be relevant in an individual patient, depression can be described as an extreme of a normal response. This can encourage a more active stance towards the symptoms, one that encourages collaboration in considering possibly related life circumstances and alternatives. But in other cases this approach may be inappropriate. Some patients with "endogenous" depression are eager to attribute their symptoms to current life problems, even when the temporal association is weak. And the idea that symptoms can be useful implies for some patients that they should not be treated. That notion can usually be scotched by pointing out the safety of physical pain relief, or by going further to describe the smoke detector principle. But clinical sensitivity is essential, as well as an accurate characterization of the individual case[391].

Treatment options and mechanisms of action can also be de-

scribed differently. Despite sophisticated clinicians avoiding this simplistic schema, many patients view their condition as caused by a "chemical imbalance". Instead of viewing medications as correcting an imbalance, it is often more helpful for patients to think of antidepressants as blocking mental pain the same way aspirin blocks physical pain. That helps to reassure patients who are worried about getting addicted; it helps to explain why the medications do not cause euphoria; and it helps to justify putting up with side effects.

In psychotherapy, understanding the real dilemmas a person is dealing with is essential for finding and correcting distorted thinking. Also, patients who come to see that unjustified pessimism and low self-esteem can be expected aspects of depression are more likely to cooperate with cognitive behavioral treatment instead of constantly trying to justify their distorted views.

A whole separate paper would be needed to explore the many ways that evolutionary approach can advance psychotherapy. Cognitive therapy in particular is ripe for integration with evolutionary thinking[237,301,392,393]. Psychodynamics has yet to incorporate the principle that mechanisms for repression and defenses increase fitness[394,395]. And modern interpersonal treatments are just starting to incorporate new findings about how relationships heal[396-400].

Finally, an evolutionary framework may help guide the search for new treatments. For instance, the standard Porsolt test, used to identify chemicals likely to reduce depression, measures how a drug influences the duration of a rat swimming in a beaker of water. Antidepressant drugs cause longer swimming. But rats that stop swimming don't drown; they float with their noses above the water, a superior strategy in the natural environment when active struggle would cause faster drowning[401,402]. Expanding the search for antidepressants to consider persistence in the face of unrewarded goals may offer new ways to identify effective medications, and evolutionary perspectives may advance psychopharmacology more generally[403-405].

Anxiety and mood disorders are only the tip of the emotional problem iceberg. Excesses and deficiencies can cause abnormalities of every emotion. Deficient negative emotions, such as hypophobia and lack of low mood, are almost completely neglected; not surprisingly, since few complain about such problems. Mild excesses of positive emotions are similarly ignored. Excess disgust limits the lives of many people. Excess boredom can be crippling. Sudden intense romantic infatuation is a desperately intense and problematic condition, while the inability to experience romantic love can wreck relationships. An evolutionary framework encourages expansion from the current focus on disorders of mood and anxiety to also consider disorders of other emotions and treatments that can help.

SUBSTANCE USE AND ABUSE

Most of our research and knowledge about substance abuse is about why some people succumb and others do not, and about what treatments are most effective. Those are the standard questions. However, an evolutionary perspective calls attention to several others: Why do plants make psychotropic drugs? Are human motivations to use substances an epiphenomenon of motivations shaped for other reasons, or are they adaptations shaped because taking drugs increases fitness? Why are some people much more vulnerable to addiction than others? Why are most people so confident that they can use drugs and stop whenever they choose?

Plants make psychoactive substances to discourage herbivores[406,407]. Chemicals that disrupt herbivores' nervous system are especially common, because small doses can have large effects. A mouse that eats a coffee bean will likely die; an ungulate that browses on tobacco will likely get sick and not do it again. However, an arms race ensues: selection shapes herbivores that can deal with toxins, creating selection for new toxins that can better deter herbivores and perhaps give advantages to specialists who can tolerate them. The monarch butterfly caterpillar has evolved the ability to feed on milkweed and store its toxins, making the caterpillars and the butterflies distasteful to birds. Humans are omnivores who cope with diverse toxins by routing products from the digestive tract to the liver, where enzymes destroy most toxins before nutrition is forwarded to the general circulation.

Explaining vulnerability to substance abuse starts with the observation that humans have used psychoactive drugs for thousands of years – alcohol for 5,000[408], tobacco for 2,000[409]; opiates, caffeine and coca for nearly as long. Different drugs induce different states with different benefits. For caffeine it is alertness; for nicotine, calm and alertness; for alcohol, disinhibition and social connection; for cannabis, pleasure and calm; for opiates, euphoria and pain relief; for cocaine and amphetamines, pleasure and energetic concentration; for psychedelics, intense experiences of diverse types. Given this diversity of drug actions, many factors will be relevant, all within the general explanation that humans are smart and learn quickly to repeat behaviors that bring benefits; those behaviors include making and selling drugs as well as using them.

Other animals also use substances[410], but only humans have discovered ways to concentrate and administer chemicals in ways that increase positive emotions, decrease negative emotions, and provide experiences otherwise not possible. Some drug use is planned and instrumental; for instance, taking caffeine to stay awake and complete a task. Some is planned for pleasure, such as drinking with friends. But many psychoactive substances act on motivation and learning mechanisms to increase intake steadily in the positive feedback pattern we call addiction. Most induce positive feelings, at least at first, but the liking systems that mediate subjective pleasure are only partially congruent with the wanting systems that motivate behavior[411]. So, what starts out as a simple pursuit of pleasure often shifts to compulsive drug use that brings little pleasure.

The reinforcement mechanisms that maintain drug taking behavior are there for good reasons: learning is an adaptation that induces repeating behaviors that increase fitness[412]. However, the system cannot tell the difference between a real orgasm and the rush from drug stimulation of dopamine receptors.

The reward system is sufficient to maintain drug use, but with-

drawal symptoms make it harder to quit. Continued stimulation by a drug induces adaptive desensitization of receptors, so withdrawal of the drug leaves the receptor unable to activate downstream processes, causing distress ranging from the headaches of caffeine withdrawal to epileptic seizures during alcohol withdrawal.

Most people are confident that they can control their behavior. This false belief greatly increases the risk of substance abuse. When they start using drugs or alcohol, people believe that they can stop whenever they choose. Depending on the drug, many people can stop using, making the risk seem abstract. But conscious decisions have a weak influence on behavior. Many people will stop using for a time, to demonstrate their control to themselves, before slipping back into a pattern of escalating use. As for so many behavioral disorders, positive feedback loops are at the root of the problem. Increased use changes the brain in ways that lead to further increased use. On top of that, substance abuse wrecks job, family and other sources of satisfaction, so that pleasure is soon available only from substances.

In summary, the standard evolutionary explanation for substance abuse is that novel substances can hijack learning mechanisms that were never protected from the effects of drugs, because these were not reliably available during most of our evolutionary history[413-416]. From this perspective, drug abuse is a product of mismatch between evolved behavioral control systems and the ready availability of substances and routes of administration that were not present regularly in our evolutionary history. It is not an adaptation; it is an epiphenomenon arising from the effects of drugs on our chemically mediated motivation mechanisms.

The alternative explanation is that natural selection has shaped systems that motivate taking certain drugs because they have given a selective advantage to our ancestors. E.H. Hagen and colleagues have long argued that individuals may have obtained selective advantages from seeking and using drugs, especially nicotine[417,418]. Indeed, nicotine is an effective anthelminthic that humans may use for deworming[419]. The interesting question is whether those benefits increased connections between nicotinic receptors and reinforcing pathways in ways that increased survival, reproduction, and the rewards of smoking.

Mutations that increased our ability to metabolize alcohol emerged about 10 million years ago, about the time when our ancestors descended from trees and began eating more overripe fruit on the ground[420]. Those with a preference for alcohol and a better ability to metabolize it would have gained advantages, but were those advantages just extra calories? Several authors have recently suggested that alcohol use may have facilitated the rise of civilization, or at least the cementing of bonds among group members[421-423], because the release of inhibitions increases bonding. Conversations over drink may be especially useful[424]. These interesting hypotheses are hard to confirm.

How can all of this be useful in the clinic? Teaching people that their behavior is not nearly as much under their conscious control as they think would provide strong protection, but people are loathe to give up that belief. It would be wonderful if we could prevent initial drug use by telling young people that natural selection never shaped mechanisms to protect us against addiction, but youth are notoriously resistant to advice from their elders – possibly for the good evolutionary reason of avoiding manipulation[425-427]. However, an evolutionary perspective on substance abuse can help to relieve stigma and encourage cooperation with treatment. Understanding the vicious cycles that escalate addiction helps in the difficult task of finding ways to stop them.

Much research is about why some individuals are more vulnerable to substance abuse than others[428,429]. The risk is heritable in a range from 72% for cocaine, to 50% for alcohol, to 3-40% for hallucinogens and opioids[430]. But a polygenic risk score predicts only about 3% of the variance, and individuals in the highest decile have risks not significantly different from those in adjacent deciles[431]. There is only moderate overlap between the risks for abuse of different drugs, so the notion of a drug seeking personality is only partially supported[431].

Men are more vulnerable than women. It is not clear if this results from the general tendency for men to take more risks, from the risks to the fetus of taking drugs while pregnant, or something else[432]. It has been also suggested that taking drugs and heavy drinking may be displays of vigor to impress potential mates. While this may occasionally be a proximate motive, it seems unlikely to have been a selection force increasing motivation for drug use.

The influence of environmental factors is obvious. Individuals with few sources of pleasure in their lives are more likely to turn to drugs to make up the deficit. Those suffering from social distress or physical pain can get relief from drugs. Both groups are especially likely to get trapped in a positive feedback cycle. A number of life experiences can influence these factors: early abuse, unfair treatment, deprivation, injury, or simply being in an unfortunate life situation[433].

Concerning genetic differences that influence vulnerability, an evolutionary perspective suggests that they are not defects, but minor variations that likely had little influence on fitness until recent generations[434,435]. Those variations might, however, have influenced normal behavior in the ancestral environment, for instance by affecting foraging strategies. If this is confirmed, there may be implications in terms of development of behavioral tests aiming to predict vulnerability to substance abuse.

EATING DISORDERS

Research on eating disorders illustrates the limitations of looking only for proximate mechanisms, and the opportunities and difficulties associated with seeking evolutionary explanations. The most fatal of all mental disorders, eating disorders have substantial symptom overlap, and their incidence has been increasing in recent decades, especially in developed countries[436].

Some papers that argue for the primacy of genetic factors[437] suggest that many patients simply lose interest in eating, but this is not consistent with evidence that preoccupation with thinness and dieting precedes eating disorders in most cases[438]. A GWAS on over 70,000 individuals found eight loci with statistically significant influences on the risk of anorexia nervosa, but effect

sizes were minuscule[439] and a polygenic score including all available genetic information accounted for only 1.7% of the variation in risk[440]. The genetic influences on anorexia nervosa are therefore unlikely to be abnormalities; they probably result from natural variation in psychological traits such as conscientiousness and neuroticism that can mediate risk in modern environments.

The evolutionary explanations proposed for eating disorders are diverse and confusing. For instance, some papers have suggested that restrictive eating might be an evolved strategy for postponing reproduction until more physical or social resources are available[441,442]. However, natural selection has shaped a much more efficient and subtle system to turn off reproductive cycling when a pregnancy would be unlikely to result in a surviving offspring. When high levels of energy expenditure are not balanced by sufficient input, the system reverts follicle stimulating hormone (FSH) and luteinizing hormone (LH) to prepubertal levels, stopping reproductive cycling even at normal body weights[443]. That is why cycling stops in some women athletes during times of intense training. This system works fine on its own; it needs no augmentation by food restriction that is likely to be fatal in a time of famine.

The "adapted to flee famine" hypothesis argues that the high exercise levels pursued by some patients with anorexia nervosa might be an evolved strategy that motivates running away from an area of famine to other locations where food is more available[444]. However, individuals with anorexia exercise not to find food but to keep body weight low. Exercising while starving is not an adaptation, it is an aspect of a disease. Most studies of starving people report lethargy, not intense activity[445].

Yet another interpretation of anorexia nervosa as an adaptation proposes that it is induced by female-female competition for status in a group. It suggests that a woman can avoid attacks from other higher-status women by losing weight and thus demonstrating that she is not competing for mates and thus is not a threat[446]. However, there are other more direct and safer ways to signal submission.

R.T. Abed and colleagues[447,448] emphasize the competition among women to have body shapes that will make them desirable. In ancestral societies, the substantial physical effort needed to get limited supplies of food kept body shape variations small. In modern environments, human food preferences have shaped industries that provide ready access to cheap foods with whatever combinations of fat, salt, sugar, protein, taste and texture that people prefer. The resulting epidemic of obesity makes appearance more important than ever in sexual competition. The effect is magnified by mass media portrayals of body shapes that are caricatures of idealized extremes. Restrictive dieting seems like an obvious strategy to get a good mate and to also gain admiration for self-control. This sexual competition hypothesis provides a convincing explanation for extreme dieting and its excess prevalence in women in modern societies, but it does not fully explain eating disorders initiated by dieting for other motives, bulimia, and why the eating control system is so vulnerable to malfunction.

The eating control system was shaped to ensure protection against starvation in a trade-off with avoiding risks from being heavy and slow. Starvation is the more potent selection force, so protection against obesity is relatively weak. However, Nettle et al[449] note that natural selection has shaped a system that adjusts fat storage to food availability. When sufficient food supplies are reliably available, extra caloric stores are a useless burden. When food supplies are limited or erratic, the system motivates finding food, consuming it fast, and increasing the body weight set point to provide insurance against starvation.

Severe caloric restriction arouses the famine protection response, but attempts to block its effects can initiate a positive feedback cycle that sends the system out of control[450]. Intense efforts at caloric restriction inevitably end in out-of-control eating episodes that magnify the fear of obesity and motivate redoubled commitments to restrict intake. The increased weight setpoint amplifies the fear. This combines with more hunger experienced at higher weights than previously, to spiral the system out of control.

Most people revert to their usual eating habits and weight after a period of deviation in either direction. Some persist in the patterns of bingeing and purging that characterize bulimia. A few control their eating, or at least their weight, by restriction, purging, extreme exercise, and the preoccupation about eating and body weight that characterize anorexia nervosa.

These ideas should be helpful in preventing eating disorders, as well as in their treatment. Learning that severe caloric restriction may finally result in weight gain should be a potent antidote to behavior patterns that initiate eating disorders. However, as in the case of substance abuse, the belief that conscious resolve can control behavior makes it hard to convince people that just deciding to stop eating is not necessarily a route to persistent thinness. Once established, eating disorders are much harder to control, because they give rise to a sense of identity that is tangled with eating and body weight, a sense of superiority compared to those with less self-control, and the determination to defy parents who are desperate to get their child to eat.

THE PERSISTENCE OF DELETERIOUS GENETIC VARIATION

The persistence of disease-causing alleles in the face of natural selection has been recognized as a paradox since the origins of evolutionary genetics[451]. Proposed explanations have inspired debate for decades, but resolution now seems within reach, thanks to newly available genetic datasets and methods. Schizophrenia is the focus of the discussion below because it is the disorder that has generated most interest and research, but the general principles are also relevant for other disorders.

As recently as the turn of the millennium, there was hope that we would soon find the genes responsible for highly heritable diseases such as schizophrenia and bipolar disorder, but these expectations have been consistently frustrated. Instead of arising from common variants with large effects that code for proteins, the majority of the risk instead arises from thousands of

non-coding alleles with tiny effects[133]. The prevalence of variants is inversely proportional to their effect size, a pattern consistent with purifying selection eliminating mutations with larger effects faster than those with smaller effects[452]. Instead of being localized on some chromosomes, the loci associated with schizophrenia are scattered across the genome, with numbers on each chromosome proportional to the chromosome size[453].

Larger sample sizes and new family methods are now looking for, and finding, rare variants with larger effects, especially copy number variants and *de novo* mutations[454]. These variants are estimated to account for only about 20% of the heritability of schizophrenia, but they could identify relevant neural circuits, and possibly suggest new treatments. As progress is made to identify all variants that increase the risk of schizophrenia, it is worth asking a large question: will finding them all provide a full explanation for schizophrenia? Most probably, it will also require understanding why the mind is vulnerable to the failure mode of schizophrenia. This may simply be the syndrome that results from a certain pattern of disorganized brain development. It is also possible, however, that the vulnerability results from a trait pushed to a performance peak despite associated risks of failure.

For fitness functions with a cliff edge, natural selection will push the trait to the point close to the peak that maximizes gene transmission over multiple generations, despite the low fitness experienced by the few individuals with values over the cliff[455,456]. The situation gets more interesting when you consider that oscillation is expected between the value that maximizes single generation fitness despite costs to offspring and the value that maximizes gene transmission over multiple generations.

Previous hopes that specific genetic constellations would define specific disorders have also been upended. The diagnostic distinction between schizophrenia and bipolar disorder turns out to be far less crisp than had been assumed. Their genetic correlation of 72% arises from the many alleles that increase the risk of both disorders[299]. Genetic correlations are pervasive among all mental disorders, much more so than for neurological disorders[299,457]. However, this is a fast-developing area, and current methods neglect the role of assortative mating in overestimating genetic correlations[458].

These findings are consistent with the hypothesis that mutation-selection balance is responsible for the persistence of most disease-causing alleles. Human individuals each have about 70 mutations that are not present in their parents, one of which, on average, is in a protein coding region. Beneficial new mutations are exceedingly rare. Deleterious ones are selected out with a speed proportional to their reduction in fitness, but new ones replace them, maintaining the balance between mutation and selection.

However, interesting evolutionary questions remain. Are some alleles maintained by selection which gives advantages in some individuals or situations balancing their costs in others? Are increased intelligence or creativity associated with some alleles for schizophrenia, autism or bipolar disorder? Do alleles with immune functions that help to shape the developing brain also protect from infection?

All these questions are of interest, but the larger evolutionary question is why certain systems are so vulnerable to failing in typical ways. Are some systems intrinsically vulnerable to failure because they have been shaped to a performance peak adjacent to a cliff edge where fitness plummets? Are some control systems shaped to high gain despite the unavoidable risk of instability? Answering these questions is an important long-term project.

Polygenic risk scores for bipolar disorder and schizophrenia can predict creativity scores[459], but it is very hard to tell if measures of creativity might be confounded by the kinds of jobs open to people who have severe disorders. Cognitive ability can be measured more reliably. Of 75 genomic loci jointly associated with schizophrenia and intelligence, 81% were associated with lower cognitive performance, while of 12 alleles associated with bipolar disorder and intelligence, 75% were associated with higher performance[460]. These are intriguing clues to an unsolved mystery.

A different approach considers the possible role of rapid selection for traits that became useful during the major transition to the social cultural niche in the past few hundred thousand years. T.J. Crow wrote extensively about the possibility that psychosis could be the price we pay for the capacity for language[461,462]. We now are on the verge of confirming that some health problems can be attributed to wrenching major transitions in which a new niche or strategy selects strongly for traits that make other traits vulnerable because of anatomic, physiologic or pleiotropic constraints. The exemplar is the transition to bipedality and its legacy of vulnerability to hernias, hemorrhoids, back pain, knee pain, plantar fasciitis, varicose veins, and omental torsion[463]. It is painful to imagine how prevalent these problems must have been in the first million years of bipedality.

The wrenching transition to the cognitive social niche may have created even more severe problems, considering the path-dependent interactions of multiple alleles that influence brain development pathways[464-466]. Imagine a new allele changing the chemical gradients that influence neuronal migration during brain development in ways that give a benefit, perhaps something like more expressive vocalization. If this gives a net selective advantage, the allele will be selected for, despite negative effects that slightly disrupt multiple other adaptations that evolved previously.

A recently proposed model[467] suggests that the development of social brain, language and high-order cognitive functions transformed many neutral alleles into risk alleles for schizophrenia. Around 100,000-150,000 years ago, there was a "turning point" when the number of those alleles plateaued. A steady decline then began due to natural selection, that also increased the proportion of protective alleles. This hypothesis is supported by the evidence that older alleles are more likely to increase the risk of schizophrenia and newer ones are more likely to decrease it, and by some epidemiological evidence suggesting that the incidence of schizophrenia is declining[317].

CONCLUSIONS

The main conclusion of this overview is simple: evolutionary biology is a basic science that has a lot to contribute to psychiatry. It provides a scientific framework that is missing from psychia-

try but foundational for the rest of behavioral science. It is not an alternative to the search for brain mechanisms; it is a complementary framework that can integrate diverse bio-psycho-social approaches. It is not a new method of treatment, but it helps all methods of treatment by putting emotional disorders in the context of normal functioning. For patients, this reduces stigma and tendencies to self-identify as diseased persons. For clinicians, this offers new ways to describe mental disorders and how treatments work. For researchers, it offers new questions whose answers will inspire new approaches to research on brain mechanisms. These practical benefits of evolutionary psychiatry are ready for application, but a larger possible conclusion deserves consideration.

A new paradigm?

Calls for new directions in psychiatry have echoed for decades, but new data give them greater urgency. Fifty years ago, the field decided to emulate the rest of medicine and find the specific abnormalities that cause mental disorders. The DSM-III categories were expected to be replaced when the responsible brain abnormalities were found. The ensuing search has produced vast new knowledge about brain mechanisms and many statistically significant differences in the brains of patients compared to controls, but no specific abnormality has been detected that accounts for any major mental disorder, and no biological test has been developed that can diagnose any disorder. New data confirm that genes influence the risk for many mental disorders, but most influences are from common variants that increase risk by less than 1%, and their effects are not specific to one disorder. Many research leaders have acknowledged that current research strategies are failing[468,469], but most suggested new approaches continue to assume that mental disorders are caused by specific brain abnormalities that we can find and use to define specific diseases.

The search for these abnormalities has been based on a tacitly creationist view of the body as a machine with discrete parts that have specific functions and simple connections that were envisioned by a sensible designer[268]. An evolutionary perspective suggests that the complexity of organic systems is not only greater than that of designed systems; it is different in kind. One function is distributed among many parts, one part can serve many functions, and organic control systems are integrated networks of recursive connections that make organic systems more robust than designed systems[470-472], but also vulnerable to failure because they are operating in new environments, because they are shaped to maximize fitness at the expense of health, and because they are riddled with trade-offs that increase performance at the cost of robustness[7,473]. As for brains, they are jury-rigged marvels, not of design, but of natural selection, that leaves them vulnerable because each genetic variant which improves one function and overall fitness may disrupt many others.

Different brain loci have different functions, but they are not as specific as we might like. For instance, the amygdala has long been described as the source of fear, but new research shows that "the amygdala is not required for the experience of fear" and that "defining brain functions in an impactful way is not trivial and it amounts to figuring out how to measure something that we often do not yet fully understand"[474].

Evolutionary psychiatry may offer a new paradigm. It asks different questions, provides different kinds of explanations, and views disorders in a new way. Identifying negative emotions as adaptive symptoms that are prone to dysregulation is fundamental. It suggests that diagnostic criteria for anxiety and depression that ignore possible causes are as invalid as a diagnosis of "cough disorder" that does not look for pneumonia or allergies. It views behavioral disorders as products of control system failures instead of specific brain lesions. And it asks why some systems are especially vulnerable to failure from many different causes, in the same way that internal medicine understands the many factors that can contribute to heart failure.

This paradigm will not be welcomed quickly for several reasons. The first is that few mental health professionals or researchers know much about evolutionary biology; many still do not realize that evolutionary explanations are needed in addition to proximate explanations. The second is that work in this area is exceptionally difficult, in large part because of conceptual confusion about what are appropriate objects of evolutionary explanation. Speculations about possible benefits from diseases and traits that are present only in some individuals are often so intriguing that they spread widely despite being false.

However, a third explanation may be the most important. It is desperately disappointing to have to acknowledge that organic complexity is a tangled bank that defies description using the simple boxes and arrows that we so crave. We love science when it simplifies. But an evolutionary view of mental disorders reveals a murky world of organic complexity that lacks the sharp boundaries and specific functions that satisfy our lust for order.

Talk about paradigms may be premature for a nascent field that is just now finding its footing. To discover what evolutionary psychiatry can accomplish and how it can help will require work by many people over many decades. The next step is providing clinicians and researchers with the basic evolutionary principles that ground the rest of behavioral biology, along with strategies for applying them critically to better understand and treat mental disorders. This paper is a first step in this direction.

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Substance use disorders: a comprehensive update of classification, epidemiology, neurobiology, clinical aspects, treatment and prevention

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Substance use disorders (SUDs) are highly prevalent and exact a large toll on individuals' health, well-being, and social functioning. Long-lasting changes in brain networks involved in reward, executive function, stress reactivity, mood, and self-awareness underlie the intense drive to consume substances and the inability to control this urge in a person who suffers from addiction (moderate or severe SUD). Biological (including genetics and developmental life stages) and social (including adverse childhood experiences) determinants of health are recognized factors that contribute to vulnerability for or resilience against developing a SUD. Consequently, prevention strategies that target social risk factors can improve outcomes and, when deployed in childhood and adolescence, can decrease the risk for these disorders. SUDs are treatable, and evidence of clinically significant benefit exists for medications (in opioid, nicotine and alcohol use disorders), behavioral therapies (in all SUDs), and neuromodulation (in nicotine use disorder). Treatment of SUDs should be considered within the context of a Chronic Care Model, with the intensity of intervention adjusted to the severity of the disorder and with the concomitant treatment of comorbid psychiatric and physical conditions. Involvement of health care providers in detection and management of SUDs, including referral of severe cases to specialized care, offers sustainable models of care that can be further expanded with the use of telehealth. Despite advances in our understanding and management of SUDs, individuals with these conditions continue to be stigmatized and, in some countries, incarcerated, highlighting the need to dismantle policies that perpetuate their criminalization and instead develop policies to ensure support and access to prevention and treatment.

Key words: Substance use disorders, addiction, brain networks, social determinants of health, risk factors, prevention, treatment, chronic care model, stigma

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For most of history, persons suffering from a substance use disorder (SUD) have been viewed as individuals with a character flaw or a moral deficiency, and stigmatized with labels such as "addict" or worse. Advances in neuroscience have expanded our understanding of the brain changes responsible for this condition and have provided the basis for recognizing SUD as a progressive, chronic, relapsing disorder that is amenable to treatment and recovery.

The prevalence of SUDs is high and varies across countries and the type of drugs used (highest for tobacco and alcohol use disorders) as well as by demographic and socioeconomic characteristics of the populations. The rates of SUDs are higher for males than females and higher for younger people, with rates decreasing as both men and women age[1].

The impact of SUDs on societies as it relates to health and mortality, economics and crime is profound, and it appears to be worsening. Indeed, among all of the risk factors associated with premature death, tobacco and alcohol use rank second and seventh respectively. The high contribution to premature mortality reflects direct effects of drugs from overdoses as well as their longer-lasting negative effects on health[2].

In 2019, the number of premature deaths attributed to smoking was estimated at 7.7 million[3], to alcohol use at 2.4 million[4], and to use of other drugs at 550,700[5,6]. Unfortunately, these negative trends have accelerated in some countries. Most notable are the increases in drug-related overdose deaths in the US, which have skyrocketed over the past decade and further accelerated during the COVID pandemic[7,8]. The annual fatalities in 2021 in the US were estimated at greater than 107,000, mostly from opioids and exacerbated by the expansion of fentanyl in the illicit drug market[9], with similar trends (though not as severe) reported in Canada and the UK[10,11].

Drugs contribute to many acute and chronic diseases – including infectious, pulmonary, metabolic, cardiovascular, psychiatric and oncological diseases – and exacerbate their outcomes. The Global Burden of Disease Study, which in addition to deaths considers years lived with disability, estimated that there were 30 million years lived with disability due to SUDs in 2017[12]. Early onset, chronic or relapsing course, association with lower quality of life, and long time to remission all contribute to the large impact of SUDs.

Stigma, discrimination against individuals with SUDs, criminalization of substance use, and severely inadequate responses from health care systems in all countries, particularly in low- and middle-income countries (LMICs), further compound the adverse consequences of these conditions[13].

Significant economic costs are accrued from the production, distribution and use of illicit drugs, and those costs affect families, consumers, industries and governments[13]. For example, individuals with SUDs are less likely to be employed and more likely to experience the consequences of financial crisis[14], whereas resources devoted to drug production or distribution, law enforcement, or treatment of SUDs cannot be devoted to other goals.

Substance use and SUDs exist on a continuum of severity. In this paper, we use the term "addiction" to correspond to moderate or severe SUDs as described in the DSM-5. In the early stage of a SUD (mild SUD), the urge for drug consumption can be regulated, and we recently proposed that this could be considered as a "pre-addiction" stage that could be targeted for early prevention

interventions[15]. As the disease advances, there is a progressive loss of control over drug-taking. Individuals have an increasingly difficult time resisting the urge to use the drug, despite its adverse consequences to their health and/or social functioning – a stage that calls for therapeutic interventions.

A confluence of interacting variables that include social and biological factors and the type of drugs used determines how readily or rapidly drug experimentation transitions to mild and then severe SUD. Individual factors that influence vulnerability to SUD include genetics, exposure to adverse childhood experiences, life developmental stage at which drug exposure first occurred, personality features, and concomitant psychiatric disorders. These factors in turn are modulated by general social factors, including the amount of family and community support, social disarray and inequalities, normative behaviors regarding drugs, and drug availability and legal status, among others. The complexity of interactions between individual and social factors explains why not everyone who is exposed to drugs develops addiction, and why some individuals recover while others progress into greater chronicity and associated negative outcomes. Pharmacological differences between drugs and their availability also play an important role in addiction risk, including the time it takes to escalate from drug use into addiction.

Fortunately, effective treatment and preventive interventions for SUDs exist. A challenge for future research will be deepening our understanding of the neurobiology of SUDs, applying that knowledge to develop more effective and sustainable prevention and therapeutic interventions, and developing and scaling of services models that can reach a larger proportion of individuals with SUDs. Interventions for special populations are also badly needed.

CLASSIFICATION AND PREVALENCE

SUDs are defined as patterns of substance use that cause damage to physical or mental health[16] or lead to clinically significant functional impairment or distress[17]. They are associated with a range of physical, mental, social and legal problems[18,19]. Their clinical diagnosis is based on two main classification systems: the ICD-11 developed by the World Health Organization (WHO) and the DSM-5 produced by the American Psychiatric Association (see Tables 1 and 2).

The ICD-11 distinguishes three separate disorders[16]: a) Episode of Harmful Substance Use, defined as an episode of use that has caused clinically significant harm to a person's physical or mental health or to the health of other people; b) Harmful Pattern of Substance Use, defined as a pattern of repeated or continuous use that has caused clinically significant harm to a person's physical or mental health or to the health of other people; and c) Substance Dependence, characterized by impaired control over substance use, increasing priority of substance use over other aspects of the person's life, and persistence of use despite harm or negative consequences. The separation between Harmful Pattern of Substance Use and Substance Dependence is intended to facilitate early recognition of SUD, and to distinguish between patterns of use that may respond to brief interventions and those requiring more intensive treatment.

The DSM-5 merges the DSM-IV diagnoses of abuse and de-

Table 1 ICD-11 diagnostic requirements for disorders due to psychoactive substance use[16]

Episode of Harmful Psychoactive Substance Use

1. An episode of use of a psychoactive substance that has caused clinically significant damage to a person's physical health or mental health, or has resulted in behaviour leading to harm to the health of others.
2. Harm to health of the individual occurs due to one or more of the following: a) behaviour related to intoxication; b) direct or secondary toxic effects on body organs and systems; or c) a harmful route of administration.
3. Harm to health of others includes any form of physical harm, including trauma, or mental disorder that is directly attributable to behaviour due to substance intoxication on the part of the person to whom the diagnosis applies.
4. Harm to health is not better accounted for by another medical condition or another mental disorder, including another Disorder Due to Substance Use.

Harmful Pattern of Psychoactive Substance Use

1. A pattern of continuous, recurrent, or sporadic use of a psychoactive substance that has caused clinically significant damage to a person's physical health or mental health, or has resulted in behaviour leading to harm to the health of others.
2. Harm to health of the individual occurs due to one or more of the following: a) behaviour related to intoxication; b) direct or secondary toxic effects on body organs and systems; or c) a harmful route of administration.
3. Harm to health of others includes any form of physical harm, including trauma, or mental disorder that is directly attributable to behaviour related to substance intoxication on the part of the person to whom the diagnosis applies.
4. The pattern of use of the relevant substance is evident over a period of at least 12 months if substance use is episodic or at least 1 month if use is continuous.
5. Harm to health is not better accounted for by another medical condition or another mental disorder, including another Disorder Due to Substance Use.

Substance Dependence

1. A pattern of recurrent episodic or continuous use of a psychoactive substance with evidence of impaired regulation of use of that substance that is manifested by two or more of the following:
   a. Impaired control over substance use (i.e., onset, frequency, intensity, duration, termination, context);
   b. Increasing precedence of substance use over other aspects of life, including maintenance of health, and daily activities and responsibilities, such that substance use continues or escalates despite the occurrence of harm or negative consequences (e.g., repeated relationship disruption, occupational or scholastic consequences, negative impact on health);
   c. Physiological features indicative of neuroadaptation to the substance, including: a) tolerance to the effects of the substance or a need to use increasing amounts of the substance to achieve the same effect; b) withdrawal symptoms following cessation or reduction in use of that substance, or c) repeated use of the substance or pharmacologically similar substances to prevent or alleviate withdrawal symptoms. Physiological features are only applicable for certain substances.
2. The features of dependence are usually evident for a period of at least 12 months but the diagnosis may be made if use is continuous (daily or almost daily) for at least 3 months.

Table 2 DSM-5 diagnostic criteria for substance use disorder[17]

A. A problematic pattern of substance use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. The substance is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control the substance use.
3. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.
4. Craving, or a strong desire or urge to use the substance.
5. Recurrent use of the substance resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued use of the substance despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.
7. Important social, occupational, or recreational activities are given up or reduced because of use of the substance.
8. Recurrent use of the substance in situations in which it is physically hazardous.
9. Use of the substance is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of the substance.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for the substance.
    b. The substance (or a closely related one) is taken to relieve or avoid withdrawal symptoms.

Note: Withdrawal symptoms and signs are not established for some substances, and so this criterion does not apply.

pendence into a single category of SUD, with eleven criteria, subdivided into four groupings: impaired control, social impairment, risky use, and pharmacological criteria (i.e., tolerance and withdrawal). Three levels of severity are distinguished, based on the number of criteria met: mild (two or three), moderate (four or five), and severe (six or more)[17,20]. Differences in diagnostic criteria between the ICD and DSM contribute to some of the discrepancies in the estimated prevalence of SUDs[21].

Prevalence estimates of drug use and of SUDs are high across most countries. Alcohol is the most frequently used substance, and it is estimated that 2.3 billion people worldwide currently use alcohol (40% of adult population), with large differences across countries (from 80% to <1% of the adult population)[22]. Worldwide estimates for tobacco use indicate that, even though the rates have been decreasing since 1990, the number of people who smoke worldwide was 1.1 billion in 2019[23]. The number of people worldwide who use drugs (other than alcohol and tobacco) was estimated to be around 275 million in 2019, with the largest share among adolescents and young adults[24]. Cannabis was used by 200 million people; it was the most frequently used illicit drug and accounted for more than half of all drug law offence cases worldwide[25,26]. On the other hand, opioids accounted for the most deaths, which in the past decade have increased by 41%[25].

Among SUDs, the prevalence is highest for nicotine use disorder (estimated at 20% in past year) and alcohol use disorder (estimated at 5.1% in past year), followed by opioid use disorder and cannabis use disorder[27]. Estimates of SUD prevalence are 2.3 to 1.5 times higher for males than for females[27]. Global surveys from 2016 estimated 100.4 million cases of alcohol use disorder (70% were males), 26.8 million cases of opioid use disorder (60% were males), 22.1 million cases of cannabis use disorder (68% were males), 5.8 million cases of cocaine use disorder (68% were males), 4.9 million cases of amphetamine use disorder (65% were males), and 3.9 million cases of other drug use disorders[27]. Estimates for nicotine use disorder in 2019 were 1.1 billion and included most of the active daily smokers (36.7% of all men and 7.8% of the world's women)[28].

Countries with the highest rates of heavy alcohol drinking are Angola, Gabon, Congo and the Democratic Republic of Congo (rates >77%), followed by Russia and Papua New Guinea (60%); whereas the highest rates for drug use disorders are in the US (3.7%), Canada (2.7%), Australia (2.4%), and the UK (2.2%)[29]. Russia (32%), Indonesia (30%) and Chile (29%) have the highest rates of daily smokers as of 2012[30].

The prevalence of opioid misuse and opioid use disorder in the US has increased over the last two decades. Due to the high lethality of opioid-related overdoses (exacerbated by the expanded access to illicitly manufactured fentanyl), opioid use disorder represents one of the greatest public health challenges in the US and Canada, and is expanding into other countries. In 2021, the annual overdose mortality for opioids in the US was estimated at 81,052[31].

NEUROBIOLOGY

Drug reward and reinforcement

An evolutionarily conserved neurobiological strategy for survival is the motivation to seek out positive rewarding stimuli (e.g., food and sex) and to avoid negative aversive ones (e.g., pain and environmental threats)[32]. Dopamine is a key neurotransmitter underlying the motivation to seek positive stimuli and avoid negative stimuli[33].

Drugs tap into this basic dopaminergic mechanism both for their rewarding effects and for the neuro-adaptations that ensue with their repeated consumption. Specifically, every drug with addictive potential increases dopamine in the nucleus accumbens, through either activation/disinhibition of dopaminergic neurons in the ventral tegmental area or activation of synaptic mechanisms that lead to increased dopamine concentration at the terminals of these neurons in the nucleus accumbens[34]. Dopamine's role in drug reward and reinforcement is associated with several components, including motivation, associative learning (conditioning), incentive salience, and prediction error[35].

Different classes of drugs increase dopamine via distinct molecular targets and mechanisms (see Table 3), with resultant differences in the magnitude and the speed of dopamine increase, which in turn are factors that contribute to a drug's addictive liability[36]. In this respect, the stimulant drug methamphetamine triggers the

Table 3 Drug classes and their main mechanisms of action

Drug class	Main mechanisms of action
Alcohol	Alcohol affects multiple targets (enhances GABA, mu opioid receptor and cannabinoid signaling), indirectly increasing dopamine in the nucleus accumbens.
Nicotine	Nicotine is an agonist at nicotinic acetylcholine receptors (nAChRs). In particular its binding to the α4β2 nAChR subtype is associated with its reward-related and reinforcing effects, directly activating dopamine neurons in the ventral tegmental area (also activates modulatory neurons in this area).
Cannabinoids Cannabis, Synthetic cannabinoids	The rewarding and reinforcing properties of cannabis are due to tetrahydrocannabinol, which is a partial agonist at the CB1R receptors. Cannabidiol is neither rewarding nor addictive. Synthetic cannabinoids' agonism at CB1R also underlies their rewarding and reinforcing effects. CB1R activation modulates presynaptic release of GABA and glutamate, activating dopamine neurons in the ventral tegmental area.
Stimulants Amphetamines, Cocaine	Amphetamines, whether legally prescribed as medications for ADHD or obtained from illicit or clandestine sources (e.g., meth labs), directly release dopamine from the terminals of dopaminergic neurons via dopamine transporter (DAT) reversal and depletion of vesicular dopamine stores. Cocaine increases dopamine by inhibiting DAT, which prevents dopamine reuptake leading to its synaptic accumulation.
Opioids Morphine, Heroin, Fentanyl	Opioids' rewarding effects are due to their agonist actions at mu opioid receptors. In the ventral tegmental area, opioid binding to these receptors on GABA cells disinhibits dopaminergic neurons, increasing dopamine in nucleus accumbens, which underlies their reinforcing properties. Opioid drugs differ in potency, with fentanyl >> heroin > morphine.
Inhalants Volatile solvents, Aerosols, Gases, Nitrites	Inhalants have effects on various neurotransmitters and their receptors (NMDA↓ glycine↑, $GABA_A$↑, nACh↓, dopamine↑), enhancing dopamine release.
Sedative/Hypnotics Benzodiazepines, Barbiturates	Benzodiazepines and barbiturates, which are used as therapeutics for anxiety, insomnia, seizures, and sedation in anesthesia, are misused for their rewarding effects. They enhance $GABA_A$ receptor function, increasing dopaminergic neuron firing in the ventral tegmental area through disinhibition, which underlies their reinforcing properties.
Classic hallucinogens Psilocybin, Lysergic acid diethylamide (LSD), Mescaline, Dimethyltryptamine (DMT)	Hallucinogenic drugs act as agonists at the 5-HT2 receptor. They are predominantly used to alter mental states and do not trigger compulsive drug taking. They are the only drugs in this table not considered to be addictive. They also have effects at other serotonin receptors.
Dissociative drugs Ketamine, Phencyclidine (PCP)	NMDA receptor antagonism dissociates the cortical control and the gating of thalamus, facilitating transmission of perceptual stimuli to sensory cortices. These drugs have additional targets, including mu opioid receptors, which might underlie their increase of dopamine in nucleus accumbens.
Mixed drugs 3,4-Methylenedioxy-methamphetamine (MDMA)	MDMA is a blocker of monoamine transporters. Its effects are similar both to those of stimulants (enhancing dopamine) and of hallucinogens (enhancing serotonin).

ADHD – attention-deficit/hyperactivity disorder, NMDA – N-methyl-D-aspartate

largest dopamine increases and is associated with the highest risk for developing addiction (moderate to severe SUD) among those exposed to it (50% risk within 2 years of exposure)[37]. The contribution of the speed at which dopamine increases occur in the brain is also influenced by the route of administration[38]. This explains why drugs are more rewarding and have higher risk for resulting in addiction when they are injected or smoked, as these routes of administration result in faster drug delivery into the brain than snorting or oral consumption[39].

Additionally, the various drug types engage other neurotransmitters based on their unique pharmacological properties, and these also contribute to their rewarding and reinforcing effects. Specifically, opioid drugs and cannabis directly activate the endogenous opioid and cannabinoid systems, respectively, which by themselves are associated with hedonic effects (pleasurable sensations)[40]. Alcohol enhances GABAergic neurotransmission, which underlies its anxiolytic effects, while also indirectly stimulating endogenous opioid and cannabinoid signaling[41]. By desensitizing nicotine receptors, nicotine can inhibit negative aversive states[42]. The involvement of non-dopaminergic neurotransmitters in drug reward is made evident by studies in dopamine-deficient mice, that are still able to show conditioned place preference for cocaine or for morphine[43].

Dopamine increases in the nucleus accumbens that result from the consumption of intoxicating doses of an addictive substance are larger and longer-lasting than the increases associated with natural rewards. In the nucleus accumbens and other striatal regions, dopamine binds to high-affinity D2 and D3 receptors. When dopamine is present at high levels, as is the case during drug intoxication, it additionally binds to low-affinity D1 receptors[39]. Dopamine also binds to D4 and D5 receptors, but their relevance to the behavioral effects of addictive drugs or to reward has been much less investigated. Note that activation of D1 receptors is necessary for drug reinforcement, while activation of D2 and D3 receptors is not[44], although maximal reinforcement occurs with concomitant stimulation of D1 and D2 receptors.

The dopamine reinforcement system is dynamic, and its responses to rewards, including drugs, change as a function of the magnitude and duration of the stimulus. The first exposure to a reward (natural or drug) triggers a robust firing of dopamine neurons (phasic firing) that results in steep dopamine increases in the nucleus accumbens at levels that will bind to both D1 and D2 receptors. However, repeated exposure transforms the reward into an "expected reward", at which point dopamine neurons fire in response to stimuli that predict the delivery of the originally rewarding stimulus[45]. However, if a reward is expected but is not delivered, then dopamine neuronal firing is inhibited, signaling a "reward prediction error"[46].

The dopamine shift from reward to stimuli that predict the reward is referred to as conditioning, and drug-predictive stimuli (objects, environments, routines or emotions) are referred to as drug cues. Conditioning, driven by stimulation of D1 receptors in the nucleus accumbens, explains the addictive potential of drugs[47,48]. Once the experience from drug reward has been turned into a conditioned memory, the cues by themselves drive the desire for the drug and energize the dopamine motivational circuit that propels the behaviors to pursue it[33]. With repeated drug use, the number of stimuli that become linked (conditioned) to the drug expands, increasing the likelihood of encountering a drug-predictive cue. Once consumed, the drug's dopamine-stimulating pharmacological effects further strengthen conditioning, and this perpetuates the cycle of drug-taking[33]. This helps explain why individuals with a SUD may engage in risky, illegal or unhealthy behaviors in order to obtain the drug reward, and why return to use is so likely in people with a SUD who are abstinent.

The stimulation of D1 receptors thought to facilitate conditioning subsequently triggers neuro-adaptations in glutamatergic and other neurotransmitter systems that strengthen neuronal excitability in meso-cortico-limbic reward pathways. These neuro-adaptations are akin to those engaged in memory processes, involving changes in synaptic levels and the subunit composition of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors, and increasing the motivational value of drug-associated stimuli[33]. Parallel neuro-adaptations in other neurotransmitter systems – including GABAergic, opioid, endocannabinoid, cholinergic, serotonergic and noradrenergic ones – contribute to the disruption of mood, cognition, sleep, and stress reactivity that occurs with repeated drug use[39].

Addiction neurocircuitry

The transition from controlled drug use into addiction manifests itself in a repetitive cycle of intoxication, withdrawal and craving[49], occurring along with a deterioration of mood that the addicted individual experiences as dysphoria/depression, anxiety, irritability and anhedonia when not intoxicated[50].

The three stages of the addiction cycle emerge as a consequence of the disruption of brain networks involved with reward and motivation (reward network), executive function (executive control network), mood and stress reactivity (salience and emotion networks), and self-awareness (interoceptive and default mode networks)[51].

The length of the cycle and the prominence of each stage varies as a function of the severity of the SUD and the pharmacological characteristics of the drug(s) consumed. The principal components of the addiction neurocircuitry are different for each stage of the addiction cycle.

Reward network

The reward network involves the midbrain dopamine neurons, along with their projections to the nucleus accumbens, dorsal striatum, medial prefrontal cortex, and anterior cingulate cortex. This network is engaged during intoxication, when it is maximally stimulated, while during withdrawal it becomes hypofunctional, contributing to the decreased motivation and reduced sensitivity to non-drug rewards (anhedonia).

Dysphoria and anhedonia during the withdrawal stage, alongside exposure to drug cues, can trigger the activation of the network, which initiates the craving stage in the cycle. Craving engages the ventral prefrontal cortex and the ventral anterior cingulate cortex, sparking the drive to seek the drug that culminates in intoxication and compulsive consumption.

In the addicted state, there is a diminished sensitivity to the drug's rewarding properties, such that increasingly higher doses are needed to produce the desired effect. Over time, this leads to seeking the drug not for its pleasurable effects, but instead to escape the aversive state of withdrawal. The emergence of withdrawal symptoms upon drug discontinuation, which is particularly severe from opioids, alcohol and nicotine, contributes to perpetuating drug-taking.

The reduced sensitivity of the reward circuit in addicted individuals manifests as lack of interest in non-drug-associated activities. Brain imaging studies in humans with various SUDs have documented a decrease in striatal dopamine release (both in dorsal and ventral striatum) during the withdrawal stage, that could underlie these manifestations[49]. Clinical brain-imaging studies have also revealed decreased activation of brain regions implicated in the processing of food, sexual or monetary rewards in individuals with addiction[35]. Reactivity of striatal and prefrontal regions to punishments (referred to as negative reinforcers) is also reduced in individuals with addiction, and this reduced reactivity is associated with worse outcomes and is believed to contribute to the lack of deterrence conferred by the threats from potential negative consequences (e.g., incarceration, loss of child custody)[52] of addictive behaviors.

Assessments of the dopamine neurocircuitry in individuals with various SUDs have consistently revealed reduced striatal D2 receptors[39], and in healthy controls the levels of these receptors are inversely associated with reward sensitivity to stimulant drugs[53]. It is believed that an impaired balance between D1 and D2 receptor striatal signaling favors cue-induced reactivity while reducing behavioral control through weakened D2 receptor signaling. In hu-

mans, the enhanced sensitivity to drug cues is associated with addiction severity and worse clinical outcomes[54]. In animal models of addiction, strengthening striatal D2 receptor signaling has been found to interfere with compulsive drug-taking[55], suggesting that interventions to enhance striatal D2 receptors could be beneficial for the treatment of addiction. Few studies have been conducted to measure striatal D1 receptors in SUDs, and the results have been inconsistent[56,57].

Executive control network

The executive control network underlies various cognitive processes, including decision-making and self-regulation. Drug-induced disruptions in the function of this network contribute to the inability to avoid risky behaviors, resist drug craving, and delay gratifications.

This network includes various regions in the prefrontal cortex, whose functions are modulated by dopamine through D1 and D2 receptors in the striatum and in the prefrontal cortex itself. Repeated drug use can result in impairments that weaken self-control and promote impulsivity, in part through dopaminergic striatal effects or by direct harm to the prefrontal cortex, including the anterior cingulate cortex, orbitofrontal cortex, and dorsolateral prefrontal cortex[58]. In humans with SUD, the loss of striatal D2 receptors is associated with impaired activity of the prefrontal cortex[58,59].

Pre-existing prefrontal cortex dysfunction due to genetic factors, head trauma, or neurodevelopmental insults is recognized as a vulnerability risk factor for SUDs[60]. Interestingly, individuals at high genetic risk for alcohol use disorder (i.e., those with a family history of the disorder) but who do not suffer from alcohol use disorder themselves, have been found to have higher-than-normal striatal D2 receptor availability, which was associated with normal prefrontal cortex activity. In these high-risk individuals, the striatal D2 receptor upregulation may be protective against alcohol use disorder by strengthening prefrontal circuits involved in self-regulation[61].

The role of the prefrontal cortex appears to shift through the stages of the addiction cycle, such that the ventral and medial prefrontal cortex, including the orbitofrontal cortex and the dorsal anterior cingulate cortex (regions involved with salience attribution), are activated during the intoxication and craving stages. In contrast, the withdrawal stage is associated with a decreased activity in these medial and ventral prefrontal regions and in the dorsolateral prefrontal cortex (a region involved in decision-making)[62]. The connectivity between the prefrontal cortex and striatal regions has been consistently shown to be disrupted in individuals with SUDs[59,63,64]. Consequently, the prefrontal cortex is a target for transcranial magnetic stimulation and transcranial direct electrical stimulation interventions for the treatment of SUDs, most of which have targeted the dorsolateral prefrontal cortex specifically. The anterior cingulate cortex has also been proposed as a promising neuromodulation target for treatment of addiction[65].

Salience and emotion network

The distress and negative emotions of withdrawal are associated on the one hand with reduced dopamine signaling in response to rewards (anhedonia) and on the other with an enhanced sensitivity of the brain's stress system, including the extended amygdala, habenula and hypothalamus[66]. These neuro-adaptations in turn negatively impact components of the salience and emotion networks (including anterior cingulate cortex, amygdala and hippocampus). Sensitization of these networks likely partly underlies the frequent comorbidity of SUD with depression, anxiety and suicidality[67].

Molecular mechanisms implicated in these neuro-adaptations include upregulation of dynorphin signaling through kappa opioid receptors, which are believed to contribute to negative emotional states, although these effects appear drug-specific[68,69]. Adaptations in the hypothalamic-pituitary-adrenal axis, which regulates cortisol response during stressful circumstances, are also induced by chronic drug exposures, leading to elevations in corticotrophin releasing factor (CRF) and cortisol levels. Upregulation of CRF in the amygdala in turn plays a role in negative emotional states during drug withdrawal[51].

Interoceptive and default mode networks

Interoceptive inputs influence the shift from goal-directed, flexible behaviors toward compulsive, reflexive ones. The insula, especially its most anterior portion, is heavily involved in interoception, by integrating information about internal physiological states and conveying that information to the anterior cingulate cortex, involved with decision-making (also in front of conflicting alternatives); the ventral striatum, involved with reward; and the ventral medial prefrontal cortex, involved with salience attribution, so that they can initiate adaptive responses[70].

The two-way communication between those limbic regions and the insula suggests that the latter may play a role in the conscious awareness of internal urges. Individuals who suffered a stroke that damaged their insula were more likely to quit smoking than those who suffered a stroke in other brain regions[71], and insular activation has been associated with craving for various drugs, including nicotine, cocaine and alcohol (although not in all studies)[72]. Consequently, the insula has become a target for transcranial magnetic stimulation in addiction treatments[73].

The default mode network is involved in self-awareness and mind wandering, and its enhanced activation in the craving stage of addiction might redirect exaggerated attention toward the internal state of craving or discomfort[74]. Imaging studies have revealed impairment in brain regions within this network, including disrupted activity or connectivity involving the anterior cingulate cortex, insula, and precuneus[74].

RISK FACTORS

Several biological and social factors have been associated with

increased risk of SUDs[75], including male sex, genetics, younger age of substance use initiation, childhood adverse experiences, and psychiatric comorbidities. Drug availability and social norms around substance use are also important contributing risk factors.

Certain risk factors for SUD are more important at specific developmental stages[76], and risk factors that occur at earlier ages predispose to exposure to other risk factors later in the individual's life, often multiplying their effect. Therefore, the effect of risk factors is often not additive, but synergistic and cascading. Interventions at earlier stages of the cascade may be more likely to decrease downstream risk for SUD. Furthermore, to the extent that risk factors for SUD are shared with other psychiatric disorders, interventions on those shared factors can have spillover effects in preventing other disorders[77].

Development

Biological risk for SUDs emerges early in life, changes at various life stages, and is differentially influenced by social factors and experiences during those different life stages and transitions[78]. This developmental conceptualization of SUDs[79] helps explain the diversity of possible pathways from the various risk factors to a SUD.

Brain development during childhood and adolescence undergoes broader changes than during adulthood. In particular, the slower rate of development of the prefrontal cortex, which does not fully mature until the mid-twenties[80], places adolescents at higher risk for risky behaviors, since this region is necessary for self-regulation. This likely contributes to the increased proneness to drug experimentation during this life stage[81].

Delays in the maturation of the prefrontal cortex due to social stressors during childhood increase the risk of later drug use[82,83]. Similarly, exposure to drugs in early adolescence can perturb cortical development, including delaying the maturation of the prefrontal cortex[60]. Dysfunction of the prefrontal cortex in adolescents has been associated with a higher risk for SUDs[84].

Social environments

Epidemiological studies have repeatedly shown that environments with high levels of stressors, poor social support, easy access to drugs, and lack of opportunities and alternative reinforcers increase drug use and addiction risk[85,86]. Adverse social environmental exposures exert some influence throughout life, but effects are more pronounced when they occur in childhood or adolescence, when the brain is rapidly developing[87]. Delayed maturation of prefrontal-limbic connectivity and smaller prefrontal cortex volumes can be consequences of adverse social environments during early childhood[88].

Adverse social environments also increase the risk of drug use and SUDs across adulthood. For instance, unemployment, housing instability, and the effects of racism and discrimination may increase SUD risk and severity[89]. Overcrowding, natural or man-made disasters (conflict and war), and social factors such as low income, uncontrolled and poorly planned urbanization, and environmental degradation can also increase the risk of substance use and SUD. Primate studies that emulate social stress through hierarchical systems of dominance and subordination have shown that being an adult male of subordinate rank is associated with reduced striatal D2 receptors and is linked to higher impulsivity and drug use[90]. In humans, having poor social support systems has similarly been associated with lower striatal D2 receptors[91].

Genetics and epigenetics

Genetic factors have been estimated to account for about 50% of overall addiction risk. There are multiple gene variants that may interact to influence risk for addiction to different drugs, including genes involved in the metabolism of drugs, in dopaminergic and glutamatergic neurotransmission, in neuroplasticity, and in brain development[92]. The genetics of SUDs appears to be part of a general genetic predisposition to externalizing disorders, though common genetic predisposition has also been reported between SUDs and internalizing disorders. These common genetic vulnerabilities help explain the frequent comorbidity between SUDs and attention-deficit/hyperactivity disorder (ADHD) as well as anxiety disorders and depression[93].

Genetic studies, including genome-wide association studies (GWAS), have identified genetic variants associated with various SUDs as well as variants that appear to be protective[94]. The gene variants with the largest effects are those associated with alcohol metabolism. Variants of genes encoding for the enzymes alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), such as certain *ADH1B* and *ADH1C* alleles, result in a more rapid conversion of alcohol to acetaldehyde, the accumulation of which is aversive, and thus have a protective effect against the risk of alcoholism[95].

Gene variants can also influence the risk of misuse and addiction via a direct impact on a drug target. Examples include variants in the *OPRM1* gene, encoding for the mu opioid receptor, which has been associated with different clinical effects of opioids[96]; and variants in the *CHRNA5* gene, encoding for the alpha-5-subunit-containing nicotine receptor, which has been found to increase vulnerability to tobacco dependence[97].

Gene variants can also exert their effects indirectly, by influencing brain development, including the rate at which frontal connections mature; personality traits that may predispose to drug-seeking, such as sensation seeking; drug metabolic pathways that result in faster or slower degradation of drugs; neurotransmitters that are directly or indirectly implicated in drug reward and neuroplasticity, such as dopamine and glutamate systems; neural circuitry implicated in the addiction cycle, or cellular physiology that influences for example the side effects of drugs[98,99]. Similar to findings for other mental disorders, GWAS reveal that addiction is a polygenic disease which is influenced by multiple genes and genetic networks[100]. Currently, the ability to predict the risk of SUDs using polygenic scores is poor[101].

Preclinical studies in animal models of addiction have evaluated epigenetic modifications of gene expression and silencing in brain regions relevant to drug reward and addiction, and associated with short- and long-term effects of drugs[102]. Epigenetic modifications are believed to drive and sustain the long-lasting changes associated with addiction[103]. Among the epigenetic markers studied are histone modifications, DNA modifications, and non-coding RNAs[104], along with the expression and function of enzymes involved with reading and silencing of genes (i.e., histone acetylases, HAT; histone deacetylases, HDAC; and demethylases).

Most preclinical epigenetic studies have concentrated on regions of the midbrain dopamine reward system, including the nucleus accumbens. These studies have shown that acute and chronic drug exposures (stimulants, opioids, alcohol, nicotine) increase total cellular levels of acetylation of histones H3 and H4[105-110], apparently by unbalancing HAT and HDAC function. Moreover, the manipulation of enzymes that control histone acetylation or deacetylation or DNA methylation in the nucleus accumbens modifies drug behavioral responses, supporting their relevance to drug reward and SUDs[111,112].

The timing of substance exposure may influence the likelihood of epigenetic changes, which in turn will modify gene expression and the function of cells and circuits in the brain (and other organs). Epigenetic modifications are likely to have particularly long-lasting consequences to the brain when they occur during fetal or early infancy stages. This is because the enzymes mediating epigenetic modifications play a fundamental role in embryonic and postnatal brain development, so that their modification with *in utero* or early postnatal exposure to drugs might contribute to a higher vulnerability to addiction later in life[113].

Frequency of use is also important, as some epigenetic changes occur with short but not with repeated drug consumption, as is the case for the hyperacetylation of histone H4 along the cFos gene promoter in the striatum, whereas hyperacetylation of histone H3 at the brain-derived neurotrophic factor (BDNF) promoters is seen only after repeated cocaine exposure[114].

In parallel, studies are evaluating the effects of adverse environmental exposures, such as stress and neglect, on epigenetic modifications. These are relevant for understanding the mechanisms underlying the impact of such exposures on brain development and their enhancement of the susceptibility to addiction[113].

Human studies to assess epigenetic modifications have been limited to measures made in blood cells or in post-mortem brain[115,116]. Though there are promising results from human positron emission tomography (PET) imaging studies that measured HDAC activity in the brain of healthy people, these measures have not yet been used to study SUDs[117-119]. Clinical studies based on blood cells have found that individuals who consume drugs show epigenetic changes that appear to relate to the frequency of use in a dose-dependent manner[113]. However, drug-independent changes in addiction vulnerability triggered by adverse childhood experiences or other environmental factors might have also contributed to the epigenetic modifications reported in individuals with SUDs[120].

As the various epigenetic markers associated with drug exposures and their role in the transition to addiction or to SUD risk are better understood, they may lead to potential new medication targets. They may also help explain sex differences in drug use and addiction vulnerability, as well as changes in drug use vulnerability throughout the lifespan.

Psychiatric disorders

The presence of a psychiatric disorder – including mood, anxiety, psychotic and personality disorders, and ADHD – is associated with an increased risk for SUDs. On the other hand, SUDs are also associated with increased risk for a mental disorder. These associations are likely to reflect bidirectional links, such that having a mental disorder increases risk of maladaptive use of drugs to self-medicate, and having a SUD increases risk for developing a mental disorder, as drugs affect neurocircuits relevant to other mental disorders. Common genetic and environmental risk factors for both SUDs and mental disorders also contribute to their high degree of comorbidity[121-123].

The Epidemiological Catchment Area Study found that the overall lifetime prevalence of any SUD among those with any lifetime psychiatric disorder was almost double that for those without a psychiatric disorder (29.8% vs. 16.7%, respectively)[124]. Specifically, prevalence of SUDs in individuals with a lifetime diagnosis of bipolar disorder was 56.1% (odds ratio, OR=6.6); that in people with schizophrenia or schizophreniform disorder was 47.0% (OR=4.6); and that in persons with panic disorder was 35.8% (OR=2.9)[125]. Conversely, among individuals with a lifetime drug use disorder, 28.3% also had an anxiety disorder, 26.4% had a mood disorder, and 6.8% had schizophrenia. Analogous findings have been documented in other US large epidemiological studies, including the National Comorbidity Survey[126] and the National Epidemiologic Survey on Alcohol and Related Conditions[126,127], as well as in studies from other countries[125-128]. Comorbidity is generally associated with greater severity of illness and lower probability of remission[129].

Of particular interest is the relationship between cannabis use and psychosis. This is likely a multidirectional relationship, and its exact mechanisms continue to be a subject of debate[130]. The risk of psychosis appears to be influenced by the age of the individual at first use, the potency of the cannabis used, and how frequently it is used. A 2022 meta-analysis found an association of weekly cannabis use (vs. no use) with a 35% increase in risk of developing psychosis; it also found an association of daily or near-daily use with a 76% increase in that risk. By contrast, there was no significant increase in risk among individuals with monthly and yearly use[103].

Another area of concern with cannabis consumption is its association with a higher risk for depression and suicidality, particularly among young people. In fact, a recent meta-analysis reported an OR of 1.37 (95% CI: 1.16-1.62) for developing depression, and of 3.46 (95% CI: 1.53-7.84) for suicidal attempt, in young cannabis users when compared to non-users[131]. A higher risk of suicidal behaviors has also been reported in cannabis users with and without a

history of major depressive disorders[132] and in men with psychotic disorders who use cannabis[133].

Tobacco smoking is recognized as a major factor contributing to the lower life expectancy of persons with mental disorders[134,135]. This is especially problematic for individuals with serious mental illness, who have the highest smoking rates and higher smoking severity[136]. Although for many years psychiatrists have been reluctant to treat comorbid nicotine use disorder in psychiatric patients, because of beliefs that these patients were not interested in quitting or concerns that quitting would negatively impact their mental state[137], the evidence indicates otherwise. Specifically, many individuals with psychiatric disorders who smoke are interested in quitting[138] and respond to smoking-cessation treatments, although they might require additional support to help them quit. Moreover, there is some evidence that smoking cessation may help reduce symptoms of depression, anxiety and stress, and might improve quality of life[139]. Indeed, a recent meta-analysis concluded that there is strong evidence that mental health does not worsen as a result of quitting smoking, while there is some evidence that smoking cessation might be associated with small to moderate improvements in mental health[140].

Treatment of patients with comorbidity should include interventions for both SUD and the psychiatric disorder, because lack of treatment of one of the disorders might interfere with the success of the treatment of the other. When using medications for the treatment of SUD in a patient with a comorbid psychiatric disorder, consideration should be given to potential undesirable drug interactions. For example, whereas the use of antidepressants alongside buprenorphine in patients with opioid use disorder and depression reduced the risk of overdose[141], the use of benzodiazepines increased it, presumably reflecting synergistic respiratory depressant effects from both drugs[142].

Comorbidities between psychiatric disorders and SUDs are also relevant to prevention efforts. Specifically, because psychiatric disorders increase the vulnerability for SUDs, their early diagnosis and treatment could help prevent SUDs. Conversely, early identification of drug use in an adolescent might be an indicator of an underlying emerging psychiatric disorder, and its treatment might prevent a more severe presentation[143,144].

CLINICAL ASPECTS

Identification of SUDs

Only a minority of persons with SUDs seek treatment[145]. Since these individuals are likely to seek treatment for other conditions, such as infections or pain, screening for substance misuse in psychiatric and general medical settings is an effective way to identify SUDs[146,147].

The goal of screening is to identify substance use that increases the risk for health consequences and to develop an action plan based on severity, co-occurring psychiatric and general medical conditions, and the patient's motivation. Although SUDs are generally associated with more severe consequences than substance misuse, the latter is much more prevalent[148-150]. Thus, at the population level, most of the health consequences accrue to individuals with substance misuse rather than SUDs.

Consequently, we recently proposed the new term "pre-addiction" to identify the early stages of a SUD (mild SUD, as per DSM-5) as a focus of attention in screening for problematic drug use[15]. The term and strategy were inspired by the introduction of the term "pre-diabetes" to bring attention to the early stages of a condition amenable to intervention, in order to halt the progression to the full-blown disease. This resulted in policies in health care that now reimburse for early screening and intervention in pre-diabetes and also incentivize education of health providers in its recognition and management.

Screening and intervention for "pre-addiction" by health care providers could similarly prevent many of the adverse effects linked with unhealthy substance misuse and halt the transition into severe SUD. They could also help to cement the need for education and resources to address this early stage. There are currently screening tools that could be used for this purpose, while ongoing work is done to further validate them. However, while some interventions have been proposed for early-stage SUD (pre-addiction), this is an area that would benefit from further development of effective therapeutic tools.

Screening tools that are brief are most likely to be of practical value in health care settings where clinicians have limited time for each patient[151]. There are brief self-report instruments with high sensitivity and good specificity[146] available for use in general health settings. These are based on single questions, such as "How many times in the past year have you had five (four for women) or more drinks in a day?" for alcohol, and "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" for drugs[152,153].

A popular, evidence-based screening instrument developed and recommended by the WHO for primary care settings is the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)[154]. Eight questions about alcohol, tobacco and drug use (including injection drug use) help identify an individual's hazardous, harmful or dependent substance use. The tool can be interviewer- or self-administered. The Tobacco, Alcohol, Prescription medication, and other Substance (TAPS) is another newer and briefer (four items) valid screening tool[155].

A checklist of diagnostic criteria or, in research settings, a structured or semi-structured interview can be used to obtain a formal SUD diagnosis. Screening for substances in blood, urine or saliva can be useful to detect current use and to help monitor progress. Drug screening can also be useful if a patient cannot participate in an in-person interview[151].

SUDs as chronic disorders: onset, remission and relapse

The rate of transition from substance use to a SUD varies by the type of substance, based on its pharmacological properties[148,156,157], availability, legality, and social acceptability[156,157]. The cumulative rate of transition has been reported to be 16-67.5% for nicotine use

disorder, 14-22.7% for alcohol use disorder, 17-20.9% for cocaine use disorder, 23% for heroin use disorder, and 8.9% for cannabis use disorder[148,158]. The risk tends to be higher with younger age of initiation[158-160].

There is a growing consensus that SUDs, once developed, tend to be chronic disorders[161], reflecting long-lasting changes in brain function[50,51], that are exacerbated by the cumulative mental health and social consequences that they trigger. Although abstinence can lead to a normalization of brain structure and function over time, the level of recovery varies as a function of chronicity, type of drugs consumed, treatment and recovery support received, and intersubject variability[51]. Most individuals with a SUD alternate between periods of remission and relapse[76].

Rates of remission vary by substance, with lifetime cumulative estimates of 83.7% for nicotine, 90.6% for alcohol, 97.2% for cannabis, and 99.2% for cocaine, based on a US study[148]. Relapse rates also differ by substance: within a 3-year period, for those in remission, they are about 20% for cocaine use disorder[162] and more than 50% for alcohol use disorder[163]. About 50% of people with nicotine use disorder relapse in the first year after quitting[164]. Rates of relapse follow a hyperbolic function, with risk decreasing the longer the person remains in remission, although risk never fully disappears[164]. This is consistent with clinical experience that more intensive interventions are needed at earlier than later points in the treatment.

Long-term care of SUDs is associated with the best clinical outcomes[165]. Indeed, the Chronic Care Model, which was developed to improve the care of chronic conditions such as diabetes[166], has been proposed as a useful framework to manage SUDs[161,167]. This model emphasizes continuity of care, as opposed to episodic discontinuous care (e.g., repeated medically supervised withdrawals), with intensity of care depending on the course of the disorder. For example, an individual who recently returned to drug use may require more frequent visits or higher medication doses than somebody who has been abstinent for several years.

Examples of lifestyle management changes consistent with the Chronic Care Model involve reduction of substance use (or abstinence if possible) and use of recovery supports such as twelve-step groups. This model facilitates integration with mainstream medical practice, enhancing its reach and decreasing the costs associated with untreated SUDs[168,169].

As described in a following section of this paper, the Chronic Care Model suggests the need to develop tiered models of care. At each time point, individuals with lower need can be treated in less resource-intensive settings (community resources or primary care), while increasing severity is matched with provision of more intensive treatment approaches, such as specialized outpatient or inpatient treatment. This approach allows for the provision of the least intrusive possible care to the individual, while optimizing the use of resources at the community level.

Overdoses

A particularly dangerous complication in the course of a SUD is overdose, which, if not treated in a timely manner, can result in death. Although opioids are responsible for the most overdose deaths, there is increased recognition of the involvement of other drugs, including alcohol, and of drug combinations.

In the US, the rate of drug-related overdoses, predominantly from opioids, has risen at an almost exponential rate over the past two decades[170]. Although opioid overdose mortality was initially driven by heroin and prescription opioids, fentanyl overdoses have become progressively more important, due to their growing prevalence, difficulty of reversal, and overall lethality[171]. Treatment with naloxone – an opioid antagonist that can be administered intramuscularly, subcutaneously, intravenously or intranasally – is the most important short-term intervention to reverse overdoses. In cases in which fentanyl is involved, higher doses or repeated administrations of naloxone may be necessary. The efficacy of naloxone in reversing overdoses might be reduced when the overdose is due to combination of opioids with other respiratory depressant drugs, such as alcohol, benzodiazepines or barbiturates. Linkage with treatment services is essential to prevent repeat overdoses.

Non-lethal overdoses are much more common than lethal ones. Although their exact prevalence is not known, it is estimated that for every lethal overdose there are at least 10 non-lethal ones. Screening and monitoring of non-lethal overdoses is clinically relevant, since they frequently precede lethal ones, but unfortunately this is not routinely done. History of a non-lethal overdose should prompt an intervention either to reduce opioids in pain patients or to initiate treatment for SUD. Medications to treat opioid use disorder are the most effective prevention intervention for overdoses due to opioids[172].

TREATMENT

Treatments for SUDs include medications, neuromodulation approaches, and behavioral interventions.

Medications

Medications approved by the US Food and Drug Administration (FDA) for the treatment of SUDs are limited to tobacco (nicotine), opioid, and alcohol use disorders. Additionally, there is one FDA-approved medication for opioid overdose reversal (naloxone) and one for managing acute opioid withdrawal (lofexidine) (see Table 4). There are no approved medications to treat disordered use of stimulants, cannabis, benzodiazepines, barbiturates, inhalants, ketamine, or 3,4-methylenedioxy-methamphetamine (MDMA).

Smoking-cessation medications

Three medications for smoking cessation are approved by the FDA: bupropion, varenicline, and nicotine replacement treatments (patch, gum, lozenge, oral inhaler, and nasal spray). A mouth spray nicotine replacement treatment is also available in the UK and

Table 4 Pharmacological treatments approved for substance use disorders (SUDs) by the US Food and Drug Administration (FDA)

SUD	Indication	Medications
Tobacco (nicotine)	Smoking cessation	Nicotine replacement therapies
		Bupropion Dopamine transporter blocker
		Varenicline Partial agonist of α4β2 nicotine receptor
Opioids	Treatment of opioid use disorder	Buprenorphine Partial mu opioid receptor agonist Nociceptin receptor agonist Kappa opioid receptor antagonist
		Methadone Full mu opioid receptor agonist
		Naltrexone Mu opioid receptor antagonist Kappa opioid receptor antagonist
	Treatment of acute withdrawal	Lofexidine Alpha-adrenergic agonist
	Overdose reversal	Naloxone Mu opioid receptor antagonist
Alcohol	Treatment of alcohol use disorder	Disulfiram Aldehyde dehydrogenase inhibitor; blocks breakdown of alcohol, thereby increasing acetaldehyde levels
		Acamprosate NMDA receptor antagonist and positive allosteric modulator of GABA receptors
		Naltrexone Mu opioid and kappa opioid receptor antagonist

NMDA – N-methyl-D-aspartate

Australia. These medications lead to significantly higher rates of smoking cessation (compared to placebo) at 6 months or longer[173]. Typical treatment duration is 12 weeks, but it can be increased to 6 months or longer.

Nicotine replacement treatments work by reducing nicotine withdrawal symptoms. The various types have comparable effectiveness, with 17% quit rates at 6 months, compared to 10% for placebo[174]. The pharmacokinetics and bioavailability of nicotine from the various products differ. Patches have a slow delivery, requiring more than one hour for nicotine to peak, but result in long-lasting nicotine plasma levels for 24 hours. Nicotine reaches peak plasma concentration in 10 min when administered via nasal spray, and in 20-30 min with oral products, but plasma nicotine levels decline rapidly toward baseline within 2 hours. Supplementing the patch with a rapid-acting nicotine replacement treatment as needed, when cravings emerge, appears to improve cessation rates[175].

Electronic nicotine delivery systems (e-cigarettes) have been proposed as smoking-cessation aids[176]. A recent Cochrane review concluded with moderate certainty that they are more effective than nicotine-replacement treatments[177], but the US Preventive Services Task Force concluded that the evidence is insufficient to recommend them for smoking cessation[178]. Instead, it recommended FDA-approved medications, consistent with other US professional organizations[179,180]. This differs from the UK, where e-cigarettes are encouraged as smoking-cessation aids[181].

Bupropion is believed to reduce nicotine withdrawal symptoms by blocking the dopamine transporter (as well as the noradrenaline transporter), enhancing dopamine levels. It also has antidepressant properties via these same mechanisms, which might facilitate smoking cessation. Bupropion led to cessation rates of 19%, compared to 11% in controls[182].

Varenicline is a partial agonist at the α4β2 nicotinic acetylcholine receptor, which is implicated in nicotine's rewarding effects. This medication reduces nicotine withdrawal symptoms, while also blocking the rewarding effects of cigarettes. At 6 months, it was associated with a 26% chance of quitting, compared to 11% for placebo[183].

Cytisine, a plant-based alkaloid, is also a partial agonist of the α4β2 nicotinic receptor, and has comparable effectiveness to varenicline[184]. Though not approved by the FDA, it is prescribed for smoking cessation in Central and Eastern Europe[185].

Although medications are effective by themselves, their efficacy might be improved when combined with behavioral treatments that alter learned smoking-associated behaviors[186]. A meta-analysis of 65 randomized controlled trials (RCTs) reported 6-month cessation rates of 20% when behavioral support was added to medications, compared to 17% when medications were used by themselves[186].

Medications for opioid use disorder

Medications are the most effective interventions for preventing overdose mortality and improving outcomes in patients with opioid use disorder[187]. There are three medications used worldwide and approved by the FDA – methadone, buprenorphine and naltrexone – but there are no evidence-based guidelines to guide selection, which is most often constrained by availability[188].

Methadone is the most frequently used medication in the Middle East, Asia, South America, Africa and some European countries. It is administered daily in an oral formulation. In many countries, including the US, it has to be dispensed in licensed outpatient clinics (opioid treatment programs), which can be a barrier to care, as there are not enough licensed clinics available to serve the needs of patients with opioid use disorder in many urban and especially rural settings. When clinics are not nearby, patients must travel long distances on a daily basis[189].

Because it acts as a full mu opioid receptor agonist, methadone is indicated in patients with high tolerance, as the partial-agonist buprenorphine could trigger withdrawal symptoms in these individuals. Overall, retention is better with methadone than with buprenorphine. Higher doses (>80 mg/day) are associated with better outcomes than lower doses[190]. As a full agonist, methadone has no ceiling effect, which increases overdose risk when it is used

at doses above the patient's tolerance or when it is combined with alcohol, benzodiazepines, heroin, or other opioids. Expanding access to methadone via office-based approaches or pharmacy dispensing is a subject of interest and discussion.

Buprenorphine (a partial mu opioid receptor agonist and a kappa opioid antagonist) received FDA approval for opioid use disorder in 2002, and its use has expanded worldwide since then. It can be prescribed by clinicians in medical offices. It requires daily dosing, and typical doses range between 8 and 24 mg, with a recommended target dose of 16 mg[191]. An extended-release formulation that requires a single monthly injection was approved by the FDA in 2017 [192], and a once-a-week formulation is available in some European countries.

In patients with opioid use disorder accustomed to high doses of heroin or fentanyl or who have been maintained on high doses of methadone, buprenorphine can precipitate acute withdrawal, as it is a partial mu opioid receptor agonist[191]. Treatment of such patients might be initiated with methadone and, after a slow taper of the dose, continued with buprenorphine. Buprenorphine is less likely than methadone to depress respiration, but it can still be lethal, particularly if it is combined with other central nervous system depressants.

Naltrexone is a mu opioid and kappa opioid receptor antagonist. The effectiveness of its immediate-release formulation as a treatment for opioid use disorder has been limited by poor adherence[193], but its extended-release (3-4 weeks) formulation, XR-NTX, significantly improves treatment retention[194]. Patients with opioid use disorder must undergo supervised medical withdrawal before being inducted on naltrexone, as its mu opioid receptor antagonist properties can precipitate acute withdrawal otherwise. Although this is a barrier for some patients, current recommendations are for patients to be abstinent for one week prior to XR-NTX induction. Some protocols for faster supervised medical withdrawal (formerly known as detoxification) have been developed, but further research is needed before they can be adopted in routine clinical practice.

Another consideration when selecting a medication for opioid use disorder is whether there are any co-occurring disorders. For example, naltrexone is also effective in treating alcohol use disorder[129], whereas buprenorphine's kappa opioid receptor antagonist properties may offer benefits for individuals with comorbid depression. Methadone or buprenorphine are recommended for pregnant women, as there are insufficient data on naltrexone's safety in this population. For patients with a history of cardiac arrhythmias, methadone might be contraindicated, due to its QT-prolongation effects, which do not occur with buprenorphine or naltrexone.

Medications for alcohol use disorder

There are three medications approved by the FDA for alcohol use disorder: disulfiram, acamprosate, and naltrexone (oral and extended-release). One additional medication, nalmefene, is approved by the European Medicines Agency (EMA).

Disulfiram is an inhibitor of aldehyde dehydrogenase, which metabolizes the alcohol metabolite acetaldehyde, thereby increasing its concentration in plasma. Acetaldehyde accumulation triggers nausea, vomiting, sweating, flushing and palpitations, so that individuals treated with disulfiram stop drinking to avoid the aversive response[195]. Disulfiram reduced alcohol consumption in open-label but not in blinded RCTs, suggesting that awareness of potential negative effects improved the placebo outcomes. The efficacy of the medication is limited by poor adherence, and supervised treatment results in better success rates than non-supervised one[196]. Also, the disulfiram-ethanol interaction can be very severe; consequently, disulfiram is only recommended for the maintenance of abstinence but not as a therapy to reduce drinking[197].

Acamprosate's mechanism of action in reducing alcohol use is not fully understood. This medication is believed to modulate NMDA and GABA receptors, helping to correct the imbalance between neuronal excitation and inhibition that occurs during acute alcohol withdrawal and with protracted abstinence[198]. While RCTs of acamprosate treatment in alcohol use disorder have not always shown benefits[197], a Cochrane meta-analysis of 24 RCTs found positive effects in reducing drinking and increasing abstinence duration[199]. Acamprosate is approved by the FDA for abstinence maintenance in alcohol use disorder, and its combination with psychosocial support is associated with better outcomes[200].

Naltrexone is an antagonist of mu and kappa opioid receptors, as well as of delta opioid receptors, although with lower affinity[201]. Its blockade of mu receptors in the mesolimbic circuit is believed to reduce the rewarding effects of alcohol, decreasing its consumption[202]. Its antagonist effects at kappa receptors might be beneficial for attenuating the negative emotional state associated with alcohol withdrawal[203]. Naltrexone significantly decreases drinking days and relapse rates in patients with alcohol use disorder[204], and has been shown to reduce alcohol's rewarding effects[205,206] and number of drinks per drinking day[207]. However, its effects are modest[208], and a meta-analysis of 53 RCTs reported significant but only modest reductions in relapse to drinking[209]. Naltrexone is available as an oral and a once-a-month injectable formulation, which show similar therapeutic profiles[210]. It carries a low risk for hepatoxicity and is contraindicated for patients with acute hepatitis or liver failure.

Nalmefene, like naltrexone, is an antagonist of mu receptors that also acts as a partial agonist of kappa receptors[211]. It is approved by the EMA for the reduction of alcohol consumption in alcohol use disorder on an as-needed basis[212]. When used as needed, nalmefene decreases alcohol consumption and heavy-drinking days compared to placebo[213]. This medication might be useful in patients interested in reducing alcohol consumption but reluctant to engage in abstinence[212].

Neuromodulation

Neuronal circuits that are disrupted in addiction are potential targets for neuromodulation. Specifically, strengthening of fronto-cortical circuitry might help prevent relapse by enhancing self-control, while inhibition of the insula (mediating interoceptive awareness) might decrease craving and discomfort, thereby

facilitating remission.

Non-invasive techniques include transcranial magnetic stimulation, transcranial direct current stimulation, and low-intensity focused ultrasound[214] targeting the dorsolateral prefrontal cortex and the insula[73]. Neuromodulation of peripheral nerves via percutaneous nerve field stimulation or trigeminal nerve stimulation offers additional promising interventions in SUDs.

Invasive techniques, such as deep brain stimulation, require a surgical procedure to implant the electrodes, and are currently being studied for the treatment of severe SUDs. Case reports and small case studies targeting the nucleus accumbens for the treatment of alcohol use disorder and opioid use disorder have shown promising results[215], but much more research is needed.

At present, the only FDA-approved SUD-related indications for neuromodulation are transcranial magnetic stimulation for smoking cessation[216], and percutaneous nerve field stimulation for treatment of opioid withdrawal[215].

Behavioral interventions

Multiple behavioral therapies have been shown to be beneficial in the treatment of SUDs, by themselves or as adjuncts to pharmacotherapy. The most frequently used interventions are motivational interviewing, cognitive behavioral therapy (CBT), contingency management, and twelve-step facilitation (see Table 5).

Motivational interviewing

About 40% of people with a SUD report not being ready to stop using, highlighting the role of motivation in the treatment process[217]. Motivational interviewing has the best empirical support among approaches that convey empathy and minimize confrontation[218]. It is defined as "a collaborative conversation style for strengthening a person's own motivation and commitment to change"[219]. It helps individuals resolve ambivalence about change[220-222]. It is superior to no treatment in decreasing substance use in the short term, but its long-term effects appear less robust[221]. Another limitation is that achieving true competence in the use of the technique requires considerable training[223-225].

Cognitive behavioral therapy (CBT)

CBT is among the best-studied behavioral interventions for SUDs[226,227]. It is based on the assumption that substance use and related behaviors are learned, having been strongly associated with the rewarding properties of the substances and related cues via the reinforcement processes described earlier. CBT seeks to disrupt these learned associations by promoting awareness of behavioral patterns and teaching the patient a series of coping skills to reduce the probability of substance use, address its consequences, and intervene quickly in the case of relapse[228]. CBT helps patients to become aware of and interrupt the thought-emotion-behavior chain and to produce more adaptive coping responses[229].

The efficacy of CBT has been documented by RCTs in several SUDs[230-234]. A meta-analysis found that it had moderate significant effects when compared to minimal treatment. CBT significantly reduced consumption frequency and quantity at early, but not late, follow-up when contrasted with a non-specific therapy or treatment as usual. However, when contrasted with any specific therapy, CBT's effects were consistently non-significant across outcomes and follow-up time points[235].

Contingency management

Contingency management is based on the hypothesis that, since disordered drug use is maintained by the reward of drug intoxication and the negative reinforcement from withdrawal, emphasizing the positive outcomes associated with reduced use or abstinence may alter this balance. Because many of the positive consequences of abstinence manifest only after long periods of no use, this technique seeks to provide positive reinforcers for drug abstinence that are more immediate and predictable, such as monetary-based ones (including vouchers or goods)[236,237].

Contingency management has been successfully used to treat various SUDs[237]. It is also efficacious in reinforcing non-drug-related behavior, such as adherence to medications for human immunodeficiency virus (HIV) infection and maintaining low HIV viral load[238]. It can be used at different points of the treatment sequence, including initial engagement[167], attendance[237,239], and abstinence[237,239,240].

To effectively reinforce the target behaviors, incentives have

Table 5 Most common behavioral interventions for substance use disorders, their hypothesized mechanisms of action, and target neurocircuitry

Behavioral intervention	Mechanisms of action	Potential target network
Motivational interviewing	Strengthening motivation and commitment to change	Motivation network
Cognitive-behavioral therapy	Understand and disrupt learned associations	Executive control network
	Improve impulse control	
Contingency management	Reinforce positive consequences of drug abstinence	Reward network
Twelve-step facilitation	Peer support, role modeling and mentoring	Salience network
	Development of coping skills	

to be sufficiently large and delivered reliably and promptly[241]. Longer-duration interventions (e.g., six months or longer) are associated with better outcomes[242] Abrupt discontinuation of the intervention has been associated with relapse; gradual withdrawal schedules with lower-value reinforcers decrease this risk [229,240].

Twelve-step facilitation

Twelve-step mutual aid groups, such as Alcoholics Anonymous and Narcotics Anonymous, can help promote abstinence on their own or as part of a more comprehensive plan[243,244]. Mechanisms underpinning the efficacy of these programs[245] include peer support, role modeling of successful recovery, and sponsors' mentoring and oversight. The sense of belonging to a community of peers appears to help diminish shame, loneliness and guilt, while exposure to successes of others can inspire and instill hope. These programs also facilitate adaptive changes in social networks, increasing self-efficacy and reducing impulsivity and craving.

A recent meta-analysis[245] concluded that, for alcohol use disorder, there was high-quality evidence that manualized twelve-step interventions are as effective or even more effective than other treatments such as CBT for increasing abstinence. However, the evidence of superiority of these interventions for other SUDs is weaker[245].

Brief interventions

Brief interventions are for individuals whose substance use causes mild to moderate interference, but who do not meet criteria for a moderate or severe SUD (pre-addiction). The evidence for their efficacy is strongest for excessive alcohol use[246]. The US Preventive Services Task Force considers the evidence insufficient for other substances[247]. These interventions are generally intended for settings in which the main purpose of the visit is not substance use, such as visits to primary care or the emergency department[248].

Most brief interventions consist of feedback, advice, and goal setting to help the patient abstain from or reduce substance use or the risk of use[249]. They are generally delivered as one to four sessions that can last from 5 to 45 min[218].

Digital interventions

Digital technologies can increase access to evidence-based treatment. The digital divide remains a barrier for many underserved communities. However, for those with access to smartphones or the Internet, digital delivery can help overcome geographical and temporal barriers and can increase engagement as well as privacy[250]. It can also improve fidelity in the delivery of behavioral interventions. The results can be automatically incorporated into electronic health records, empowering individuals to be more actively involved in their own care.

Digital interventions for SUDs have demonstrated efficacy for screening and assessment[251-253], treatment[254,255] and recovery [250,256], as stand-alone tools or as adjuncts to clinician-delivered interventions. They can be equally or even more effective than clinician-delivered interventions[253]. A meta-analysis of digital interventions for cannabis use disorder found that cannabis use was significantly reduced following both prevention and treatment interventions as compared with controls. However, while the effects of prevention interventions remained significant at follow-ups of up to 12 months, effects of treatment interventions did not [257].

Perhaps the best-studied digital treatment intervention to date is the computer-based training for cognitive behavioral therapy (CBT4CBT), a six-session self-guided web-based CBT intervention for SUD[254]. CBT4CBT helps users to identify patterns of substance use and develop coping skills using video and other multimedia content. Examples of digital relapse prevention and recovery support interventions following intensive treatment include the Addiction Comprehensive Health Enhancement Support System (A-CHESS)[258] for alcohol use disorder, and the Educating and Supporting Inquisitive Youth in Recovery (ESQYIR)[259] for young people with substance abuse.

Advances in mobile and wearable sensing technologies and complex machine-learning strategies are creating new opportunities for passive identification of substance use behaviors and associated risks, potentially allowing for interventions to be delivered at moments when the patient is at high risk of return to use[260]. Future development of regulatory frameworks to evaluate the safety and efficacy of these technologies is needed.

Harm reduction

Harm-reduction interventions seek to minimize the adverse consequences of continued substance use. They include a diverse set of strategies, such as syringe services programs, access to naloxone, overdose prevention centers, and drug checking.

The distribution of sterile injecting equipment through syringe services programs is an effective intervention for preventing HIV and hepatitis C virus (HCV) infections[261]. These programs can also serve as sites for low-barrier treatment of substance abuse[262].

Naloxone, when given promptly and at adequate doses, is very effective in reversing opioid overdoses, including those from fentanyl. Wide distribution and access to naloxone in the community is one of the most effective interventions to prevent overdose deaths[263].

Overdose prevention centers provide a safe space for individuals to inject drugs under supervision. Some sites only provide supervised consumption, whereas others offer integrated services that include treatment for SUD, medical referrals, and housing, among others[264]. Mobile units ensure a more flexible deployment of services, but are limited in their capacity. Research on overdose prevention centers, while limited, has shown that they are effective in preventing overdose deaths in those who use them[264]. They also

facilitate SUD treatment engagement, and help prevent HIV and HCV infections[265].

In the US, fentanyl is the most common adulterant in heroin, counterfeit prescription pills, and stimulant drugs, and is responsible for more than half of all overdose deaths[266]. Drug checking, including through use of fentanyl test strips, allows people to test whether a drug they are planning to consume contains fentanyl or some of the common fentanyl analogues[266].

Organization of treatment services

The organization of services for delivering SUD treatments varies by countries and, within countries, by organizations responsible for SUD care. It further depends on funds, clinical infrastructure, and severity of cases treated.

The United Nations Office on Drugs and Crime (UNDOC)-WHO International Standards for the Treatment of Drug Use Disorders have set principles for the treatment system. Specifically, they recommend that treatment services should be accessible, affordable, evidence-based, diversified, and focus on improved functioning and well-being. Provision of services should be person-centered, equitable, and data-driven.

Consistent with the Chronic Care Model and with evidence that severity of disorders varies across the population and within the individual over time, it is necessary to organize service provision across a continuum of intervention intensity[151]. One way to think about this is by imaging a pyramid in which, at any given time, the lower levels require the most interventions, whereas more intensive ones (e.g., inpatient treatment) are only needed for a very low proportion of cases. Treatment systems designed with this in mind tend to be more cost-effective, because they better match need with resource utilization intensity.

Implicit in this type of model is the integration of substance use services with services for other mental disorders as well as primary care. This approach is cost-effective and person-centered and facilitates integrated care of co-occurring mental and general medical disorders in individuals with SUDs. At lower levels of need, individuals can receive informal community care through support of friends and family or self-help groups. At the next level, primary care health services can provide screening and brief interventions, referral to a specialist (when needed), and follow-up of individuals who may no longer need higher-intensity interventions. Greater need levels can benefit from outpatient or inpatient specialized treatment services. At all levels, social determinants of health and social needs should be addressed. These service models can be structured as one-stop shops, community-based networks of treatment providers, or a combination of both[151,267].

There are several models of care that have been proposed for expanding the delivery of SUD treatment in health care settings[268]. An example is the hub-and-spoke model, which has been used effectively to expand access to treatment of opioid use disorder. Services are organized around a main hub that has the expertise with use of medications for opioid use disorder; the hub is associated with treatment settings (spokes) that provide ongoing care and maintenance treatment[269].

Despite the conceptual appeal of these models, the evidence of their efficacy is still limited[270]. Furthermore, their implementation can be complicated, due to stigma and discrimination against individuals with SUDs, suboptimal allocation of resources in the treatment system, scarcity of trained personnel at different levels of the treatment services pyramid, and lack of financing or payment mechanisms for some of the interventions[271,272]. For example, if primary care physicians are insufficiently reimbursed to provide interventions for SUDs, they are unlikely to offer them to most patients that might need them.

PREVENTION

Substance use and SUDs are multidetermined, with the different risk factors playing varying roles at different life stages, from the prenatal period and childhood to early and late adulthood[78,79,164]. The goal of SUD prevention is avoiding the use of psychoactive substances, in order to foster healthy development and ensure that young people are best able to realize their potential and engage positively with their families, schools and communities[273].

Most prevention efforts have been targeted at childhood and adolescence[274], because these are periods characterized by major behavioral changes and, for adolescence, increased exposure to psychoactive substances and peer pressure[275,276]. However, risks are also present during other life stages, and there is a need to develop preventive interventions for additional age groups[146].

Preventive interventions work by mitigating risk factors (e.g., deviant behavior, drug-using peers, social neglect) and enhancing protective factors (e.g., parental support, education), and they can be implemented in family, school or health care contexts, as well as other community settings (see Table 6). Based on the risk level of the target population, they are classified as universal, selective or indicated.

Universal interventions target an entire population (e.g., an age range or a community); for example, all students in a school may be trained to improve impulse control and self-regulation. Selective preventive interventions target sub-populations at increased risk of SUDs, such as those with high-risk personality traits or living in low-resource communities. Indicated prevention, also known as early intervention, targets individuals with early signs or symptoms of substance use problems but who do not yet meet full criteria for a SUD.

The most common prevention strategy is universal school-based drug education[277,278]. The most effective programs adopt a comprehensive social-influence approach with four components: provision of information, education about the prevalence of substance use among peers, refusal skills training, and social competence or life skills. The effects of universal school-based prevention programs are generally modest[279]. Furthermore, resource limitations often preclude sustainable implementation[280].

There is also some evidence that visits in the prenatal period or during infancy to provide mothers with parenting skills[281], or offering education services to children growing up in disadvan-

Table 6 Prevention strategies for substance use disorders

Modifiable risk factor	Interventions
Impulsivity	Self-regulation training
Poor social skills	Social skills training
Exposure to stress	Stress resilience training
Insufficient parental supervision	Parenting skills training
Low self-confidence	Educational interventions; tutoring
Early substance use	Early prevention interventions
High drug availability	Supply reduction policies; community policing
Misperceptions of drug use norms	Norms training
Peer substance use	Refusal skills training
Permissive drug culture	Community-level interventions
Poverty	Jobs training; community-building interventions

taged communities[282], can help prevent substance use later in life, but additional studies are needed before these interventions can be considered evidence-based.

Communities That Care (CTC) is probably the best-known community-based approach to adolescent substance use prevention. It seeks to prevent multiple youth problem behaviors including violence, risky sexual behavior, and school dropout, in addition to substance use. CTC trains local community members on how to select which evidence-based activities to implement, based on the unique needs of the community[283]. Communities that receive CTC tend to experience reductions in risk factors for substance use and delayed initiation of delinquent behavior.

One example of a selective school-based preventive intervention is Preventure[284]. This is designed for high-risk youth with personality traits that are associated with substance use and psychopathology: hopelessness, high anxiety, high impulsivity, and sensation seeking. Preventure uses approaches based on CBT and motivational interviewing to teach young people personality-specific coping skills aimed to prevent substance use.

Parent- or family-based preventive interventions target risk factors concerning family relationships as well as peer and other social influences. They include programs focused on provision of skills to parents (e.g., communication, rule setting, monitoring), strategies for improving family dynamics, and combined student-parent interventions[285]. Parent-based interventions (i.e., focused solely on parents) and combined student- and parent-based prevention programs have been shown to produce beneficial effects on adolescent substance use outcomes[286]. Studies of primary outcomes have found that family-based programs can prevent alcohol, tobacco and drug use in young people, with effects persisting longer than 12 months. Intensive programs delivered by a trained facilitator are more consistently effective than single-session or computer-based interventions. Effective gender-specific interventions targeting mothers and daughters also exist[273].

The evidence base for substance use prevention delivered outside of school settings is limited. Yet, individuals may start using or misusing substances, such as opioids, after their school years[287]. There is still a need for research to develop and test preventive interventions for people who are at increased risk of developing SUDs, especially young adults[288]. There is also a need to study the efficacy of after-school activities (e.g., sports) and interventions targeting youth at increased risk[273]. Greater knowledge of the influence of media in the psychosocial development of young people and their risk for substance use is also needed.

Prevention interventions can also be delivered via digital media, such as videogames developed primarily for educational purposes[289]. Digital interventions have the advantage of not requiring onsite trained prevention specialists. This flexibility allows them to overcome some of the barriers to the delivery of traditional school-based programs, which require trained teachers. The portability of digital interventions also allow for their delivery in other settings, such as the home or community. Mobile health interventions, such as smartphone applications and text messaging, are commonly used to target a wide range of health behaviors in adults and represent a rapidly growing area among youth[290]. The limited existing evidence suggests that digital interventions are well accepted in this latter age group, but more systematic knowledge is needed to assess safety and efficacy[291]. There is also a need to develop quality measures for these interventions and to develop payment and reimbursement models to ensure their financial viability and stability.

In addition to existing research gaps, a common barrier is the lack of dedicated funds for preventive interventions outside research settings. Without ongoing funding, prevention interventions are difficult to implement and evaluate, leading to downstream pressure on the treatment system.

SPECIAL POPULATIONS

Opioid use disorder and pain

Chronic pain is significantly more prevalent among people with SUDs than in the general population, and this is a factor that can contribute to drug-taking[292,293]. Managing patients with co-occurring chronic pain and SUD – particularly opioid use disorder – presents unique challenges[294,295], including sometimes lack of trust between patients and clinicians regarding symptoms of pain and patterns of opioid use. Patients may fear that clinicians are unwilling to continue prescribing opioids or are going to reduce the amount prescribed. Clinicians may be concerned that patients deny or minimize aberrant patterns of opioid use or other symptoms of opioid use disorder, or that they may obtain medication through doctor shopping or from the illicit market. Moreover, it may be difficult to establish whether functional impairment or use of opioids in amounts larger than prescribed are the result of undertreated pain or represent symptoms of opioid use disorder[171,294].

Physical dependence, a neurobiological adaptation that occurs in any individual taking opioids, must be distinguished from opioid use disorder, which is a psychiatric condition with specific symptoms and diagnostic criteria[296]. Inappropriate treatment of

pain can lead to hyperalgesia, but untreated pain is a risk factor for opioid use disorder and for relapse. Since most addiction clinicians receive little training in pain management, and most pain experts receive limited training about SUDs[297], a team approach helps ensure that patients receive appropriate pain treatment while minimizing risk of opioid use disorder.

A first step in preventing opioid use disorder is limiting the use of opioids in patients not already receiving them, unless there are no alternatives for pain management[298]. However, it is important to recognize that non-opioid analgesics often yield small to moderate short-term effects on chronic pain[299], while non-pharmacological treatments for chronic pain are time-consuming and costly. Cannabinoids can provide some relief of neuropathic and cancer-related pain, but their effects are small and tend to diminish over time, and they can have significant side effects[300].

If opioids are needed to manage pain, clinicians should conduct a risk assessment that includes a comprehensive clinical history[301,302]. Modifiable risk factors, such as co-occurring disorders, should be addressed. Patients should be periodically re-evaluated to assess potential changes in their opioid treatment regimen. Clinicians should also be aware of unintended consequences of tapering opioids – including acute opioid withdrawal, uncontrolled pain, and even suicide – and balance the risks and benefits of continued opioid use[303]. If tapering is not appropriate, an alternative is to use opioids that treat both chronic pain and opioid use disorder, such as buprenorphine and methadone.

Managing acute pain in patients who are taking medications for opioid use disorder is another common clinical problem. Good communication and coordination of care are necessary to decrease the risk for undertreatment of pain. Patients on methadone should continue taking their verified daily dose, and short-acting opioids can be added for relief of acute pain[304]. Some patients may need higher dosing of opioids (up to 1.5 times higher than usual), due to increased pain sensitivity and opioid cross-tolerance, and they may require pain medications at shorter intervals.

There is no consensus yet on how to manage acute pain in patients on buprenorphine. Some proposed options include: a) adding short-acting opioids while continuing buprenorphine; b) dividing buprenorphine dosages and administering a dose every 6-8 hours, or using supplemental buprenorphine if necessary to relieve pain; c) discontinuing buprenorphine and using full-agonist opioids, then resuming buprenorphine after full-agonist opioid analgesia is no longer needed; and d) converting buprenorphine to methadone at 30-40 mg/day to prevent withdrawal and adding short-acting opioids, then resuming buprenorphine prior to discharge[304].

HIV and HCV infections

Substance use and SUDs increase the risk of HIV and HCV infections, accounting for approximately 10% of the former[305] and 38-79% of the latter[306] globally. Injection of drugs also increases risk of bacterial endocarditis, cellulitis, and abscesses and embolisms of the heart, brain and spleen, among other infections[307]. Sharing of needles and other paraphernalia increases risk. Additionally, intoxication with drugs or alcohol increases high-risk behaviors, such as engaging in unprotected sex and failing to follow preventive practices[308]. Substance use and SUDs can also negatively affect adherence to medications for HIV and HCV infections[309].

Several strategies can be used to decrease risk of HIV infection among individuals with SUDs[310], including pre-exposure prophylaxis and syringe services programs for injection drug users.

Pre-exposure prophylaxis refers to the practice of taking tenofovir (a nucleotide reverse transcriptase inhibitor) daily to decrease the risk of HIV infection. Although it can reduce risk by close to 80%, this prophylaxis has had limited uptake, probably due to its cost, the need for housing stability and access to a regular prescriber, and the difficulty of adhering to a daily medication regimen[311].

Syringe services programs reduce HIV transmission by 34-58% [312]. As already noted, it is not only distribution of sterile injecting equipment that confers positive effects to these programs. They are also sites for overdose education and naloxone distribution, linkage to SUD treatment, and HIV testing[313].

Despite these strategies, the treatment of SUDs among individuals with HIV remains challenging. Integrated care strategies in which SUD treatment, HIV care and prevention, and primary care are offered in the same clinic are recognized as best practices, but have not been widely adopted[151]. Implementation research is needed to develop, test and scale up evidence-based interventions and determine optimal approaches for each population and setting.

Adolescents

Substance use in adolescence is common. Monitoring the Future, a yearly national survey of middle- and high-school students in the US, estimates that by the time adolescents finish high school, close to 60% have used alcohol and 50% have tried an illicit drug[314]. The emergence of vaping is an important and evolving new development. Vaping devices can deliver nicotine, cannabinoids or other products, and are often supplied with flavors and packaging that are appealing to youth.

Although most adolescents who use a substance do not develop a SUD, any level of use during this period is concerning, due to youth's increased vulnerability to SUDs and the potential for long-lasting brain changes. Furthermore, research suggests that many adolescent SUDs persist into adulthood, even until midlife[315].

Efficacious interventions for adolescents with substance misuse or SUD include family-based treatments, motivational interviewing, and CBT. Screening for substance use in routine clinical visits is recommended by some professional organizations[316,317], although the US Preventive Services Task Force considers that there is currently insufficient evidence to support its efficacy[318].

There is also a paucity of evidence on pharmacotherapies for SUDs among adolescents. In the US, buprenorphine-naloxone is approved by the FDA for treating opioid use disorder in individuals 16 years of age and older. To date, no other pharmacotherapies have been approved for adolescents with SUDs, although positive

findings in RCTs have been obtained for some medications, including sustained-release bupropion and the nicotine patch for smoking cessation[319], N-acetylcysteine for cocaine use disorder[320,321], and naltrexone for alcohol use disorder[322]. In general, pharmacotherapies should be reserved for adolescents with moderate or severe SUDs who have not responded to psychosocial treatments.

Older adults

Older adults are more likely than younger people to underreport their substance use[323]. Furthermore, recognizing SUDs in elderly patients can be challenging, because clinical indicators (e.g., unsteady gait, cognitive impairment, insomnia) may reflect other common physical or psychiatric problems in this population.

Most primary care physicians do not routinely screen older adults for SUDs, even in the presence of well-known risk factors such as anxiety or depressive symptoms, increased social isolation, and poor physical health[324]. Furthermore, even among individuals with known substance use, including use of tobacco or alcohol, clinicians often fail to discuss treatment options, because they often assume that older individuals will have low motivation to change.

Although diseases resulting from tobacco use remain the leading causes of premature death in older adults, alcohol and psychoactive prescription drugs, especially opioids and benzodiazepines, are substances often used in this age group that are associated with adverse consequences[325-327]. For example, older individuals taking opioids may experience constipation, fatigue, pruritus, anorexia, somnolence, mental status changes, and nausea. Sleep apnea is also a serious risk in older adults, especially in those who have respiratory difficulties or take other medications, such as benzodiazepines, with respiratory-depressant properties.

When medically supervised withdrawal is needed, it has to be tailored for older individuals, who may have had more prolonged exposure (i.e., decades of use) and may have greater difficulty ceasing use. Slower, longer tapers (e.g., over several months) should be considered to minimize rebound symptoms, withdrawal and relapse.

Women

Although SUDs remain more prevalent in men than in women, the gender gap has been narrowing[150,328-330], possibly in part due to changes in gender roles[331]. While women have traditionally initiated substance use at a later age, this difference too may be disappearing. This is particularly concerning because, for many (although not all) substances, women progress more rapidly from use to SUD[332,333]. Patterns of comorbidity also vary between men and women: men are more likely to have multiple SUDs, while women tend to have greater rates of mood, anxiety and eating disorders in addition to a SUD[330,333].

Biological factors often make the effects of substances on women more deleterious than on men. For example, women have lower concentrations of gastric alcohol dehydrogenase, the primary enzyme for alcohol metabolism, and a lower total percentage of body water, leading to higher blood alcohol levels and greater levels of intoxication after consuming equivalent amounts of alcohol as men[334]. Similarly, women who smoke have a greater risk than men of tobacco-related heart disease, lung disease, and other health problems[335].

There are also sex differences in how likely people are to seek treatment. Men are more likely than women to seek treatment for alcohol use disorder, but less likely to seek treatment for drug use disorders, even after adjusting for sociodemographic characteristics and co-occurring disorders[336]. By contrast, there is no evidence of sex differences in treatment outcomes[337]. Some studies have reported that female patients metabolize medications at lower rates, suggesting the need to consider these differences to minimize side effects[338].

Relatively little is known about treatment of pregnant women with SUDs using medications, probably in part due to the deterrent effect of the legal consequences of perinatal substance use in some countries, as well as to regulations for the participation of pregnant women in clinical trials. The standard of care for opioid use disorder in this population includes pharmacotherapy with either methadone or buprenorphine, as part of a comprehensive treatment program that provides perinatal care and behavioral interventions. Medically supervised withdrawal or use of naltrexone are not recommended during pregnancy[339].

Evidence about smoking-cessation treatment in pregnant women is also very limited. There are no published studies on the efficacy of varenicline or electronic nicotine delivery systems. Studies of nicotine replacement treatments have not shown them to be more effective than placebo[340]. Only one small study has evaluated bupropion. We are not aware of any controlled trials of medications for alcohol use disorder in pregnant women.

Sexual and gender minorities

Individuals from sexual and gender minorities often experience discrimination and face multiple health challenges, including higher rates of substance use than other people. These higher rates are due to a combination of marketing directed at this population (e.g., tobacco); the reinforcement from increased energy, sexual drive and self-esteem experienced during intoxication with stimulants and club drugs; and the temporary relief from stress due to stigma and discrimination. Furthermore, drug use increases risk of unprotected sex and HIV infection[308].

Clinicians can help these individuals by recognizing their unique risk factors and health needs, including their fear of discrimination leading them to delay care[341]. The fundamentals of psychopharmacological and psychosocial SUD treatments are the same for patients from sexual and gender minorities as for other patients. Nevertheless, consultation with or supervision by colleagues with greater experience in treating these individuals may help clinicians whose knowledge of this population is limited.

Justice-involved populations

Individuals with SUDs are more likely than other people to come into contact with the justice system[342]. Well over half of people in state prisons and jails in the US have a SUD, and drug use – including injection drug use – is very prevalent in prisons. One in every three prisoners worldwide is estimated to have used an illicit substance during incarceration. Use of contaminated needles and syringes by prisoners increases the risk of HIV infection.

In justice-involved populations, evidence-based SUD treatment is effective in reducing substance use as well as re-offending and re-incarceration, and in facilitating recovery[343-346]. These approaches lead to better outcomes than those based on criminalization and punishment of substance use, and they are cost-effective[347,348]. Thus, it is important to intervene at every possible step in the cycle of drug use and involvement with the justice system.

Although many activities related to substance use remain illegal in most countries, failures of approaches based on criminalization of SUDs have led to a growing interest in linkage of individuals with these disorders to treatment instead of punishment[349], and a movement toward dismantling policies that perpetuate criminalization. Factors that have influenced a move away from criminalization of substance use behavior include the lack of increases in substance use in jurisdictions in which this use has been decriminalized, the increased recognition of substance use as a medical problem, and the risk of violation of human rights espoused by the United Nations[350]. Nevertheless, barriers to decriminalization remain[351]. For example, the idea that drug use is a deviant behavior engaged in by undesirable elements in society and, more broadly, stigmatization and discrimination against individuals who use substances, create resistance against policies that promote decriminalization.

A wide range of alternative measures, applicable at various points along the continuum from pre-trial through trial and post-trial phases, exist. For example, individuals can be diverted from the justice system at pre-arrest and linked to clinical and social services, including harm reduction or case management. Individuals can also be referred to the treatment system through drug courts[352].

Drugs courts are based on the recognition that charges and traditional punishments for drug possession seldom change addictive behaviors and often lead to relapse after release and new arrests. Drug courts emphasize rehabilitation, with the judge being considered part of the treatment team[353]. Having contact with the judge and random drug testing appear to be two of the most effective interventions of drug courts, while continued supervision after drug-court participation may be the most effective measure to prolong abstinence and prevent criminal activity.

The optimal approach for justice-involved individuals with SUDs should depend on the severity of their disorder and any comorbidities. According to the United Nations Standard Minimum Rules for Non-Custodial Measures[354], imprisonment should always be the last resort. The special circumstances of justice-involved women should also be considered[355].

Individuals in contact with the justice system should be systematically screened and assessed, following the procedures described above, to facilitate entry into the treatment system at the appropriate level. Linkage to services could occur during contacts with law-enforcement officers, first detention or court hearings, jails, courts, criminal justice system re-entry, and community correctional programs including probation and parole.

As a general rule, the care provided to individuals in the justice system should meet the same standards as health services in the community, based on the principle of equity. Thus, diagnostic assessment should include all the individual's medical, mental health, or social problems, as well as any factors affecting the individual's risk for reoffending or recidivism. However, resource constraints, societal attitudes, or other factors can interfere with this approach.

The vast majority of incarcerated persons eventually return to the community. However, most prisoners with SUDs do not receive treatment during their incarceration and, when released from correctional settings, they face numerous challenges in connecting with community-based treatment, social services, housing, and other essential supports[356]. This makes community re-entry a high-risk period for substance use relapse and also for overdosing. Consequently, improved connections between the justice and health care systems are essential for providing effective SUD screening, treatment, and discharge planning, including referral to services, for this population.

CONCLUSIONS

SUDs are recognized as chronic disorders that have different presentations and outcomes and frequently co-occur with other psychiatric and physical disorders. Prevention interventions, particularly if deployed in childhood and adolescence, decrease the risk for SUDs and can also reduce risk for other mental illness. Treatment interventions should be tailored to the severity of the SUD and the presence of comorbid conditions, and they should be delivered within the context of a Chronic Care Model, with the intensity of intervention adjusted on the basis of time in treatment and relapse history. Changes in policies from punitive approaches, such as incarceration, to therapeutic ones are not only cost-effective but also lead to better outcomes as it relates to drug-taking and mortality.

In the meantime, research is needed to generate knowledge with which to develop more effective prevention and therapeutic interventions that are personalized to the characteristics of the individual but also sustainable. This broad perspective can be conceptualized into five distinct domains:

a) *Basic research on the interactions between genetics, adverse childhood exposures and other social experiences (including social determinants of health), and brain development*. Large comprehensive longitudinal data sets, such as the Adolescent Brain Cognitive Development (ABCD) study[357] and the recently launched HEALthy Brain and Child Development (HBCD) study[358], are starting to generate the data needed to build such

knowledge. Similarly, analyses of large genetic databases linked with epigenetic information could help uncover the mechanisms underlying risk and resilience to drug use and SUDs. Research that identifies new molecular or circuit-based targets for treatment is also needed, as is research that links epidemiological findings to their underlying neurobiological substrates.

b) *Epidemiological research, including wastewater epidemiology, coupled to electronic health records and medical surveillance systems*. Such research could help provide more timely metrics of the nature and type of drug problems, which is essential to better tailor interventions, allocate resources, and monitor outcomes. Epidemiological research can also help generate hypotheses about the causes of SUDs and identify targets for prevention and treatment. It can provide information to test or simulate the effects of policies and to estimate the effects of interventions when they cannot be tested using randomized designs.

c) *Therapeutic development*. Translational research to expand the medications available to help treat SUDs, as well as research on various central and peripheral neuromodulation interventions (including studies to determine which brain areas to stimulate, optimal frequency and duration of stimulation, and the value of these interventions as adjuncts to improving retention in treatment when combined with medications), is another opportunity area. Importantly, research on alternative outcomes for medications for SUDs other than abstinence – such as improvements in sleep, depression, anxiety and craving – will expand the pipeline of treatments that can benefit patients even when they do not result in abstinence. The expansion of telehealth and other digital technologies (as well as hybrid models) needs to be accompanied by a better understanding of how to optimize their use and for whom. Similarly, further research on the use of virtual technologies for treatment of SUDs is needed. Finally, development of biomarkers that can help guide treatment selection beyond the information provided by clinical variables would help advance personalized care in SUDs.

d) *Research on implementation, services and economics of substance use treatment and prevention*. This research is needed to help develop optimal evidence-based care models that are effective, equitable and sustainable, and can be adapted to the needs and preferences of various communities.

e) *Policy research*. Understanding the consequences to the community and individuals, including those from marginalized groups, of policies pertaining to drug legalization, decriminalization, treatment reimbursement, and regulation of scheduled drugs will provide guidance on strategies to minimize risk for populations and to prevent stigmatization and discrimination against individuals who use drugs, to ensure equity across groups.

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Violence and schizophrenia: the role of social determinants of health and the need for early intervention

In November 2022, the Mayor of New York City issued a new directive instructing police to transport homeless persons with apparent severe mental disorders, such as schizophrenia, to the psychiatric hospital if they appear unable to meet their basic needs, departing from the previous standard that required someone to be a danger to him/herself or others in order to be hospitalized. This directive represents a major setback to decades of efforts by human rights activists and mental health professionals to limit involuntary treatment for schizophrenia through community-based care, social interventions, and peer-supported decision-making.

Unfortunately, this Mayor's policy aligns with the public misperception of people with schizophrenia as being dangerous or violent, reinforced by rancorous and ill-informed media reporting on rare episodes of gun violence and stabbing by persons with psychosis. This public misperception seems to be further validated by recent scientific publications[2] which suggest an association between schizophrenia and violence. Here we critically appraise the available evidence in this respect and argue that common interpretations of this evidence are deeply flawed.

First, many samples included in these publications[2] are based on obsolete diagnostic criteria and/or diagnoses other than schizophrenia, and the operationalization of violence is often vague (e.g., "broad interpersonal violence perpetration" or "serious trouble with the law").

Second, these analyses[2] fail to fully adjust for confounding risk factors linked with social determinants and correlated with both violent behaviour and schizophrenia. Amongst these shared risk factors are male gender, young adulthood, non-White race, marginalized subgroups or ethnic minorities, and social adversity/poverty[3]. The social determinants associated with schizophrenia trigger "social biases" leading to a greater likelihood of being perceived as violent or threatening, and an escalation of encounters with the police or forensic pathways.

Perhaps the most important examples of such social biases are those which are racially motivated. The 2017 Race Disparity Audit by the UK government (www.gov.uk/government/publications/race-disparity-audit) indicated that non-White individuals are more likely to come into contact with mental health services through the police, and to be referred to forensic pathways. The audit also established that Black men are over ten times more likely to be compulsorily detained in psychiatric hospitals than Whites. In the US, structural racism continues to affect all aspects of society, not least the law and its enforcement and the practice in health care systems, worsening the historic socio-economic disparities associated with violence and trauma experienced by Black people with schizophrenia.

Third, the above research[2] ignores the clinical stages of the disorder. Violent behaviour by people with schizophrenia is relatively infrequent, and most people with schizophrenia are not dangerous[4]. However, a small number may become aggressive, mostly during the acute or first episode stage, when their hallucinations and delusions are not yet detected and adequately treated (i.e., during untreated psychosis)[4]. Comorbidity with substance use and antisocial personality disorder or previous forensic history, themselves major risk factors for violence, are often present in acute psychotic stages, further complicating the association between schizophrenia and violence. Generalizing the occurrence of aggressive behaviour, which predominantly occurs in these acute stages, is a misrepresentation of the lived experience of schizophrenia.

Fourth, it is challenging to disentangle unprovoked violence, such as that resulting from responding to a command hallucination, from reacting antagonistically to a person behaving threateningly. This is not an infrequent occurrence for persons with schizophrenia, particularly those who are homeless. Indeed, the lived experience of people with schizophrenia indicates that such individuals are the victims of violence by others in the community more often than the general population[5], for example, reporting higher rates of childhood trauma (odds ratio: 2.87)[3]. People with a lived experience of schizophrenia also report high victimization rates by mental health professionals and families, including physical violence, verbal violence, restraint, neglect of basic human needs and rights, deception, and lack of informed consent. National registry studies have confirmed that the onset of schizophrenia is associated with an increased risk of being subject to crime, and violent crime in particular[6].

Fifth, the above research[2] ignores that the most common form of violence associated with schizophrenia is not directed at others but at oneself, which is very often the result of social exclusion, harassment and stigmatization. A recent meta-analysis of 135 cohort studies demonstrated a nine-fold increase in suicide risk compared to the general population (risk ratio: 9.76)[7], with most self-harming acts reported during a first acute episode and in younger patients[8].

For all these reasons, there is a high risk of reverse causality and confounding in the observed association between schizophrenia and violence[2], which is not fully accounted for by epidemiological studies. One must interpret such studies in the broader context of the lived experience of people with psychosis, especially for persons who belong to historically marginalized or discriminated groups, such as Black and Indigenous peoples in White-majority countries. Simply reporting epidemiological findings, without controlling for such contextual factors, risks perpetuating the public fear of persons with schizophrenia, stigmatizing people affected by this condition, and exposing them to further discrimination and violence, which may itself trigger aggressive responses.

Future epidemiological studies must not only control for all known social determinants and substance use, but also for the clinical stage of psychosis. Such studies must triangulate data from in-depth case series of persons deemed violent to unpack

the complex cause-effect relationships between schizophrenia and violence. Findings should be critically and cautiously appraised, actively including the views of persons with lived experience of schizophrenia[5] and human rights activists, as in the present paper, to better balance the power between patients and health care providers and to have patients fully included in all policy processes[9].

In conclusion, we argue that research which reports an association between violence and schizophrenia has too often been flawed by methodological limitations, and its findings risk exposing people with schizophrenia to further discrimination, violence, and loss of fundamental freedoms and human rights. Policies that seek to reduce the association of schizophrenia and violence, including self-inflicted harm, must not focus on involuntary hospitalization and coercive treatment of persons with schizophrenia. They should instead prioritize more effective training of police and emergency services to avert these outcomes and address the social determinants associated with schizophrenia, including insufficient access to housing and community-based health care. Importantly, policies should fund and support community-wide preventive and early intervention services, to reduce the duration of untreated psychosis and implement timely evidence-based treatment[5].

These latter policies respect the dignity and agency of persons with psychosis and align with the human rights protections set out in the Convention on the Rights of Persons with Disability and the charters developed by patients and family organizations (www.gamian.eu/patient-charter-schizophrenia).

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Cannabis, cannabinoids and psychosis: a balanced view

The laws legalizing recreational cannabis use, the increasing strength of cannabis and cannabis derivatives, and the growing availability and commercialization of cannabis call attention to the possible implications for mental health, and specifically for the incidence of psychosis.

Several lines of evidence suggest that exposure to cannabis and synthetic cannabinoids may contribute to the risk for psychosis[1]. The spectrum of psychosis outcomes linked to cannabis and cannabinoids range from short-lived psychotic states to chronic psychotic disorders. In addition to observational data, experimental laboratory studies provide compelling evidence that cannabis, its principal psychoactive constituent delta-9-tetrahydrocannabinol, and synthetic cannabinoids induce acute brief psychotic states characterized by positive, negative and cognitive symptoms resembling the symptoms of schizophrenia[2].

Cannabis may induce a psychotic disorder (cannabis-induced psychotic disorder, CIPD) lasting days to weeks, that often requires clinical intervention, resolves with the termination of use, and recurs with re-exposure. In Denmark, the increasing potency of cannabis has been associated with an increased incidence of CIPD[3]. Interestingly, up to 50% of patients diagnosed with CIPD are re-diagnosed years later with schizophrenia or bipolar disorder, suggesting that CIPD may be a harbinger of a chronic psychotic disorder[4]. Furthermore, the rate of "conversion" to schizophrenia seems greatest for CIPD relative to other substance-induced psychoses. However, whether CIPD evolves into schizophrenia, or whether CIPD and schizophrenia are related yet distinct, remains unclear.

Beyond the above brief syndromes, epidemiological studies link cannabis exposure to a higher risk (2- to 4-fold) for schizophrenia. The dose-response relationship is linear, such that more frequent and heavier use, and use of higher potency cannabis, carries a greater risk. Other moderating factors include an earlier age of exposure, childhood trauma, and exposure to other drugs.

Whether the relationship between cannabis and psychosis is causal should be considered separately for the psychosis outcomes in question. The tight temporal relationship between exposure to cannabinoids and the emergence of psychotic states observed in experimental studies provides strong evidence to support a causal relationship. Likewise, with CIPD, the emergence of psychosis with exposure to cannabis, its resolution with abstinence, and its recurrence with resumption, also make a compelling case for causality. In contrast, the evidence linking cannabis and schizophrenia is mostly from epidemiological studies, which are not without limitations. While these studies attempt to adjust for confounders, including other drug use, latent psychosis, pre-existing cannabis exposure, and other psychiatric disorders, any accurate estimate of causality is limited,

and dependent on capturing and measuring all relevant known and unknown confounders.

The relationship between cannabis and schizophrenia fulfills, to varying degrees, a number of the classic Hill criteria of causality, including the strength, consistency, specificity, temporal characteristics, direction, biological gradient, coherence and plausibility of the association and supporting experimental evidence.

Regarding the strength of the evidence, there is a linear dose-response relationship (2- to 9-fold) driven by the frequency, amount of use and potency of cannabis[5]. For perspective, cigarette smokers are 15-30 times more likely to get lung cancer or die from lung cancer than non-smokers, and ~85% of cases of lung cancer are linked to smoking. In terms of specificity, while cannabis use increases the risk of depression, the evidence is strongest for psychosis. Furthermore, while other drugs (e.g., amphetamines) are associated with psychosis, the risk of psychosis seems greatest with cannabis.

The fact that the endocannabinoid system is involved in neurodevelopmental processes supports the biological plausibility for cannabis exposure during adolescence to disrupt neurodevelopmental processes and, in doing so, increase the risk for schizophrenia. However, regarding temporality, the reverse causation hypothesis has been proposed, according to which the risk for schizophrenia confers risk for cannabis use rather than the risk for cannabis conferring risk for schizophrenia. Genome-wide association studies (GWAS) provide evidence for a bidirectional causal relationship between cannabis use and schizophrenia, but suggest a larger contribution of reverse-causal mechanisms and common genetic risk for both schizophrenia and cannabis use (genetic confounding)[6].

The classic criteria for causality have limitations, especially when applied to multifactorial disorders. Schizophrenia, or the "group of schizophrenias" as termed by Bleuler, is likely heterogenous in etiopathogenesis. Perhaps cannabis exposure might be linked to a specific psychosis subtype that is buried within the group of schizophrenias. Furthermore, in line with a multifactorial etiopathogenesis, cannabis is neither necessary nor sufficient to cause schizophrenia. More likely cannabis is partly causal, interacting with other factors such as genetic liability to confer greater risk for schizophrenia.

If cannabis confers a higher risk for developing psychosis, then changes in the cannabis landscape should be accompanied by increased rates of psychosis. Indeed, some studies suggest increasing rates of psychosis linked to cannabis[7]. However, it may be too early for the public health impact of the changes to be fully realized. In this regard, the history of cigarettes and lung cancer may be instructive. While suspected, it took half a century to recognize that cigarettes cause lung cancer. Despite compelling epidemiological data, evidence from animal studies, cellular pathology and chemical analyses was necessary to establish that cigarettes *cause* lung cancer. In contrast, schizophrenia has no signature pathology and is likely heterogenous, and the risk for psychosis with cannabis is lower than that of lung cancer with smoking. Therefore, at the present time it may be unrealistic to expect the same level of evidence and/or certainty that cannabis causes schizophrenia. More likely, evidence may accumulate linking cannabis to a subtype of schizophrenia.

While the spotlight has been on whether cannabis *causes* new cases of psychosis, we risk overlooking the impact of cannabis on those with established psychotic disorders. The high rates of cannabis use by individuals with schizophrenia have been attributed to "self-medication", but there is little evidence to support that hypothesis[8]. In contrast, there is clear evidence of cannabis having a negative impact on the course of schizophrenia, with greater positive symptoms, relapse rates, emergency department visits, hospitalizations, homelessness and legal problems. Schizophrenia ranks amongst the top fifteen leading causes of disability and is financially burdensome. Therefore, additional costs from the consequences of comorbid cannabis use may be substantial.

To conclude, it is tempting to speculate what impact reducing or eliminating cannabis exposure in adolescents might have on the rates of psychosis. For example, the EU-GEI study found that, if high-potency cannabis was no longer available, depending on the region, a substantial proportion (12-50%) of first-episode psychosis cases could be averted[5].

Reducing the rates of psychosis by just 10% is well worthwhile. Towards that end, we need to identify factors that place individuals at greatest risk for developing psychosis in the context of exposure to cannabis. Furthermore, the public needs to be educated about the contribution of cannabis use to the risk of psychosis. Likewise, greater efforts are necessary to educate patients with psychosis about the negative impact of cannabis on illness course, to discourage their use of cannabis, and to develop effective treatments.

In what may be an ominous development, as cigarette sales decline worldwide, the tobacco industry, with its vast experience in mass-production, advertising, marketing, lobbying and legal defense, is investing in the cannabis industry! With the cannabis landscape continuing to evolve, we must remain concerned about the risk of psychosis outcomes related to cannabis.

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Keeping Dr. Google under control: how to prevent and manage cyberchondria

The Internet has become the main source of health information, which is usually obtained via online health search using relevant engines – a behavioral pattern also known as "Dr. Google". Online health search has had an empowering effect, allowing an easy access to hitherto difficult-to-find health information. However, it can also become problematic and lead to cyberchondria.

Cyberchondria is an excessive and/or repeated online health search that is associated with increased distress or health anxiety and persists despite interference with functioning and negative consequences[1]. The latter may include disruptions in the relationships with physicians and in the usual patterns of seeking and receiving health care[2].

It has been suggested that cyberchondria represents a compulsive form of "problematic usage of the Internet"[3], with the key issue being a precarious control over online health search. This search is driven by a need to alleviate health anxiety, which however increases with persisting search, and then spirals out of control[4]. Studies have confirmed strong relationships between cyberchondria and health anxiety, problematic Internet use, and symptoms of obsessive-compulsive disorder[1].

Prevention of cyberchondria may entail improvement in online health information literacy, because people with greater literacy have been found to have lower levels of cyberchondria[5]. A specific approach to prevention requires addressing the factors that increase the risk of cyberchondria, including erroneous expectations of the Internet, poor coping with information overload, uncertainty, and confusion about trustworthiness of the sources of online health information[4].

A prevention program needs first of all to clarify what the Internet can and cannot do. It is important to debunk unrealistic expectations, e.g., that the Internet can provide definitive explanations for all health-related queries. Accumulation of information does not necessarily translate to a better understanding or more knowledge. In the context of online health search, having more information does not equate to also having an explanation, for instance a diagnosis. Attempting to diagnose oneself via Dr. Google should be discouraged, because it can spiral out of control, cause more distress and thus lead to cyberchondria.

Second, an abundance of online health information (information overload) during online health search, especially when that information is inconsistent or conflicting, can lead to a sense of being "stuck" or losing control whilst performing the search. Providing education about the effects of information overload and improving coping with this overload may afford protection against cyberchondria.

Third, an adequate uncertainty management may also play an important role in preventing cyberchondria. Online health information is often ambiguous and can be confusing, thereby amplifying uncertainty. Intolerance of such uncertainty and trying to cope with it through further search to arrive at a "closure" (e.g., a diagnosis) opens a pathway to a vicious cycle of reassurance seeking. Therefore, if online health search makes no progress and seems to only generate distress, the strategy needs to change and relevant health information should be obtained from an alternative source, including one's physician.

Fourth, an ability to distinguish between trustworthy and untrustworthy sources of online health information provides an additional layer of security when engaging in online health search. Health information obtained from reputable sources (e.g., academic and research organizations or governments) is usually more trustworthy, although it may be "impersonal". Health information found in forums and blogs often reflects personal experience and may be valuable as such, but it is not necessarily applicable to others.

People with cyberchondria usually do not seek help for it directly, perhaps because of the perception that this is not a "recognized" condition. Instead, they tend to present to clinical services with hypochondriasis, anxiety disorders, problematic Internet use or even "Internet addiction". Largely due to cyberchondria's ambiguous conceptual status and its relatively "hidden" nature, approaches to its management are still in their infancy.

Management of cyberchondria should be based on an understanding of each person's circumstances. In other words, why is that person presenting with cyberchondria at this particular time? What precipitated cyberchondria and what is its purpose? Is it a specific symptom or health concern that initiated online health search, and is the person primarily seeking reassurance? What are the consequences of cyberchondria and how has one's life changed because of excessive online health search? For example, has the person been avoiding his/her doctor or visiting the doctor too often? Why does excessive online health search persist despite the problems it has caused? Is it because the search is experienced as a way of coping with uncertainty? Answers to these questions are likely to shape the management approach and determine treatment targets.

Common treatment targets in cyberchondria include certain facets of psychopathology (e.g., health anxiety and obsessive-compulsive symptoms), personality traits (e.g., perfectionism, trust/mistrust imbalance, intolerance of uncertainty, and poor time management), behavioral responses to anxiety-provoking or distressing stimuli (e.g., reassurance seeking or avoidance), information management issues (e.g., poor coping with abundant or conflicting online health information), and specific aspects of the interactions with computers and the Internet (e.g., unrealistic expectations of the Internet or assumption that the order in which the results of online health search are presented reflects the likelihood of these results providing an explanation for health-related queries). These targets can be addressed using a combination of educational and psychotherapeutic approaches.

Existing psychotherapeutic methods can be adapted to treat

cyberchondria. One study has demonstrated that a modified Internet-delivered cognitive-behavior therapy (CBT) for hypochondriasis/health anxiety that also addressed cyberchondria was efficacious in the treatment of both[6]. In that study, cyberchondria-specific components of CBT included measures that improved online health information literacy and psychoeducation about ways of making search productive and avoiding excessive and unnecessary search.

Cyberchondria is increasingly regarded as a public health problem[3], which is uniquely and largely related to its potential to affect health care. In view of this recognition, developing prevention and management programs for this condition and testing their efficacy should be prioritized.

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The Wellcome Trust: new funding for mental health science

The Wellcome Trust is one of the world's largest health research funders. The charity has committed to spend £16 billion over the coming decade (2022-2032) on just four priorities. First, to fund curiosity-driven basic research on any topic that advances understanding of life, health and well-being, through thrice-yearly open schemes available to researchers at different career stages. Second, third and fourth, to address three global health challenges that are in urgent need of scientific solution, where Wellcome funding and convening can have maximum impact: infectious diseases, climate and health, and mental health. The fact that mental health is one of these priorities makes Wellcome potentially the largest independent funder of mental health research globally. We seek to use this position to advance our vision of a world where no one is held back by mental health problems.

We wish to encourage mental health researchers to apply for all forms of Wellcome funding to help make this vision a reality. They can do this through our regular researcher-driven curiosity-led schemes, where applications can be on any aspect of mental health or neuroscience. Proposals must be led by a researcher in the UK or a low- or middle-income country, but can involve collaborators from all countries across the world. Researchers could also consider applying to specific calls related to infectious diseases or climate and health where relevant, which are generally open to the global community.

We also wish researchers to consider applying for our targeted Mental Health Awards, which are designed to advance Wellcome's specific mission to create a step-change in early interventions for anxiety, depression and psychosis. Applications for Mental Health Awards are generally open to researchers in any country globally (with the exception of those not permitted by national policy or UK sanctions) and at any career stage.

Over the next few years, we plan to run two Mental Health Awards per year. These will be on key topic areas where Wellcome feels that bold science may lead to breakthroughs in relation to its mission. Awards launched so far (now closed) focused on new ways of addressing cognitive deficits in psychosis; research to illuminate the relationship of sleep and circadian rhythms with anxiety, depression or psychosis; and back-translation projects designed to understand how effectively treatments work for one or more of the target conditions. Details of Mental Health Awards planned up to 2024 are available on our website (https://wellcome.org/what-we-do/mental-health).

We are committed to meaningfully involving people with lived experience of mental health problems in our work. Within our mental health team, lived experience experts shape our governance, direction, decision-making and daily work. Our team of lived experience consultants includes people based in the UK, Rwanda, Kenya, South Africa, Indonesia, India and Australia. Unless in exceptional circumstances, we require lived experience to be a key part of everything that we fund.

To achieve our mental health mission, we fund with the intention of advancing three goals: a) better understanding of how the brain, body and environment interact in both the development and resolution of the target mental health conditions; b) better ways of identifying and grouping (stratifying) people with, or at risk of, these conditions, so that we can provide more timely and personalized interventions; and c) new and improved ways of intervening at the earliest possible stage in anxiety, depression and/or psychosis.

Below we share some examples of projects we have funded so far. These by no means represent a comprehensive review of our portfolio, but are intended to give a flavour of the diversity of projects with potential for achieving our goals.

To advance basic understanding, we need to unpick the complex interplay between biological, psychological and social determinants of both the origins and solutions to mental health problems. This includes an interest in the collection and analysis of longitudinal data. We have funded Sage Bionetworks, US to lead a collaboration testing different models of stewardship for mental health data in the UK, South Africa and India. We are funding Prof. L. Kenny from the University of Liverpool, UK to supplement a new cohort to collect microbiome data at birth in the UK, with follow-up to assess impacts on anxiety and depression at later stages. We have also commissioned a global mapping of large-scale longitudinal datasets relevant to our focus worldwide to encourage use by mental health researchers and to consider oppor-

tunities for enrichment with additional data or recruitment. The team has identified over 3,000 datasets so far.

We are committed to funding research that can help us find more suitable ways of stratifying populations to identify mental health problems, predict their course, and allocate treatment more effectively. We are funding Prof. A. Loch from the Universidade de São Paulo, Brazil to apply language analysis using machine learning to explore if this can predict risk of schizophrenia in a general population. We have launched a major call (open to applications until early Summer 2023) named "Finding the right treatment, for the right people, at the right time for anxiety and depression". This call aims to support validation of biological, psychological, social or digital markers to enable stratification in anxiety and/or depression as early as possible. Stratification is expected to allow targeted treatment and ensure that the right people get the right treatment at the right time.

Wellcome is also committed to funding science that can lead to new and improved pharmacological and non-pharmacological interventions. These could involve actions that individuals do for themselves, or are provided by a health care professional, or are supported by policies or practices in wider society. For example, we are funding Prof. P. Garety of King's College London to examine the effectiveness of a digital simulation (avatar) therapy to reduce the impact of auditory verbal hallucinations[1]; and we are funding Prof. P. Amminger and his team from the University of Melbourne, Australia to run a randomized controlled trial of cannabidiol among people who are considered to be at high risk of developing psychosis[2].

To create the change we seek, we wish to help the field of mental health science to cohere and develop. This includes commissioning teams to undertake living reviews and priority-setting to help the wider community identify the most promising areas for future research, and supporting use and uptake of a core set of common metrics for measuring mental health outcomes. We support the convening of diverse groups to advance cross-disciplinary understanding as well as policy change to support our mission, such as around work to clarify the regulation of digital tools in mental health. We also fund work considering the history of theories and debates in mental health science.

The field of mental health is complex and often controversial. We have no illusions about the challenge ahead of us in delivering a diverse yet focused programme of activities that will provide the progress and transformation which is so badly needed by people living with mental health problems worldwide.

We are prepared to take risks and recognize that not all projects will bring the impact we seek. If none of the projects we fund fail, then we are not being brave enough. We are open to bold ideas from those working in the field, and beyond, that can bring us a step closer to effective early intervention for anxiety, depression and psychosis. We are trialling a suggestions box on our website where anyone can share ideas for how we should target our funding, advocacy or convening to best achieve our mission. We encourage the readers of *World Psychiatry* to share their thoughts with us.

The funding that Wellcome has committed to mental health is both a great responsibility and a unique opportunity to transform the state of this vital aspect of human and societal health. We look forward to working with many of you to achieve our shared vision.

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Candidate biomarkers in psychiatric disorders: state of the field

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The field of psychiatry is hampered by a lack of robust, reliable and valid biomarkers that can aid in objectively diagnosing patients and providing individualized treatment recommendations. Here we review and critically evaluate the evidence for the most promising biomarkers in the psychiatric neuroscience literature for autism spectrum disorder, schizophrenia, anxiety disorders and post-traumatic stress disorder, major depression and bipolar disorder, and substance use disorders. Candidate biomarkers reviewed include various neuroimaging, genetic, molecular and peripheral assays, for the purposes of determining susceptibility or presence of illness, and predicting treatment response or safety. This review highlights a critical gap in the biomarker validation process. An enormous societal investment over the past 50 years has identified numerous candidate biomarkers. However, to date, the overwhelming majority of these measures have not been proven sufficiently reliable, valid and useful to be adopted clinically. It is time to consider whether strategic investments might break this impasse, focusing on a limited number of promising candidates to advance through a process of definitive testing for a specific indication. Some promising candidates for definitive testing include the N170 signal, an event-related brain potential measured using electroencephalography, for subgroup identification within autism spectrum disorder; striatal resting-state functional magnetic resonance imaging (fMRI) measures, such as the striatal connectivity index (SCI) and the functional striatal abnormalities (FSA) index, for prediction of treatment response in schizophrenia; error-related negativity (ERN), an electrophysiological index, for prediction of first onset of generalized anxiety disorder, and resting-state and structural brain connectomic measures for prediction of treatment response in social anxiety disorder. Alternate forms of classification may be useful for conceptualizing and testing potential biomarkers. Collaborative efforts allowing the inclusion of biosystems beyond genetics and neuroimaging are needed, and online remote acquisition of selected measures in a naturalistic setting using mobile health tools may significantly advance the field. Setting specific benchmarks for well-defined target application, along with development of appropriate funding and partnership mechanisms, would also be crucial. Finally, it should never be forgotten that, for a biomarker to be actionable, it will need to be clinically predictive at the individual level and viable in clinical settings.

Key words: Biomarkers, neuroimaging, GWAS, treatment response, precision medicine, autism spectrum disorder, schizophrenia, depression, bipolar disorder, anxiety disorders, post-traumatic stress disorder, substance use disorder

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The search for biomarkers in psychiatry is motivated by the need for objective measures to inform diagnosis, prognosis, and treatment choices. The ultimate purpose of a biomarker is to improve management of a disease towards better outcomes[1], allowing for preventive and therapeutic interventions that are tailored to a particular person's genes, environment and lifestyle (i.e., a precision medicine approach).

The US Food and Drug Administration (FDA) separates classes of biomarkers based on their applications[2], and several of these are likely to impact the clinical management of mental disorders: a) *susceptibility biomarkers*, aimed at estimating the likelihood of developing an illness, which may inform allocation of preventive interventions; b) *predictive biomarkers*, aimed at estimating the likelihood of experiencing a therapeutic drug effect, which may consequently inform treatment selection; and c) *safety biomarkers*, aimed at predicting side effects, which may further aid in therapeutic decisions by anticipating poor tolerability.

Non-invasive biomarkers, for example those based on magnetic resonance imaging (MRI) and electroencephalography (EEG), are of particular interest for developing personalized approaches. This is not only because they are relevant to the pathophysiology of interest, but also because it is hoped that they may be scalable and adoptable in the clinic – either now or in the near-term future.

The general litmus test for biomarkers in psychiatric disorders is their ability to change clinical practice. To achieve this goal, several steps in their development are required.

The first stage is to identify a target clinical question that a particular biological measure may be appropriate to address. The most valuable target applications for biomarkers are those that can inform "high-risk, high-reward" decisions. For example, targeting decisions to prescribe a medication with potential life-changing benefits but also serious side effects (e.g., clozapine for schizophrenia[3]) may take priority over targeting decisions bearing less potential benefits or risks. Another relevant consideration is the extent to which a biomarker may optimize decision-making above and beyond clinical data. In this respect, diagnostic biomarkers may be less clinically informative in cases where they are unlikely to override decisions based on patients' complaints and clinical presentation. A final consideration is that the value of biomarkers will necessarily evolve with novel therapeutic options. For example, susceptibility biomarkers for conversion to psychosis, or for the emergence of autism spectrum disorder, would become particularly valuable in the case that interventions capable of preventing these outcomes become available.

The second stage is internal validation. In this stage, it must be demonstrated that a relevant biomarker reflects the underlying process of interest, instead of confounds or other epiphenomena. Confounds may include demographic characteristics, illness chronicity or severity, treatment, co-occurring psychiatric and medical conditions, and site characteristics, among

others. There may also be methodological confounds, such as head-motion artifacts that are inextricably tied to the disorder or psychopathological trait itself (e.g., impulsivity[4]), and therefore are not amenable to traditional statistical covariation[5]. Unfortunately, most biomarkers under development fail to move past the internal validation step.

The third stage is external validation. In this stage, it must be demonstrated that a biomarker has sufficient predictive validity in a sample independent from the one used to develop it. A critical impediment to external validation is overfitting. This refers to a model that excessively reflects the idiosyncratic (noisy) features of the dataset in which it is developed, so that it underperforms when applied to new data[6]. This stage of biomarker development thus focuses on minimizing overfitting and maximizing generalizability. It further focuses on considering and managing issues such as lack of diversity in clinical trials, failure to account for common comorbidities, or a potentially evolving biology over the course of a disorder. Statistical methods such as cross-validation and resampling allow one to measure the generalizability of a model without applying it to an independent sample[7]. However, this does not replace the critical step of confirming generalizability in a fully independent sample not used for model training[6].

At the stage of external validation, the most relevant performance metrics no longer pertain to significant statistical associations; instead, out-of-sample discrimination or predictive performance are most important[8]. Common metrics include the area under the curve (AUC) in receiver-operator curves, and the hazard ratio for time-to-event predictions [9]. The AUC captures a trade-off between true positives and false positives, with higher AUC values indicating improved discriminative ability to identify true positives without excessive false positives. As a general reference, the American Psychiatric Association Work Group on Neuroimaging Markers of Psychiatric Disorders suggested an AUC >0.8 as a minimally useful threshold[10]. Nonetheless, what is considered useful may at least partly depend on contextual factors such as the performance of available predictive models and the consequences of inaccurate prediction[11], or the value of the expected information gain. For example, although available predictive models in suicide prevention have accuracy near zero[12], incorrect predictions are catastrophic, and therefore even a marginal increase in accuracy could be highly valuable from an individual and public-health standpoint. As a final step in external validation, *calibration* of trained models can be used to assess, and fine-tune as necessary, the prediction performance across the entire range of outcome probabilities[8].

The fourth and final stage requires demonstrating clinical utility. At this stage, biomarkers will have to exhibit added value relative to existing tools for clinical decision-making. They must also be scalable and, ultimately, cost-effective. This may involve model comparison against current methods of prediction, such as expert prognostication of relevant outcomes or clinical judgments[13,14], in addition to chance-level prediction. However, once again, the designation of clinical utility may be partly context-dependent. For outcomes with especially high stakes (e.g., suicide, drug overdose, conversion to psychosis), expensive and/or marginally accurate new biomarkers may still provide high clinical value in comparison to the *status quo*, and ultimately may be cost-effective if they can prevent the catastrophic outcome from occurring, particularly if they are proximal predictors of that outcome.

The goal of this paper is to describe and discuss candidate biomarkers – encompassing genetic, molecular, neuroimaging and/or peripheral assays as warranted – for autism spectrum disorder (ASD); schizophrenia spectrum disorders (hereafter referred to as schizophrenia for simplicity); anxiety disorders and post-traumatic stress disorder (PTSD); mood disorders, encompassing major depressive disorder (MDD) and bipolar disorder (BD); and substance use disorders (SUDs). Recognizing that a listing of all potential biomarkers could be overwhelming and lack coherence, we do not provide an exhaustive list of the candidate biomarkers for each disorder that have been proposed or evaluated to date. Rather, we list and critically evaluate the evidence only for selected biomarkers which we view as especially promising for the field.

Biomarker development may be generally viewed as following a stepwise pipeline akin to that in drug development[11]. For some indications, the biomarkers reviewed here are farther along in development and closer to being clinically actionable; for other indications, the focus is on biomarkers which are earlier in development but are seen as having strong potential for breakthrough advancement once validated. We end each section with a brief summary of the reviewed literature, as well as a shortlist of what we consider to be especially promising (if applicable). These especially promising biomarkers could be prioritized for future large-scale, highly powered studies, which in turn can provide the definitive evidence of that particular biomarker's ultimate success or failure.

BIOMARKERS IN AUTISM SPECTRUM DISORDER

Biological markers have been a focus in autism since its initial description in 1943 by L. Kanner, who noted large head size in five of eleven children[15]. Over time, research on biological markers in ASD has ranged from crude measures of head size to longitudinal imaging of the brain to sequencing of the entire genome.

Like all psychiatric diagnoses, ASD describes common behavioral features across individuals, instead of being a "disease" with a unifying pathophysiology. ASD spans a broad range of function and impairment: some patients require lifelong 1:1 care, while others are successful professionals and parents. Yet, unlike in other diagnostic categories reviewed here, ASD is a developmental disorder that presents in early childhood, with less time to identify biomarkers that predict onset, and with longitudinal outcomes typically measured in years rather than in weeks to months. Additionally, treatments are lacking for the core symptoms of autism – behavioral interventions show benefit primarily for IQ or language[16], and medications primarily treat associated symptoms such as agitation or hyperactivity[17].

ASD biomarkers that have been investigated to date primarily correspond to the susceptibility biomarkers discussed elsewhere in this review more than to predictive or safety biomarkers. Some have been

described as stratification or subtyping biomarkers, given that they have sought to parse ASD into subgroups with common features. Truly unifying biology is expected at the level of single genes implicated in ASD, but peripheral or brain-based biomarkers may identify larger subgroups that may predict prognosis or treatment response. Each of these approaches has some emerging data pointing to future utility, but to date only genetic testing is regularly used in the clinic.

Note that, throughout this section, we have endeavored to recognize the strong preference of many in the autistic community for identity-first language ("autistic person") over person-first language ("person with ASD")[18], except when referring to the DSM diagnosis of ASD. This is in contrast to other mental disorders, such as SUDs, where it is suggested to avoid labeling a person by his/her disease[19].

Genetic biomarkers

More genes are implicated in ASD than in any other DSM diagnosis. Most genetic variants are not inherited from either parent but are instead *de novo* mutations. These include single nucleotide variants (SNVs) and small insertions or deletions (indels) that disrupt single gene function, collectively implicating more than 100 genes to date[20-23]. *De novo* copy number variants (CNVs) are also implicated in ASD, most of which either delete or duplicate multiple genes[24]. Emerging data also point to rare inherited SNVs and CNVs that contribute to ASD risk[25-27]. Collectively, rare ASD-associated SNVs and CNVs are found in about 15% of autistic individuals, although no single variant is found in more than 1%.

Rare ASD-associated genetic variants are best conceptualized as identifying genetic syndromes within the overall population of autistic individuals. This extends our knowledge beyond syndromes that are typically identified before an ASD diagnosis, such as fragile X syndrome and tuberous sclerosis[28]. None of these rare variants leads to an ASD diagnosis in every individual, and many resulting syndromes also include dysmorphic features or involvement of other organ systems. Rare ASD-associated variants are more often identified in individuals who also have intellectual disability (ID), but are still enriched in those without ID[29,30]. Evidence therefore supports genetic testing, including fragile X testing, chromosomal microarray to detect CNVs, and whole exome sequencing, for *all* autistic individuals[31,32], although clinical uptake remains low[33]. This is unfortunate, as neurodevelopmental CNVs are enriched for congenital disorders and are correlated with multiple psychiatric and medical ailments[34], suggesting that they could potentially be used to assess risk even beyond ASD.

Genetics-based biomarkers could also be used to identify larger subgroups of individuals with unifying biology. As one example, the fragile X mental retardation protein (FMRP) binds to the mRNA of multiple genes implicated in ASD[23,29], and individuals with disruption of any of these genes could potentially respond to a common treatment. A more concrete approach would be to cluster rare genetic variants into larger groupings that have defined impact on a signaling pathway, such as mTor signaling disinhibition in tuberous sclerosis and PTEN hamartoma syndrome[35].

Common genetic variation may be another pathway to identifying biomarkers in ASD. The first five significant genome-wide association studies (GWAS) loci were recently reported in ASD, presenting an opportunity to begin studying common variants that confer risk[36]. Thus far, polygenic risk scores (PRS) predict less than 3% of risk in ASD[36], although this is likely to grow with larger GWAS sample sizes. Approaches to partitioning high and low PRS values already suggest avenues toward clinical utility in schizophrenia risk prediction or treatment response[37,38], and similar opportunities may also open in ASD.

Peripheral biomarkers

Considerable effort has gone toward identifying and understanding potential peripheral biomarkers in ASD, beginning with the first description of elevated blood serotonin levels or hyperserotonemia in 1961[39]. Numerous peripheral findings have been reported in ASD blood, saliva and stool samples, including tests that have been approved for use by the FDA, but none of these has been sufficiently developed to warrant its use in the clinic. In many cases, research on peripheral biomarkers has focused on searching for correspondence to brain or behavioral features of ASD, without necessarily establishing a clear target for the biomarker's clinical utility, such as prediction of diagnosis or response to treatment.

The serotonin system provides an instructive example of the approaches taken to peripheral biomarkers in ASD. The description of hyperserotonemia was an early indicator of a biological origin for ASD[39], in contrast to early attribution of the condition to parenting style[40]. Even while the diagnosis of ASD has climbed from very rare to about 2% of school-aged children[41], rates of hyperserotonemia (>95th percentile) have remained stable at more than 25% in ASD (meta-analysis $p=10^{-12}$)[42]. Various approaches to validation have been applied, including demonstration that hyperserotonemia is specific to ASD[43], heritable[44], primarily seen in boys[45], and more commonly seen in families with multiple affected children[46], but not associated with a particular clinical pattern[47]. Despite investigations spanning six decades, no prospective study has yet assessed whether hyperserotonemia may predict ASD risk in infants or whether it may predict treatment response to medications that target the serotonin system[47].

Numerous other candidate peripheral biomarkers have been identified, although with less consistency across studies or specificity to ASD. Elevated pro-inflammatory cytokines, particularly interleukin-6 (IL-6) and IL-1β, have been described in several studies and are supported by meta-analysis [48]. Increased markers of oxidative stress have also been reported, again supported by meta-analysis[49]. Multiple groups have found differences in components of the stool microbiome in ASD, with some support but also inconsistency noted in meta-analysis[50].

Overall, these peripheral studies have identified broad patterns of difference between groups of autistic children or adults and comparison groups, but have not evaluated their utility as clinical biomarkers. As noted in other sections below, these markers may be largely non-specific, due to overlap with other psychiatric and medical con-

ditions. One group, though, has been systematically evaluating folate receptor-α autoantibody as a potential biomarker in relation to treatment[51]. Initial data are intriguing, indicating that those with the antibody are more likely to show improved verbal communication following folinic acid administration in a placebo-controlled pilot trial[52]. External validation of the biomarker and direct replication of these effects are still needed.

Finally, some groups have focused on composite biomarkers, including transcriptome and metabolome profiles, primarily focused on predicting ASD diagnosis. Initial studies of 100-200 participants provided some hope that lymphocyte transcriptome profiles might separate autistic children from typically developing controls, but lacked a prospective approach[53] and/or were not specific to ASD versus developmental delay [54]. An industry-funded study of 880 participants failed to find any transcriptome or metabolome signature with potential clinical utility in predicting diagnosis in preschoolers recruited prior to ASD evaluation (NCT01810341). In contrast, an industry-funded study of 708 preschoolers with ASD versus non-referred controls reported a cluster of "metabotypes" that predicted ASD diagnosis with a sensitivity of 53% and specificity of 91%[55], with 17% having a branch chain amino acid profile with higher sensitivity. This *NeuroPointDx ASD Test* is currently marketed to consumers without any evidence that it prospectively improves ASD screening or diagnosis, or that it is useful to guide potential treatment. This marketing of a test without requiring FDA approval or prospective evaluation is a cautionary tale for clinician-scientists collaborating with industry to test biomarkers in ASD.

Central nervous system biomarkers

Researchers have sought a brain signature of ASD since the advent of neuroimaging. In the last three decades, many studies have focused on potential brain-based biomarkers quantified by a variety of indicators and techniques. These include head size as a proxy for brain size, structural MRI (sMRI) to delineate the morphology of brain structures, functional MRI (fMRI) and EEG to elucidate brain function, and cerebrospinal fluid (CSF) sampling as a measure of brain neurochemistry.

Kanner's original description of autism noted macrocephaly in some but not all cases. Consistent with this, later systematic examinations of head size in autism found macrocephaly in a subgroup that showed increased head growth after birth through early childhood[15,56]. Subsequent work suggested an initial surge in head growth in infants followed by a regression of growth in late childhood, but methodological problems weaken these results[57]. A recent longitudinal study confirmed the initial observation: a subgroup of ~15% showed persistent macrocephaly, primarily driven by gray matter and cortical surface area, whereas the rest of the ASD sample showed no difference from the control population[58]. Further, those with macrocephaly showed more cognitive impairment and less improvement over time[59].

While the early observation of macrocephaly pointed to the origins of ASD in the brain, structural neuroimaging studies have not consistently found particular brain regions to be implicated in ASD[60,61]. Resting-state functional connectivity studies have found complex patterns of altered connectivity in ASD, with evidence for both over-connectivity and under-connectivity in short- and long-range networks[62,63]. Most promising as potential biomarkers are the findings of longitudinal neuroimaging studies in infants who have an older sibling with autism ("baby siblings") and are therefore at elevated familial risk. In this population, changes in gray matter growth and white matter connectivity across a child's first 6-24 months show robust prediction of later ASD diagnosis[64,65]. These studies have also found increased extra-axial fluid volume in babies and toddlers who are later diagnosed with ASD[66,67], and in toddlers after diagnosis[68].

Only a minority of autistic children can tolerate an MRI scan, and EEG approaches may offer a more feasible alternative. Like MRI measures, EEG results suggest diminished long-range connectivity, but there is inconsistency across studies[69,70]. EEG offers the benefit of low cost and high temporal resolution, despite poor spatial resolution. Investigators use event-related potentials (ERPs) to evaluate processing of sensory stimuli, including social cues. The ERP response to faces is particularly characteristic, with a negative deflection at approximately 170 milliseconds (N170) showing a delay in many autistic children[71,72]. This N170 signal has been well replicated and validated across multiple groups, and is the only ASD biomarker to date to be submitted to the FDA. The initial target of the FDA submission is subgroup identification within ASD, but there may be future potential as a marker of treatment response as well[73,74].

Neurochemical markers have also generated considerable interest in ASD. Magnetic resonance spectroscopy (MRS) studies have suggested possible regional changes in GABA or glutamate levels, though findings are inconclusive[75,76]. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies have indicated decreased serotonin receptor 5-HT_{2A} binding[77], which could inform treatment studies using medications that block 5-HT_{2A} in addition to other receptors.

Recently, decreased CSF vasopressin in neonates has been associated with later ASD diagnosis[78]. Parallel findings indicate an association between CSF vasopressin levels and symptom severity in ASD[79]. Following an initial pilot study with promising results for intranasal vasopressin in ASD[80], it would be logical to assess CSF vasopressin as a potential biomarker of treatment response.

Finally, eye-tracking is sometimes described as a biomarker in ASD. However, most eye-tracking studies represent a fine-grained analysis of behavior, rather than a biomarker *per se* – except perhaps for pupillometry, which is occasionally applied. Non-biased approaches to behavioral observation are quite promising in ASD, but are beyond the scope of this review.

Summary of autism biomarkers

Biomarker development in ASD has rarely been systematic, but several potential biomarkers hold promise for future studies.

Genetic testing is now recommended for every child with an ASD diagnosis, with findings identifying genetic syndromes that often explain most of a child's risk, but are not specific to ASD. Some peripheral findings

are well replicated, but most have not been assessed prospectively and none has been adequately tested for clinical utility.

Brain-based markers show promise for subgrouping individuals, and there is some initial evidence in baby sibling studies showing that longitudinal neuroimaging can provide neural signatures that precede ASD diagnosis. After diagnosis, the EEG/ERP N170 signal has been most rigorously tested as a biomarker, with promise for identifying a subgroup within ASD and some potential as an indicator of treatment response. Finally, signals across domains support further study of serotonin- and vasopressin-based biomarkers in relation to subgrouping or response to targeted treatment.

BIOMARKERS IN SCHIZOPHRENIA

The specific relevance of biomarkers for schizophrenia lies in the large burden related to this disease[81] and the costly consequences of trial-and-error approaches to clinical decision-making. Delays in effective treatment involving repeated failed trials unnecessarily prolong social impairment and personal suffering, and can increase danger to self or others. Furthermore, multiple failed trials can undermine treatment engagement, which is generally already tenuous in schizophrenia, especially in the early phases of the illness[82].

Schizophrenia is the psychiatric diagnosis with the most research on personalized biomarker approaches after depression[83]. Recent papers have provided a broad overview of biomarkers for this disorder[84,85], including target biomarkers for drug development[2,86] and diagnostic biomarkers for pathophysiological interrogation[84]. This section will mainly focus on candidate neuroimaging biomarkers that have shown potential for eventual clinical applications by virtue of their ability to allow out-of-sample predictions at the individual-subject level (i.e., beyond in-sample statistical associations at the group level). Discussed topics include prediction of conversion to psychosis, treatment response, treatment discontinuation, and relapse risk, among others. We will, however, make exceptions in the case of relevant potential applications for which predictive performance has not yet been evaluated. In such cases, we will discuss statistical associations as examples of the preliminary stages of biomarker development.

Susceptibility biomarkers of conversion to psychosis

Susceptibility biomarkers to estimate the risk of conversion to psychosis at the individual level could be highly useful in many ways. They could indicate which subjects at clinical high risk (CHR) for psychosis are most likely to develop a full-blown psychotic disorder, which could motivate earlier initiation of available treatments[87,88] to reduce the duration of untreated psychosis and its associated impact. Prognosis associated with these biomarkers would also have inherent value in preparing patients and families for what to expect in terms of chronicity and prognosis. Finally, susceptibility biomarkers could facilitate personalized treatment selection of novel disease-modifying agents as they become available[89-91].

Prognostic models based solely on clinical data are reasonably developed. For example, the North American Prodrome Longitudinal Study (NAPLS2) individualized risk calculator[92] predicted conversion to psychosis with an AUC of 0.71 in the development cohort, and subsequently was externally validated in two large independent cohorts with an AUC ranging between 0.63 and 0.79[93,94]. A machine-learning model from the Personalized Prognostic Tools for Early Psychosis Management (PRONIA) consortium achieved substantial prognostic accuracy using only clinical data, showing a balanced accuracy of 76.9%[14]. Similar predictive accuracy was achieved with the Columbia risk calculator (i.e., 73%), based on data from the Structured Interview for Prodromal Syndromes[95]. A major challenge for clinical predictive models is that they are unlikely to modify clinical practice, as high-scoring individuals will have greater symptom burden and may already be allocated additional resources.

Neural susceptibility biomarkers could be clinically useful if they improve predictions above and beyond what is possible using clinical data. Investigators from the PRONIA consortium trained machine-learning algorithms using clinical and gray matter volume maps to predict impaired function in a CHR cohort of 116 individuals, of whom 66 met impairment criteria at one-year follow-up[14]. The model using clinical data predicted social function at outcome with a balanced accuracy of 76.9%, which improved to 82.7% when adding volumetric MRI data.

In another study, the same group optimized a predictive algorithm for conversion risk in CHR states by sequentially integrating clinical-neurocognitive-based, expert-based, PRS-based, and sMRI-based risk estimates for individual subjects, which resulted in a combined balanced accuracy of 85.9% (84.6% sensitivity, 87.3% specificity) using leave-one-site-out cross-validation[96]. The accuracy for the algorithm combining risk estimates across modalities surpassed that based solely on clinical and neurocognitive data or other individual modalities. Notably, this stepwise algorithm only required additional modalities that were deemed necessary (i.e., MRI data would be required only if clinical data were insufficient), a feature that could improve the feasibility of its clinical implementation by reducing costs and diagnostic burden.

In a smaller study, striatal glutamate measured by MRS showed promise in 19 individuals, including 7 converters. The accuracy of a predictive model based on clinical information alone was 82.1%, and this increased to 86.9% when adding a striatal glutamate measure into the model[97].

Other biological measures that could be integrated in predictive algorithms show some promise. One example is a neuroanatomical-maturity marker developed by the NAPLS2 consortium: in secondary analyses of 275 CHR adolescents (39 converters), a "brain-age-gap" marker showed an AUC of 0.63 in predicting conversion in the development sample using 10-fold cross-validation[98]. Another promising candidate is the EEG-based mismatch negativity (MMN): in a study of 62 research participants who were categorized into high or low risk based on MMN, the respective hazard rate for conversion was 85% versus 13%[99].

These and other encouraging results showing in-sample associations[100,101] call for additional studies directly testing the

predictive ability and generalizability of MMN as a susceptibility biomarker for conversion. Similarly, while resting-state fMRI measures, including indices of cerebello-thalamo-cortical connectivity[102], have shown robust results in association studies, their ability to improve upon the predictive capabilities of structural, neurochemical or MMN-based measures – alone or in combination – remains to be studied. Overall, though, most susceptibility neural biomarkers for conversion have not yet been tested against models using clinical information.

It is important to note that the candidate markers reviewed here have undergone varying levels of validation. For instance, the volumetric MRI model from PRONIA[14] showed internal validity in several analyses, ruling out scanner/site effects by using nested leave-one-site-out cross-validation and assessing various effects of site, image quality, follow-up interval, and baseline social function. Similar internal-validation steps were taken for the NAPLS2 brain-age-gap marker[98], but not for the striatal glutamate biomarker[97]. With respect to external validation, the initial gray-matter-volume PRONIA biomarker[14] used rigorous cross-validation but so far lacks validation in independent samples. In contrast, the subsequent multimodal algorithm for conversion risk from PRONIA was externally validated in independent samples, yielding a balanced accuracy of 65.3-70.4%. This exception withstanding, lack of independent validation remains a caveat that applies to most candidate biomarkers.

Finally, striatal dopamine excess has been measured with PET in CHR subjects[103,104]. Elevated striatal [^{18}F]DOPA uptake precedes the onset of psychosis[105], correlates with greater severity of prodromal symptoms and neuropsychological impairment, predicts conversion, and, in both the prodrome and schizophrenia, relates negatively to prefrontal cortical activation during cognitive tasks[106,107], although findings are not consistent[108,109]. Uptake is also predominant in the associative striatum[110,111]. Thus, striatal [^{18}F]DOPA uptake could advance to validation in multisite studies as a predictive diagnostic biomarker, but the cost and limited availability of PET facilities may limit its practicality. Neuromelanin-sensitive MRI[112], a non-invasive and reliable measure of nigrostriatal dopamine function relevant to psychosis[113], could provide an alternative. However, more work is needed to show its potential and justify the investment in broader testing and validation.

Susceptibility biomarkers of complications in psychosis

Susceptibility biomarkers could be clinically useful if they predict the development of complications over the course of schizophrenia. One example is the prediction of violent and/or self-injurious behavior, for which individuals with schizophrenia are at risk[114,115]. Some models using clinical information have shown fair in-sample associations[116,117], but their generalizability needs to be evaluated. Neuroimaging studies have similarly shown associations of certain structural and functional features with dangerous behaviors[118], and in some cases these neuroimaging measures have been studied alongside clinical variables[119]. Further biomarker development is needed in this area.

Predictive biomarkers of treatment response

Acute psychosis

Around 20-30% of individuals may have treatment-resistant schizophrenia[120], and for these patients clozapine is the only approved drug[39,40,120,121]. Despite its clear superiority over other antipsychotics, clozapine has response rates neighboring 40% and carries potentially life-threatening side effects[3]. Thus, expediting clozapine treatment for those likely to exhibit treatment resistance and who may benefit most from clozapine represents a relevant target for predictive biomarkers. More broadly, biomarkers of treatment response could further aid in personalized treatment selection, as more treatments with distinct mechanisms of action, such as cholinergic agents [122], become available.

Perhaps the most advanced treatment-response biomarkers along the development pipeline focus on striatal resting-state fMRI measures, including the functional striatal abnormalities (FSA) index[123] and the striatal connectivity index (SCI)[124].

The FSA index has been conceptualized as a diagnostic classifier. It was developed using data from 1,100 participants across seven sites, incorporating measurements that included fractional amplitude of resting-state derived low-frequency fluctuations[125] of striatal voxels as well as intra- and extra-striatal functional connectivity of those voxels. A support vector machine (SVM) classifier was first trained to predict the diagnostic status of each individual using these features, and the FSA for any given individual was defined as the distance in the SVM feature space to the hyperplane separating cases and controls. Using leave-one-site-out cross-validation, the FSA discriminated cases from controls with 80% accuracy[123].

In a second step, the investigators measured the association between FSA scores and symptom change over six weeks of antipsychotic treatment in a subset of 91 individuals from two of the sites. At both sites, more control-like FSA scores showed moderate-to-strong correlations with improvements in total symptom severity ($r=0.62$, $p<0.001$ and $r=0.42$, $p<0.001$, respectively). Substantial efforts were made to rule out confounding factors associated with antipsychotic treatment, head motion, baseline symptom severity, and site effects, and to show specificity of the FSA relative to other psychiatric diagnoses and markers based on non-striatal fMRI features[123]. However, a caveat is that the FSA's predictive ability was not externally validated, as the demonstration of treatment-response prediction relied on data trained to classify diagnosis (although in orthogonal tests).

The SCI was first developed on a cohort of 41 individuals undergoing initial treatment with aripiprazole or risperidone, 24 of whom responded to treatment over 12 weeks. Functional connectivity maps for six bilateral subregions within the striatum[126] were used to identify pairwise connectivity features associated with time to response in univariate tests. Ninety-one features were identified and weighted according to their association with time to response, and this information was used to estimate a scalar value summarizing the connectivity profiles for each individual, albeit using uni-

variate methods without cross-validation. Nonetheless, external validation was demonstrated in an independent cohort of 40 individuals with multi-episode schizophrenia, where individual SCI scores, calculated with the same methodology as the discovery cohort, discriminated between responders and non-responders with an AUC of 0.78[126]. Further studies have linked the SCI to processes implicated in treatment responsiveness, such as duration of untreated psychosis[127], relapse[128], and interactions with cannabis use[129], providing some support for its internal validity.

Non-striatal functional biomarkers have also been examined. Resting-state functional connectivity between bilateral superior temporal cortex and other cortical regions was used in an SVM classifier model to predict 10-week risperidone response in 38 medication-naïve individuals[130]. This classifier showed a leave-one-subject-out cross-validation accuracy of 82.5%, although checks of internal validity were limited. Other studies have tested measures of hippocampal functional connectivity[131,132], or anterior cingulate cortex glutamate levels measured with spectroscopy[133-136], as potential biomarkers of treatment response, but so far these studies have only provided support for in-sample statistical associations and are awaiting further validation. This is also the case for neuromelanin-sensitive MRI[112], which is currently being tested[137] as a potential biomarker of treatment response, building on previous dopamine PET work[138].

While elevated dopamine levels in the striatum are linked to antipsychotic treatment responsiveness[139,140], no prospective studies have assessed their potential utility as a biomarker for treatment response. This relates to the difficulty in implementing PET biomarkers at large scale and the limited therapeutic choices from which to select, in the case that patients were found to be non-responsive to currently used antipsychotics, which are all acting on D2 receptors.

Psychosis relapse

Another major problem in schizophrenia is the frequency and burden of relapse, underscoring the need for predictive biomarkers of this important clinical outcome. About 80% of patients with schizophrenia will relapse at least once over the course of their illness, and many of these patients will relapse numerous times[141,142]. Relapse correlates to increased potential danger to self or others, and to cumulative decrements in treatment responsiveness[142,143].

Antipsychotic drugs, in addition to mitigating acute psychotic symptoms, are efficacious in preventing relapse[144]. So, relapse usually occurs after interruption of maintenance antipsychotic treatment[145], although many patients relapse while on maintenance treatment[146]. Because pathophysiological differences may exist between relapse that occurs while patients are on or off antipsychotics, these two scenarios warrant separate lines of investigation[147]. Biomarkers could allow identification of low-relapse-risk individuals as candidates for monitored interruption of maintenance treatment, and for high-relapse-risk individuals as requiring more intensive and consistent intervention[148]. To date, the literature on this topic is fairly limited, and no validated biomarkers have shown predictive value as yet. Nonetheless, exploratory analyses suggest that the SCI may be distinctly sensitive to relapse associated with treatment interruption[128], which encourages its study in the future as a potential biomarker of relapse risk, in addition to its utility in diagnostic prediction.

Cognitive dysfunction

Although most biomarkers to date have aimed to predict and intervene on positive symptoms of schizophrenia, interest has recently emerged in developing predictive biomarkers for interventions addressing cognitive dysfunction. MMN has been studied for this purpose, based on its favorable test-retest reliability[149,150] and the relationship between its deficits and cognitive dysfunction in schizophrenia[149-151].

To date, no investigations have reported cross-validated performance of MMN in predicting treatment response to cognitive training, but several studies are suggestive in this respect. For example, one trial found that the change in MMN after 1 hour of auditory cognitive training was associated with the final improvements seen with a full course of treatment[152]. Two other studies found that baseline MMN deficits predicted greater gains across various cognitive domains in response to a similar type of training[153,154]. Thus, converging data suggest the potential for developing MMN as a predictive biomarker for treatments addressing cognition. However, internal validity remains to be established, particularly as MMN may reflect illness duration and nicotine smoking[155]. Moreover, utility for this class of biomarkers will ultimately depend on the availability of effective interventions for cognitive dysfunction in schizophrenia.

Other pragmatic outcomes

A critical aspect of successful biomarker development is real-world implementation. For example, the SCI was related to length of hospital stay[123], speaking to its potential impact in real-world clinical settings. Other early examples include a study predicting treatment discontinuation on the basis of subfield hippocampal volumes[156], which reported that dentate gyrus volume predicted treatment disengagement with an AUC of 0.75.

However, as real-world implementation must follow other necessary steps in the biomarker development pipeline, most candidate biomarkers are not ready for testing in real-world clinical settings.

Predictive biomarkers of medication side effects

The prediction of treatment side effects, while highly important, is likely among the most challenging goals for neurophysiological biomarkers in schizophrenia. This is because some side effects may be partly due to non-neural mechanisms (e.g., atypical antipsychotics modulating insulin effects on adipocytes[157]), and some of the most serious side effects, such as neuroleptic malignant syndrome[158], are relatively rare.

Bearing in mind these limitations, neural markers for weight gain have been studied based on observations that atypical antipsychotics can enhance anticipatory reward activations to food in the striatum[159] and

affect the hypothalamic histaminergic system[160]. Some initial data suggest that striatal function may predict antipsychotic-induced weight gain. For example, in a trial with amisulpride in 69 early-phase patients, weight gain was associated with low reward-related activation of the right putamen[161]. In another clinical trial in 81 early-phase patients treated with atypical antipsychotics, baseline left putamen volume and lower sensory-motor connectivity at rest correlated with weight gain[162].

This area of biomarker development is thus at a preliminary stage and requires more work. Similarly, other side effects for which neural measures may be appropriate, such as tardive dyskinesia[163], represent a potential target for future development.

Summary of schizophrenia biomarkers

Recent efforts are advancing biomarker development for schizophrenia, particularly in clinically relevant areas of prediction of conversion to psychosis in at-risk individuals and prediction of treatment response in acute psychosis.

In the area of conversion prediction, we have discussed examples of well-validated multimodal algorithms incorporating sMRI and clinical information (and in some cases genetic and other data), which have reached the third stage of external validation in the biomarker development pipeline. In the area of treatment-response prediction, we have also discussed reasonably well-developed candidate biomarkers, mostly those based on striatal resting-state fMRI (FSA[123] and SCI[124]), which show different levels of generalizability in external samples.

While none of the reviewed candidate biomarkers have established clinical utility – the fourth and final stage of biomarker development required for incorporation into clinical practice – the highlighted candidates are cause for optimism. For these most promising candidates, definitive demonstrations of external validity by independent groups or via large-scale international studies are recommended, followed by demonstrations of clinical utility. Investing in these studies, particularly those using relatively accessible measures (e.g., sMRI, PRS, resting-state fMRI) for clinically actionable indications (e.g., conversion and treatment-response prediction) seems well justified, given supportive evidence and high potential impact on clinical practice. Further development of multimodal sequential algorithmic workflows with the ability to decrease costs and diagnostic burden[96] also seems a fruitful area for future work. Finally, since there is no guarantee that these highlighted candidate biomarkers will show clinical utility, development of other reliable, broadly accessible, and well-motivated measures (e.g., EEG MMN and neuromelanin-sensitive MRI[112]) currently at the early stages is still warranted.

A potential genetic biomarker is the PRS derived from the latest GWAS in schizophrenia, which can index substantial differences in liability between individuals. Compared with the lowest centile of PRS, the highest centile of PRS has an odds ratio for schizophrenia of 39 (95% CI: 29-53). However, the clinical utility of the PRS as a diagnostic biomarker is limited, since the median area under the receiver operating characteristic curve (AUROC) is only 0.72, meaning that the liability explained is insufficient for predicting diagnosis in the general population[164].

BIOMARKERS IN ANXIETY DISORDERS

Anxiety disorders – encompassing specific phobias, social anxiety disorder, agoraphobia, panic disorder, generalized anxiety disorder (GAD), separation anxiety disorder, and selective mutism – are the most frequent mental disorders, with a 12-month prevalence of 10-14%[165-167]. These disorders generate a substantial socioeconomic burden [168], as well as significant direct and indirect health care costs[169]. They are also highly comorbid with each other, and carry an increased risk of sequential comorbidity with depression[170] and SUDs[171].

Cognitive-behavioral psychotherapy (CBT) and various psychotropic medications have proven efficacy in anxiety disorders, but treatment response is achieved in only half to two thirds of cases[172-174]. Accordingly, these disorders often follow a chronic course, with a high rate of recurrence (32.1%), and may even show stable treatment resistance (8.6%) at nine-year follow-up[175].

Given this high burden and limited treatment efficacy, the identification of valid biomarkers for anxiety disorders is critical. Multiple biological mechanisms that may potentially serve as biomarkers of pathogenesis or treatment response to psychotherapy or pharmacotherapy have been identified[176-181]. Selected findings based on genetic, neuroimaging, neurochemical, neurophysiological and/or neurocognitive assays, which could potentially lead to biomarkers with additional validation, are presented below.

Susceptibility biomarkers

Genetics

Candidate gene studies have found that *COMT* (rs4680, G [val] allele), *NPSR1* (rs324981, T allele), *TPH1* (rs1800532, AA genotype), *HTR2A* (rs6313, T allele), and *MAOA* (uVNTR, long alleles) gene variants are most consistently involved in the pathogenesis of panic disorder. *OXTR* (e.g., rs2254298 GG genotype), *SLC6A4* (5-HTTLPR, short [s] allele), *MAOA* (uVNTR, long alleles), and *HTR1A* (rs6295, G allele) gene variation is most consistently involved in other anxiety phenotypes[182-185]. However, since replication has largely been elusive, candidate gene studies have mostly given way to GWAS, a more powerful and unbiased approach.

GWAS conducted in cooperative efforts – such as the ANGST (Anxiety NeuroGenetics Study) consortium, the UK Biobank, and the Danish iPSYCH study – have suggested that several single nucleotide polymorphisms (SNPs) in genes such as *ESR1, GLRB*, *MYH15*, *NTRK2*, *PDE4B*, *RBFOX1*, *SATB1, TMEM132D*, *TMEM106B*, and a non-coding RNA locus associated with the *CAMKMT* gene, are linked to anxiety-related traits, current anxiety symptoms, or lifetime anxiety disorders[186]. The largest GWAS of anxiety traits to date, using the Million Veteran Program dataset, identified genome-wide significant associations with the Generalized Anxiety Disorder 2-item (GAD-2) score near genes involved in global regulation of gene expression (SATB1) and the

estrogen receptor alpha (ESR1)[187]. These are promising leads, but the effects require confirmation as more data are acquired.

Given the close interaction of genetic factors with environmental influences in the pathogenesis of anxiety disorders, studies are increasingly testing gene-environment (GxE) interaction effects using both candidate gene (e.g., *RGS2*[188]) and genome-wide[e.g.,189] approaches. These, too, have produced initial, but as-yet unreplicated results. The GxE concept has recently been expanded to include a dimension of "coping", yielding a three-dimensional model (GxExC). For instance, replicated evidence has been reported for an interactive effect on trait anxiety of a neuropeptide S receptor (*NPSR1*) gene variant, early adversity, and coping factors, such that adaptive coping compensates for the otherwise deleterious effects of a GxE risk constellation[190].

Finally, growing evidence is emerging for epigenetic mechanisms that can bridge between genetic and environmental levels[191]. For instance, altered DNA methylation patterns in the *MAOA*, *OXTR*, *BDNF*, *NET*, *GAD1*, *CRHR1* and *NR3C1* genes have been associated with panic disorder or social anxiety disorder[192,193]. In addition, still-underpowered epigenome-wide association studies (EWAS) in panic disorder and social anxiety disorder suggestively point to altered DNA methylation in previously unidentified risk genes[194-197].

Given the small effect sizes of individual genetic variants, a combination of genetic, epigenetic and further molecular markers might be more informative than genetic or epigenetic data alone. For example, as the field matures, PRS such as those used to predict illness course in schizophrenia[198] could be developed for anxiety disorders. An important caveat in epigenetic studies is that they have largely relied on peripheral tissues (with the exception of investigations in post-mortem samples), and epigenetic changes in peripheral tissues do not provide direct evidence of changes in the central nervous system[199]. Providing some optimism, though, studies that compared peripheral and central tissue have often reported considerable functional overlap[192].

Neuroimaging

Numerous structural and task-related fMRI, PET, SPECT and MRS studies have been conducted in anxiety disorders. Structural studies have not provided consistent results, in terms of regions or directionality. In functional studies, altered brain activation elicited in response to words or pictures with anxiety- or fear-related content has been observed in the "fear network". This includes both increased and decreased inhibitory control-relevant activity in the orbitofrontal and in the dorsolateral, dorsomedial and ventrolateral prefrontal cortex, as well as mostly increased activity in limbic structures such as the amygdala, insula, anterior cingulate cortex, bed nucleus of the stria terminalis (BNST), and striatum. The BNST may be involved in sustained rather than phasic anxiety[180,200].

Particularly consistent evidence has emerged for increased amygdala reactivity towards negative emotional stimuli in combination with insufficient prefrontal control[201]. One interpretative constraint, though, is that this activation phenotype tends to be seen across anxiety, stress-related and mood disorders, limiting its value as a biomarker able to distinguish between clinical presentations.

Psychophysiological assays and challenges

In general, "fear"-based disorders are often characterized by heightened physiological reactivity to salient threat stimuli, as measured by skin conductance response, fear-potentiated startle, pupillometry, cortisol, alpha amylase, or heart rate variability. In contrast, "anxiety"-related disorders are often characterized by a more blunted pattern of physiological reactivity using these same assays[202]. This is a potentially noteworthy dissociation providing some support to the notion that these biological measurements may be at least partly disorder-specific and developed as potential biomarkers.

An exemplary longitudinal study demonstrated the utility of the error-related negativity (ERN) as a specific, albeit not highly sensitive, electrophysiological biomarker predicting the first onset of GAD over 1.5 years in adolescent girls: ΔERN increased the odds of GAD onset to 1.64 even after controlling for clinical risk factors[203]. There is also evidence for altered interoceptive sensitivity as a marker or mechanism of anxiety disorders[204]: for example, hypersensitivity to carbon dioxide (CO_2) introduced during a laboratory challenge has been proposed as a relatively specific and heritable predictive marker for subsequent panic attacks, but not necessarily panic disorder, during long-term follow-up[205,206].

There are also pharmacological challenges that have the potential to serve as risk or diagnostic biomarkers, particularly in panic disorder. In one study, a yohimbine challenge increased panic symptoms in patients with panic disorder more than healthy controls, and the extent of the yohimbine-induced symptoms in patients (but not controls) correlated with a trait measure assessing fear of publicly observable anxiety[207]. Similarly, another study showed that m-chlorophenyl-piperazine (mCPP) provoked panic symptoms in patients with panic disorder but not in those with generalized social anxiety disorder[208], showing some diagnostic specificity. Finally, cholecystokinin tetrapeptide (CCK-4) induces panic symptoms in individuals with panic disorder at a greater frequency than in healthy controls[209], and the extent of symptom expression seems to be dose-dependent[210].

Predictive biomarkers of therapeutic response

Genetics

The 5-HTTLPR/rs25531 variant in the *SLC6A4* gene has been extensively explored in the context of psychotherapy-genetic studies of anxiety disorders, which however have produced mixed results. A recent meta-analysis incorporating 10 independent samples totaling 2,195 patients could not confirm a role of this genetic variant in moderating the effect of CBT on anxiety disorder outcomes[211]. Similarly, limited studies investigating other serotonin-related

(e.g., *HTR1A*, *HTR2A*, *MAOA*, *TPH*, *TPH2*), dopamine/noradrenaline-related (e.g., *COMT*, *DRD2*, *DAT1*), or neurotrophic factor-related (*BDNF*, *NGF*) genes did not report consistently replicable results[212]. The largest therapygenetic GWAS meta-analysis of CBT treatment response in adults with anxiety disorders or major depressive disorder and in children with anxiety disorders (total N=2,724) failed to detect any sufficiently robust association of genetic variation with treatment outcome[213]. Finally, some recent studies have focused on potential epigenetic predictors of psychotherapy response in anxiety disorders, mostly pointing to a potential role of predictive DNA methylation patterns in the *MAOA*, *SLC6A4*, and *FKBP5* genes[192].

Pharmacogenetic studies in anxiety disorders have investigated candidate genes involved in pharmacokinetics (i.e., drug availability, metabolism and degradation) such as *CYP2D6* and *CYP2C19*, or candidate genes involved in pharmacodynamics (i.e., receptors, transporters) of the serotonin, dopamine and noradrenaline systems; hypothalamic-pituitary-adrenal axis (HPA); stress pathways; and neurotrophic factors. Thus far, the results have been inconclusive[186,214]. One study used a commercially available test (*NeuroIDgenetix*®) in GAD[215], but industry-sponsored pharmacogenetic tests have yet to be implemented in daily clinical practice. To the best of our knowledge, only one GWAS to date has investigated genetic markers of treatment response to venlafaxine in GAD, but there was no genome-wide significant association[216]. Pharmacoepigenetic research in anxiety is still in its infancy and has yet to yield any consistently promising findings[193].

Neuroimaging

A systematic review of 17 studies on neuroimaging markers predicting psychotherapy response in anxiety disorders revealed the most compelling evidence for: a) mostly increased pre-treatment dorsal anterior cingulate cortex activity during relevant fMRI tasks (e.g., emotional face processing/matching, anticipation of emotional pictures, or differential fear conditioning); and b) increased resting-state anterior cingulate cortex-amygdala coupling[212].

Similarly, a quantitative meta-analysis of primarily emotion processing/regulation task-based fMRI studies observed that increased dorsal anterior cingulate cortex activity was related to CBT response in 17 datasets comprising 442 patients with various anxiety and stress disorders[217]. This meta-analysis further revealed associations between treatment response and activations spanning the larger salience and interoception networks (i.e., comprising not only the dorsal anterior cingulate cortex, but also the right inferior frontal gyrus, anterior insular cortex, and dorsomedial prefrontal cortex). A sub-analysis restricted to patients with social anxiety disorder revealed positive correlations between CBT response and activity of the bilateral Rolandic operculum, subgenual anterior cingulate cortex, right precentral gyrus, right dorsolateral prefrontal cortex, right supplementary motor area, and posterior cingulate cortex[217].

Perhaps most promising of all, the first multimodal study integrating clinical data with resting-state and structural brain connectomics imaging data using a machine learning approach predicted CBT outcome at a single-subject level in social anxiety disorder with an accuracy of 84%; there was a five-fold improvement in predictive power compared to clinical measures of severity and single connectomic measures alone[218].

Additional studies have examined potential neuroimaging biomarkers of response to pharmacotherapy. An exemplary fMRI study in social anxiety disorder applying the Multi-Source Interference Task revealed that greater pre-treatment dorsal anterior cingulate cortex reactivity predicted better response to combined psychotherapy and selective serotonin reuptake inhibitor (SSRI) treatment with 83% accuracy[219]. In a pilot study of patients with the same diagnosis, higher baseline activity in the anterior and lateral parts of the left temporal cortex and the lateral part of the left middle frontal regions, measured by Tc-99m HMPAO SPECT, predicted non-response after a six-eight week regimen of citalopram[220].

Also in social anxiety disorder, a PET study discerned task-based negative left amygdala/rostral anterior cingulate cortex and positive left amygdala/dorsomedial prefrontal cortex co-activation patterns in SSRI responders. However, this study and further comparable investigations in other anxiety disorder phenotypes applied a longitudinal pre-post design and thus followed a mechanistic rather than a predictive study approach[see221].

In GAD, a favorable response to eight-week treatment with venlafaxine was predicted by greater rostral anterior cingulate cortex activity and lower amygdala activity in response to fearful faces, and by increased pregenual anterior cingulate cortex activity in anticipation of aversive and neutral images[222,223].

Other measures

Cardiovascular markers – including tonic and/or phasic heart rate, heart rate variability, and blood pressure – as well as markers of the adrenergic system – including adrenoceptor density and plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) levels – have been proposed as potential markers of CBT response. Studies testing these biological assays, however, have largely used suboptimal study designs and/or relied on limited sample sizes[212]. Their potential to serve as biomarkers for anxiety disorders, therefore, remains to be determined.

Summary of anxiety disorder biomarkers

The majority of studies to date have failed to identify valid biomarkers of anxiety disorder pathogenesis or treatment response. Only a few studies have actually assessed sensitivity, specificity, or positive/negative predictive values[203,218,219,224,225], and are potentially actionable. For instance, ERN showed a modest overall accuracy in predicting future GAD, with an AUC of 0.60, but marked elevations of ERN were quite informative about risk, and predicted onset above and beyond clinical risk factors[203]. Notably, because EEG can be widely deployed in clinical practice and the ERN marker is malleable by attention bias modification training[226], this could be a promising and practicable risk marker of GAD.

Some task-based MRI findings have also shown satisfactory prediction of treatment response[218,219,224,225]. Biomarkers based

on connectomics neuroimaging methods (resting-state fMRI, diffusion MRI)[218] might offer some additional advantages over activation mapping markers, as connectomics-based measurements can be acquired more consistently and reliably across settings, are independent of task performance confounders, and can be performed even in infants[218]. It should be noted, however, that MRI-based biomarkers ultimately might prove less clinically viable than neurophysiology-based markers, since fMRI technology and analysis expertise are currently expensive and typically only available in large academic medical centers.

Apart from the few exceptions illustrated above, the majority of studies reported findings on a merely correlational or associative level, and did not assess sensitivity, specificity or positive/negative predictive values. According to the criteria for biomarker discovery[11], markers of anxiety disorder pathogenesis and treatment proposed so far remain at stage 1 ("target identification") and have not explicitly ruled out confounding factors such as stress, comorbidity, physical activity and/or psychotropic medication (stage 2, "internal validation"). Most presently available findings also warrant replication in validation samples independent of the discovery samples (stage 3, "external validation"), and await testing in trials demonstrating "clinical utility" (stage 4). Therefore, their potential remains unclear[223].

BIOMARKERS IN POST-TRAUMATIC STRESS DISORDER

A distinct literature has developed on biomarkers for PTSD. This research frequently operationalizes post-traumatic stress with continuous scores on measures such as the PTSD Checklist (PCL-5)[227]. The most well-established pharmacotherapies for PTSD are SSRIs, but they have limited efficacy[228]. Consequently, PTSD research has focused on developing susceptibility and diagnostic biomarkers.

Genetics

GWAS have revealed that contributions of individual genetic polymorphisms to PTSD are very small[229]. For example, in the largest GWAS to date (48,221 individuals with PTSD and 217,223 without), the effect size of the top single-nucleotide polymorphism (SNP) was trivial (odds ratio, OR=1.06)[230]. However, PRS that combine effects of hundreds of thousands of SNPs show meaningful, albeit modest effects. The strongest PRS was correlated at r=.20 with the PTSD Checklist for DSM-5 (PCL-5) score. This estimate is likely optimistic, because it was assessed using internal replication. Other studies have observed effect sizes of r=.10 to r=.16 in independent samples using an earlier version of this PRS[231,232].

Neuroimaging

Numerous neuroimaging studies have investigated potential biomarkers of PTSD, but they have produced mixed results, also due to small sample sizes[233]. Meta-analyses have revealed clear links of PTSD to smaller hippocampal, amygdala and total brain volume, and lower structural connectivity of the corpus callosum[234,235]. Few studies examined other regions, making conclusions about them less reliable. Moreover, meta-analyses are vulnerable to publication bias (e.g., primary studies reporting only on regions where significant effects were found).

Mega-analyses can address this limitation by pooling voxel-level data from multiple samples to perform whole-brain analyses and present an unbiased picture of neural correlates. The Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium performed a mega-analysis of cortical volume comparing 1,379 people with PTSD to 2,192 without[236]. Significant differences were found in 21 regions, all showing smaller volume in PTSD, but the largest group difference was only 0.17 standard deviations (SD). Another ENIGMA study examined subcortical volumes in 794 individuals with PTSD and 1,074 without[237]. Hippocampal volume was lower in PTSD by 0.17 SD. Amygdala volume and total brain volume were also smaller, but these differences did not reach significance. ENIGMA mega-analysis was also conducted on structural connectivity in 1,426 people with PTSD and 1,621 without[238]. Significant differences emerged in only one region, tapetum of corpus callosum, where structural connectivity was lower in PTSD by 0.11 SD.

Overall, these ENIGMA studies used rigorous methodology, and alignment with previous meta-analyses further increases confidence. However, their results have not been confirmed in sufficiently powered independent studies yet, and their relevance for developing biomarkers of susceptibility, prediction, or treatment response is questionable.

As links between PTSD and regional structural morphology are weak, at least for standard neuroimaging modalities, one potential avenue for improvement is if regions or voxels are combined into a composite biosignature, especially using machine learning techniques. Reliable composites will likely require larger sample sizes than currently available for PTSD. For example, research to estimate a participant's age from sMRI found that a biosignature developed in a sample of 35,474 individuals correlated at r=.69 with age in an independent sample[239]. Performance of this biosignature was proportional to the sample size used to develop it, although most of the increase occurred by the sample size of 5,000.

Peripheral biomarkers

Numerous peripheral measures have been explored as potential biomarkers of PTSD, and we consider only the most studied ones.

Psychophysiology research has linked PTSD to autonomic nervous system functioning. Meta-analyses of heart rate variability and respiratory sinus arrhythmia found differences between people with and without PTSD of 0.16 to 0.50 SD[240,241], though some of this signal may be due to potential confounders such as low socioeconomic status or physical comorbidities. Another possible marker is startle response to an acoustic probe (i.e., sudden loud sound) when the person expects danger (e.g., possible electric shock) (fear-potentiated startle). This paradigm produces reliable differences in startle magnitude between danger and safety conditions,

but the link to PTSD is unclear. It appears that some patients with PTSD show potentiation, while others are indistinguishable from healthy participants[242]. This casts doubt on fear-potentiated startle as a viable biomarker.

Biomarker research has also focused on developing relevant assays from blood, urine and saliva. Evidence suggests that these assays are informative, albeit imperfect, surrogates for brain tissue[243-246]. Initially, peripheral tissue studies focused on candidate markers, such as cortisol and inflammation markers[247,248]. They reported elevated inflammation in PTSD, but the findings were quite mixed and may have been confounded by physical comorbidities.

Omics studies seek to investigate tissues comprehensively. The largest methylome-wide study included 878 participants with PTSD and 1,018 without, finding four significant methylation sites, all in gene *AHRR* [249]. Two of these sites were replicated in an independent sample[250]. However, the difference between groups was small even for the top site, and a composite methylation signature was not attempted.

The largest transcriptome-wide study included data on 977 participants and did not find any significant associations between PTSD and expression of individual genes[251]. However, it did not attempt to develop a transcriptomic signature. Two previous studies constructed such signatures and observed moderate accuracy, with an AUC of 0.64 to 0.76[252,253], but neither signature was evaluated in an independent sample.

Proteomics is a new modality in PTSD research. The most comprehensive study to-date included 276 plasma proteins, finding significant links between numerous proteins and PTSD[254]. A multiprotein signature showed a moderate association with PTSD within-sample, but these results require replication.

Summary of PTSD biomarkers

PRS for PTSD has passed the first three stages of biomarker development. It is an informative measure of susceptibility, reliable and non-invasive. However, its links with PTSD are too weak to be useful clinically. Even as performance of PRS improves with increasing discovery sample sizes, it is unlikely to reach the level needed for clinical utility. Nevertheless, it may become useful when combined with clinical and demographic risk factors[255].

The other potential biomarkers need rigorous replication and careful control for confounds. Moreover, their links to PTSD are quite weak. Integration of data across the whole brain, methylome, transcriptome and proteome is needed to improve effect sizes and replicability. However, this approach requires very large sample sizes.

BIOMARKERS IN MOOD DISORDERS

Mood disorders (MDD and BD) are among the most prevalent and costly illnesses[167], and the development of clinically actionable biomarkers is therefore a critical research and therapeutic goal. Early biomarker efforts throughout the 1970s and 1980s centered on urinary levels of various catecholamine metabolites, measures of platelet monoamine oxidase activity, and hypothalamic-pituitary-adrenal axis (HPA) function[256,257], with inconclusive results.

Neuroimaging modalities, such as gaseous encephalography, were used as early as the 1950s[258], and structural imaging methods were increasingly employed throughout the 1980s in attempts to define major structural and volumetric differences in the brains of individuals suffering from mood disorders[259]. The use of neuroimaging in mood disorders dramatically increased in popularity over the last 20 years, with the introduction of novel, minimally invasive MRI and MRS techniques that allow for structural, functional and neurochemical investigations. These emerging modalities were paired with novel pathophysiological and treatment concepts such as neuroinflammatory pathology, neurometabolic contributions to behavioral disorders, circuit/network based disorders, and neuroplasticity enhancing treatments. The field of psychiatric genetics has also leveraged technical and conceptual advances to perform ever larger studies aiming to identify genetic variation contributing to disease risk and treatment response.

However, despite decades of work attempting to identify clinically meaningful diagnostic tools and procedures, there has been limited progress in developing biomarkers that meaningfully aid in the diagnosis, prognosis, or personalization of treatment choices for mood disorders. Below, we present an overview of the current state of knowledge.

Susceptibility biomarkers

Genetics

The hope of identifying genetic biomarkers for mood disorders is bolstered by the clear epidemiological evidence of heritable factors contributing to these disorders, such as the moderate level of genetic contribution found in the Scottish Family Health Study for MDD[260], and the heritability estimates of approximately 70-90% for BD[261]. However, the identification of specific genetic contributions to these disorders has proven extremely challenging.

Several large, recently-completed GWAS have provided new information on the genetics of mood disorders. For example, a GWAS study identified 17 loci – relating to aspects of brain function ranging from excitatory neurotransmission to neuron spine/dendrite functions – that were associated with depressive phenotypes in ~114,000 people[262]. These findings are generally in line with a meta-analysis of post-mortem studies, which reported lower levels of synaptic protein or mRNA across MDD and BD (protein levels of SNAP-25, PSD-95 and syntaxin in MDD, and PSD-95 mRNA levels in BD)[263].

More recent GWAS efforts with growing sample sizes continue to expand the number of genome-wide significant hits[264,265]. These large studies provide additional evidence that the genetics of depression maps onto the broader genetic structure of mental disorders and cognition. Furthermore, transcriptional signatures in MDD have been found to be gender-specific[266,267], suggesting an important further area of investigation.

A GWAS study in ~42,000 patients identified 15 genes linked to BD[268]. However, the pattern that emerges most consistently is that BD shares many common weak genetic risk factors with MDD and schizo-

phrenia[269]. Ultimately, it seems likely that these genes will each have a small impact on the susceptibility to mood disorders, and progression to disorder will importantly depend on interactions with environmental factors, such as (perceived) uncontrollable stress.

Neuroimaging

Much of the neuroimaging work related to mood disorder susceptibility seems to parallel the effects of stress on the central nervous system. Large meta-analyses of the structural correlates of mood disorders show volume reductions in the areas commonly associated with the stress response, including the hippocampus and frontal lobe[259].

The large multi-site ENIGMA consortium study, comprising ~2,000 participants, found reduced hippocampal volume, lower cortical thickness in multiple regions, and white matter alterations in MDD[270]. Similar to the genetic studies, the ENIGMA findings indicate relatively small overall effect sizes and common abnormalities in MDD, BD and schizophrenia, making it unlikely that the measures will prove useful in providing diagnostic biomarkers at the individual level. However, newer work using PET and MRI methodologies may be uncovering the cytoarchitectural correlates of the above structural findings, by demonstrating reductions of synaptic density in MDD[271].

Functional imaging studies, conducted at rest or during the performance of emotional or cognitive tasks, have increased dramatically over the last decade. Although these studies have provided support for circuit and network contributions to mood disorder pathophysiology, few findings reliably distinguish mood disorders from other conditions[272], similar to the structural and genetic findings previously described. Overall, prefrontal dysfunction may be a trait feature of mood disorders, while increased activation in limbic regions such as the anterior cingulate cortex and the amygdala may be associated with symptom expression[273]. However, medication and the presence of comorbid conditions – such as anxiety or substance abuse – may affect these findings. Much more work is needed at both the technical and conceptual levels before functional imaging can have more direct clinical applications in mood disorders.

The findings of MRS studies are far from consistent or conclusive, and are often complicated by methodological and technical heterogeneity. However, they have provided evidence to suggest the involvement of the amino acid neurotransmitter systems, including GABA and glutamate, in the pathophysiology of mood disorders[274-277]. These findings again appear not to be pathognomonic of these disorders, but common among a range of psychiatric conditions[278-282].

Early-stage MRS studies also suggest a role for pathophysiological effects related to oxidative stress as a contributor to mood disorders. Newer proton-MRS has enabled the quantification of glutathione concentrations in the brain, allowing for *in vivo* investigations of oxidative stress neurochemistry[283]. Although only a limited number of MRS studies have been completed to date, there is some indication of reduced glutathione measures in mood-disordered patients compared with healthy controls, with possible differences between MDD and BD[284], and specific regional associations with anhedonia in MDD[285]. Most recently, glutathione concentrations in the anterior cingulate cortex were found to be inversely correlated with depression scores and white matter hyperintensities associated to COVID-19 infection, further suggesting a link between neuroinflammation, oxidative stress, and mood[286].

In sum, the emergence of novel MRS methodologies has allowed unique *in vivo* explorations related to neurochemistry, brain metabolism, and neuroenergetics of mood disorders. While various technical and methodological limitations of the existing studies prevent firm conclusions about relationships to mood disorder susceptibility, the emerging data are generally in line with rodent models and post-mortem studies[287,288], and with predictions from large genetic studies showing effects on synaptic density and excitatory/inhibitory neurotransmitter pathways[265,268], and may reflect the reduction of synaptic density observed in MDD[271]. However, the methodology to date is not meaningfully helpful in providing prognostic markers, or in differentiating clinically relevant phenotypes of mood disorders.

Peripheral biomarkers

A myriad of peripheral measures attempting to capture monoaminergic neurotransmitter functioning have been employed over the years, with limited to no success in modifying diagnostic or treatment approaches. More recently developed metabolomics approaches, however, allow dynamic measures of large numbers of metabolites over time. Meta-analyses of these studies have found several metabolic abnormalities associated with mood disorders, including decreased levels of tryptophan, kynurenic acid and kynurenine, and increased glutamate levels in MDD patients. Pathway and network analyses of these data indicate disturbances of amino acid and lipid metabolism, especially the tryptophan-kynurenine pathway and fatty acid metabolism[289]. Overall, these findings support the involvement of several pathophysiological processes – including cellular signaling systems, components of the cell membrane, various neurotransmitter systems, hormonal regulation, moderators of circadian rhythm and sleep, as well as inflammation and immunological factors. However, no specific abnormalities can be associated with clinically meaningful differences to date.

Peripheral HPA axis measures have also been studied in large numbers of patients over the last five decades. The findings generally indicate HPA hyperactivity in depression, providing evidence of a link between MDD and comorbid conditions such as diabetes, dementia and coronary heart disease, especially in older and more severely depressed inpatients with melancholic or psychotic features[290]. However, the results are quite heterogeneous, and the effect sizes are modest, limiting the utility of these measures as diagnostic tools[291].

A relatively large number of studies, conducted over the past two decades, have examined peripheral measures of relevant neurotrophic factors. Much of this work has demonstrated a relationship between abnormally low peripheral measures of brain-derived neurotrophic factor (BDNF) and mood disorders. Reduced plasma and serum BDNF levels are commonly reported in depressed

patients and may be altered with treatment response[292,293]. Although fitting nicely with data suggesting that BDNF gene expression and function contributes to the pathophysiology of depressive-like behaviors, these findings lack specificity, and notable inconsistencies pervade research related to gene expression changes in human and rodent studies[294].

Interest in peripheral markers of immune function and inflammation has also increased over time. Abnormalities in several inflammation markers – including C-reactive protein (CRP), IL-6, IL-12 and tumor necrosis factor alpha (TNFα) – are consistently observed in major depression, often with medium sized effects. Nevertheless, the specificity and selectivity of these markers has not yet been convincingly demonstrated[295].

Finally, an emerging but potentially exciting body of research has begun to examine susceptibility biomarkers related to circadian rhythms. Mounting evidence suggests that abnormalities in circadian phase may precede mood disorders[296-304]. Indeed, change in sleep is one of the diagnostic criteria for MDD[305], and sleep difficulties are present in >85% of cases[298,306-308] and are correlated with greater depression severity[309,310]. Depressed patients exhibit reduced motor activity during the day[309,311], and lower rhythm-adjusted mean (or midline estimating statistic of rhythm, MESOR) has been reported as a diagnostic indicator of depression, with up to 80% accuracy[312]. A phase shift in activity is also present, as time to peak activity (acrophase) is delayed[309,312,313], and this delay may be associated with greater depression severity[309,313]. Disrupted sleep is also a diagnostic criterion for BD[305,314]. BD patients are also likely to have lower amplitude of motor activity when depressed[315] or euthymic[316].

Interestingly, circadian markers may have the potential to distinguish MDD from BD[317]. In particular, while further studies are needed, initial evidence suggests that MDD is associated with a phase delay[318,319], whereas BD is associated with a phase advance during mania[320], and a phase delay during euthymia[321], mixed mania, and depression[320,322]. Additional information may be gleaned by measuring melatonin during sleep/wake cycles[304,323,324], or by measuring awakening cortisol levels in euthymic BD patients[325].

Further work has indicated that the 3111T/C clock gene polymorphism, related to circadian rhythms, is associated with a higher recurrence of initial, middle and early insomnia in homozygotes for the C variant and a similar trend concerning decreased need of sleep in BD patients[326]. Moreover, expression of the clock genes *PER1* and *NR1D1* from saliva of BD patients in manic episodes is phase advanced relative to depressive episodes[327].

Prediction of treatment response

The best predictors of treatment response in mood disorders have traditionally included demographic and clinically-defined factors, such as age, severity and duration of illness, number of comorbidities, and the presence or absence of psychotic or mixed features[328,329]. However, several large-scale efforts aiming to identify biological predictors of treatment response have been implemented in the last decade. The international Study to Predict Optimized Treatment of Depression (iSPOT-D)[330], the Predictors of Remission in Depression to Individual and Combined Treatments (PReDICT)[331], and the Genome-Based Therapeutic Drugs for Depression (GENDEP)[332] studies all used large sample sizes to study and identify possible biomarkers for treatment response in depression.

The iSPOT-D study randomized over 1,000 depressed patients to 8 weeks of treatment with escitalopram, sertraline or venlafaxine, and assessed a large number of outcome variables, including clinical, daily functioning, cognitive, genetic and psychophysiological (e.g., EEG, event-related potentials, heart rate) markers. At least some outcome predictive value was found for various EEG measures (such as alpha connectivity)[333]; genetic factors (including variants in the *CRHBP* gene[334], and regulators of the gene coding for P-glycoprotein, which limits brain concentrations of certain antidepressants[335]); structural markers (such as hippocampal tail volume[336]); functional measures (such as activation in the frontoparietal network during response inhibition[337]); and environmental factors (such as early childhood trauma[338]). Further evidence also suggested that measures of functional connectivity of cognitive control and reward circuits could selectively and differentially predict antidepressant treatment responses[339,340].

The GENDEP study identified baseline levels of macrophage migration inhibitory factor (MIF), IL-1β, and TNF-α as "predictors" of antidepressant treatment response. That is, higher levels of pro-inflammatory cytokines predicted lack of antidepressant response, but lower levels did not predict a positive antidepressant response[341]. Interestingly, modulation of the glucocorticoid receptor complex and measures related to neuroplasticity were associated with a therapeutic antidepressant effect.

The Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression (EMBARC) study was a randomized sequential treatment study. In phase 1 of the study, nearly 300 patients were randomized to either sertraline or placebo. In phase 2, non-responders were randomized to placebo, sertraline (except previous non-responders), or bupropion. The goal was to identify potentially treatment-predictive endophenotypes of MDD, using electrophysiological methods, functional imaging, and peripheral markers[342-344]. Pre-treatment brain reward was somewhat predictive of individual antidepressant response[345]. Similar to reports from the CO-MED trial[346], the study also found evidence suggesting that CRP levels had some value in predicting treatment response, though the effect may be gender-specific[347].

The familial aggregation of BD (particularly the lithium-responsive type) among responders to lithium prophylaxis[348] has prompted recent attempts to identify genomic correlates of lithium response. The largest GWAS study[349] found a single associated locus on chromosome 21. The authors demonstrated that the response-related alleles were associated with lower rates of relapse in an independent sample of 73 patients treated for two years of lithium monotherapy. However, the predictive power of genomic data remains unknown, since GWAS are not designed to evaluate predictive capacity[350].

Summary of mood disorder biomarkers

Numerous biomarkers have been proposed in MDD and BD, and multiple studies including large-scale initiatives have identified potential candidates for future validation. There are several reasons underlying the limited gains achieved to date. These include the extreme heterogeneity of mood disorder diagnoses, limited treatment options, incomplete understanding of how the biomarkers actually reflect pathophysiological states, and the specific technical limitations and costs of the individual modalities.

Neuroimaging modalities, particularly those based on emerging spectroscopy approaches, may hold promise for improving prediction. However, at present, it remains a challenge to distinguish such findings in MDD or BD from similar effects in other mental disorders, such as schizophrenia, perhaps partly due to the imaging measures capturing a generalized "stress" phenotype rather a disorder-specific signature.

Similar challenges of sensitivity and specificity confront the use of peripheral biomarkers, such as neurotrophic factors as well as markers of immune function and inflammation. Future research may aim to integrate these measures with emerging approaches, such as those related to circadian rhythms, which may have the capability of differentiating MDD and BD biologically and behaviorally.

Acquiring combinations of available markers may also be useful[351-353], potentially providing complementary information while reducing noise and alternative explanations that compromise internal validation efforts. Future studies will also need to continue unraveling the formidable heterogeneity in mood disorder prediction, which may depend on factors such as gender and early childhood adversity, among many others.

BIOMARKERS IN SUBSTANCE USE DISORDERS

Among psychiatric disorders, SUDs are unique in the sense that the presence of a potentially addictive drug within the context of use-related dysfunction provides biological evidence for a disorder. Yet, beyond the presence of a drug in individuals' biological fluids, SUDs reflect repeated, compulsive substance use patterns mediated by complex (and not well-understood) interactions between biological drug effects, genetic predispositions, early life experiences, external stressors, and central and peripheral nervous system adaptations. Only an estimated 1 in 7 individuals who use substances will progress to use disorder[354], and such estimates vary according to which substance is used[355]. Considering that stable use with limited adverse consequences may describe a substantial group of substance-using individuals[356], it is vital to determine which susceptible individuals will eventually transition into full SUD.

Furthermore, among those diagnosed with SUD, there is a huge treatment gap. Epidemiological data indicate that 19 out of 20 individuals classified as needing treatment for SUD do not think that they need it[357], and this low perception of treatment need tends to persist over time[358]. Multiple factors likely drive this low perception, including minimization of the signs/symptoms of dysfunction associated with substance use, fear of stigmatization[359], and possibly neurocognitive impairments that might affect insight[360,361]. Thus, it is vital to develop and validate biomarkers that can help predict who is more likely to engage and succeed with treatment.

The area of neuroimaging has attracted the greatest attention in the search for biomarkers in SUDs[362,363], for several reasons. First, there are now well-established substance-related brain circuitry changes that involve: a) disruption in executive control, underpinned by dysregulation of prefrontal-subcortical processing, and b) increased salience processing of substance-related stimuli, spanning subcortical and cortical structures[364]. Second, neuroimaging can be used to integrate mechanistic models of substance effects (e.g., increasing dopaminergic tone via the transporter[365] or vesicular sources of intracellular dopamine[366]) with adaptations of brain systems to repeated use (e.g., decreased dopamine receptor availability and release measured with PET), which are some of the most reliable findings in the addiction literature[367,368]. Third, some studies support the idea that individual differences in neuroimaging assays may be of sufficient effect size to be used for predictive purposes[369]. On the other hand, several studies show clear evidence of limited associations between brain and behavior[370], and even large-scale studies show only modest correlations between psychopathology and structural or functional brain characteristics[371]. Despite these challenges and uncertainties, several studies have successfully used neuroimaging markers to predict important substance use outcomes.

Susceptibility biomarkers of transition to problematic use

In one large cohort study, transition from no use to frequent drinking in early to mid-adolescence was predicted by blunted activity of the medial orbitofrontal cortex during reward outcome[372]. Also in adolescents, structural characteristics – such as a larger cingulate gyrus – were predictive of resilience to problematic use after 3 years[373]. In a review of 44 longitudinal neurobehavioral studies predicting substance use in youth[374], functional vulnerability markers of substance use – i.e., markers that predict onset of subsequent substance use – included increased fMRI activation during reward feedback and risk evaluation in prefrontal and ventral striatal regions, and fronto-parietal hypoactivation during working memory. Altered neural patterns during response inhibition and differences in structural markers, including smaller fronto-parietal and amygdala volumes and larger ventral striatal volumes, were also observed.

In one examplary study of this approach, occasional stimulant users completed a Risky Gains Task during fMRI and were followed up to three years later to determine whether or not they transitioned to problematic use. Compared with participants who stopped their occasional stimulant use, those who later transitioned to problematic use made riskier baseline decisions after winning feedback, and exhibited lower baseline frontal, insular and striatal blood oxygen level dependent (BOLD) responses to win/loss feedback after making risky decisions[375]. In another study, initially alcohol-naïve adolescents were tested with fMRI during a reward task and were followed for 3 years to determine whether or not they initiated alcohol drinking. Compared with adolescents who

did not initiate alcohol use, those who did displayed increased baseline fMRI activation to loss in the left dorsal striatum (putamen) and right precuneus[376]. Finally, a study used connectome-based predictive modeling with leave-one-out cross-validation to uncover stress-linked connectivity patterns that differentiated risky from non-risky drinkers, finding that the stress-linked network profiles of the risky drinkers predicted loss of control of drinking in the entire sample[377].

These brain-based assays complement well-established behavioral predictors of problematic substance use. Investigators have found that non-planning and affect-based impulsivity, as well as reward-related valuation, were predictors of SUD vulnerability[378]. Other investigators have additionally found support for relatively poor control, early substance use initiation, binge patterns of use[379], and lower efficiency of evidence accumulation[380]. However, regardless of whether these neuroimaging or behavioral markers can serve as predictive biomarkers, a fundamental question persists of how these markers can be used in a predictive context. In fact, no study in SUD has used prospectively predictive biomarkers to examine their ability to affect outcomes or guide clinical decisions.

Predictive biomarkers of relapse and abstinence

Among individuals who have already met criteria for SUD, another important goal for biomarker development is the prediction of relapse versus abstinence. Prediction of relapse to substance use has been a major focus for biomarker development in SUD research for some time[381], and several investigators have been intrigued by findings that individual differences on various biological or behavioral measures provide predictive information[382,383], although there is increasing recognition that such outcomes are only a small part of the many possible clinically relevant measures[384], and that a comprehensive approach using complementary outcomes for prediction has been missing.

In a cue-reactivity study conducted among individuals with alcohol use disorder, fMRI activation in the ventral striatum during viewing of alcohol vs. neutral pictures predicted a shorter time to relapse[385], perhaps reflecting a heightened vulnerability to drug cues that culminates in drug-seeking and drug-taking behavior during abstinence. Consistent with this, an EEG study was conducted in a cohort of individuals with cocaine use disorder who were subsequently subgrouped based on length of cocaine abstinence. Results showed that the EEG-measured late positive potential (LPP), acquired in response to viewing cocaine images (and previously linked to craving[386]), showed a quadratic (inverted U-shaped) pattern as a function of abstinence length[387]. These results were interpreted as potentially reflecting an objective biological marker of craving "incubation", where drug-cue reactivity is counterintuitively potentiated after short- and medium-term abstinence[388,389].

In cue-reactivity research, one potentially important consideration is the contrast examined. While many studies have historically tested a standard drug vs. a neutral contrast, a drug vs. a pleasant contrast may be more ecologically valid[390,391]. This latter contrast better reflects diagnostic criteria, for example as specified in the DSM-5, where time, effort and resources need to be allocated toward the pursuit and consumption of the addictive drug at the exclusion of other activities[392,393]. They also better tap into theories of addiction that emphasize a shift in salience and hedonic value from pleasant reinforcement to drug reinforcement[394,395].

Beyond cue-reactivity, other studies have reported that reduced functional resting-state connectivity within the executive control network, and between the executive and salience networks, could serve as a marker of relapse risk[396]. There may also be important clinical outcome predictive effects of brain areas involved in inhibitory control, such as the inferior frontal gyrus, dorsal anterior cingulate cortex, and dorsolateral prefrontal cortex[397], as well as brain areas involved in stress reactivity, such as the ventromedial prefrontal cortex and ventral striatum[398]. For stress reactivity, a recent study of patients with alcohol use disorder first found case-control differences (i.e., ventromedial prefrontal cortex and ventral striatal hypoactivity to stressful, threatening images) (Study 1), and then found that these same imaging phenotypes predicted a faster relapse to drinking in a new sample (Study 2)[399]. The finding of clinical implications in a new sample lends support to this imaging phenotype as a target for biomarker development into the future.

An alternate, but related strategy has been to examine functional and structural correlates of sustained abstinence[400]. A recent systematic review concluded that drug abstinence tracked with increased gray matter volume in multiple cortical regions spanning the frontal, temporal, parietal and occipital lobes. There were also volumetric increases in the insula, cerebellum, hippocampus and thalamus, though not the striatum[400].

Functional studies were relatively less clear, though some evidence indicates changes in subcortical areas such as the midbrain and striatum. For example, an earlier study scanned individuals with cocaine use disorder using a drug-Stroop task that incorporated monetary payouts for correct performance. Results showed that midbrain activation during this rewarded cognitive control task increased from baseline to six-month follow-up, during which participants were abstinent and/or treatment-seeking. Furthermore, the more the midbrain task activation increased from baseline to follow-up, the greater was the reduction in scores on a simulated drug-seeking task[401] that itself has been associated with real-world drug use/severity[402,403] and dopamine D2-type receptor availability[404].

The finding of midbrain activation enhancement to monetary reward in cocaine addiction was since independently replicated: relative to pre-treatment measurements, post-treatment was associated with increased activity in anticipation of reward in the midbrain, thalamus and precuneus; and increased activity in midbrain correlated with one-year cocaine abstinence, while an increase in ventral striatal activity during loss anticipation correlated with fewer negative urine screens[405]. Insula functioning may also play a role, depending on the task: in one examplary study with methamphetamine-addicted individuals in early abstinence, insula fMRI activation during risky decision-making predicted relapse with greater sensitivity and specificity than standard clinical variables (e.g., days since

last use)[406]. Studies like these highlight the utility of imaging phenotypes as complementary markers of relapse prediction, but further development and validation needs to occur before they may be deployed as clinically-actionable biomarkers.

The application of rigorous machine learning approaches to avoid overfitting has provided evidence that it should be possible to use markers for disease stage prediction. In a recent review, a state-of-the-art approach was proposed to develop predictive biomarkers within the context of relapse, which entailed computing connectivity patterns that generated out-of-sample predictions of outcomes[369]. For example, in one of the studies[383], cocaine abstinence was predicted by increased connectivity between frontoparietal and medial frontal networks; increased connectivity among salience, motor/sensory and subcortical networks; and decreased connectivity between these two systems. Importantly, the results were replicated in an external sample, providing some predictive validity. Such studies and perspectives provide a blueprint for addiction biomarker research into the future.

Summary of substance use disorder biomarker research

The development of biomarkers for addiction has been impeded by multiple difficulties. First, as this field is still maturing, study designs have been largely limited to case-control or longitudinal follow-up approaches, and even most longitudinal studies predicting substance use outcomes have not provided additional data or methodologies confirming the predictive value of the measurements. Randomized intervention trials, such as neurostimulation approaches that directly modulate addiction-related neural signatures[407], will be important to use prospectively in order to examine the utility of these markers.

Second, addiction describes the compulsive use of different classes of substances that, while usually acting upon a largely common final neural substrate, have fundamental differences in their mechanisms of action and treatment approaches – even for different classes of "stimulants", encompassing cocaine and methamphetamine[408]. This substance heterogeneity also complicates the search for genetic biomarkers in addiction. For example, as much as 38% of the variation in opioid addiction may be due to genetic factors specific to opioids (i.e., not shared with other substances)[409,410].

Third, different biomarkers may be more appropriate depending on a person's current stage of addiction trajectory. For example, a large body of preclinical work has shown that initial drug-taking may be largely mediated by ventral striatal ("reward") pathways, whereas later-stage addiction may be largely mediated by dorsal striatal ("habit") pathways, and some human neuroimaging work has revealed a similar pattern of results[411-413].

Fourth, arguably more than in other psychiatric disorders, environmental exposure is important, as someone can never become addicted if he/she never tries a particular substance. As an illustrative example, estimates have suggested that as much as 62% of the variance in cannabis misuse was shared with cannabis initiation[412,414], highlighting the importance of substance availability for the eventual addiction phenotype. It should be noted that one exceptional counterexample is the alcohol dehydrogenase genes protecting against alcohol consumption and dependence[415].

Fifth, SUDs do not exist in isolation, but frequently co-occur with other behaviors and mental health conditions that are likely to have a profound influence on various biological markers. For example, most clinical studies of SUDs, by necessity, allow some amount of commonly occurring psychiatric comorbidity, such as depression or PTSD. Such constraints argue against the utility of potentially accessible, scalable and affordable – but largely non-specific – biomarkers such as genetic or blood-based measures, because these kinds of non-specific assays may be difficult to interpret mechanistically.

In this vein, recent work suggests that extracellular vesicle-associated miR-29a-3p plays a crucial role in methamphetamine use disorder and might be used as a potential blood-based biomarker for detecting chronic inflammation and synaptic damage[416]. However, blood-based measures indicating substance-induced metabolic or inflammatory changes[417] may be additionally influenced by poor lifestyle (e.g., lack of exercise, poor diet and disrupted sleep) and other mental health conditions (e.g., comorbid mood or anxiety disorders), and so specificity remains a concern.

Nevertheless, an objective marker of substance use severity, not unlike a blood glucose or hemoglobin A1c measurement, might help to facilitate evaluation of treatment need (among clinicians) and treatment acceptance (among patients), and could be a low-hanging fruit in the search for biomarkers in SUDs if an appropriate biomarker could be devised and confirmed for efficacy.

GENERAL DISCUSSION AND RECOMMENDATIONS

A review of candidate biomarkers for predicting diagnosis and treatment responsivity in ASD, schizophrenia, anxiety disorders and PTSD, MDD and BD, and SUDs, encompassing genetic, molecular, neuroimaging and/or peripheral phenotypes, reveals that most are in the very early stages of development and validation, and, for this reason, an assessment of their clinical utility is premature.

The immature state of the biomarker development in mental disorders is unsurprising, given its many challenges. One of the most fundamental challenges to overcome is that psychiatry research to date has most often relied on case-control designs, contrasting behavioral and/or biological assays between patients with chronic illness and healthy comparison participants. This is even the case for large-scale imaging datasets such as ENIGMA and similar consortia. Such consortia have been, and will likely continue to be, important for summarizing statistically robust group differences and associations in patients and controls, and will have the power to illuminate novel brain-behavior findings that might otherwise remain hidden. Nevertheless, consortia data built from case-control studies are unlikely to deliver clinically applicable biomarkers for relevant clinical indications understood in terms of the FDA, because the constituent case-control studies themselves generally lack an actionable biomarker target (i.e., not diagnosis, but rather susceptibility or treatment response).

Our perspective is that studies should be designed from the outset to have as their designated end goal the development of a biomarker for a particular indication, in the right population for that indication (e.g., CHR for conversion, drug-naive adolescents to predict development of SUD, acute unmedicated psychotic patients to predict response to first-line treatments). In this way, psychiatry as a field can begin to move away from pursuing large studies relying on non-specific big-data approaches, and instead pivot toward designing a pipeline for a given target in a manner more akin to drug development. The Adolescent Brain and Cognitive Development (ABCD) study [418] has the potential to drive new biomarker knowledge on SUD susceptibility, for example. The PRONIA consortium has the potential to advance biomarker development for CHR for psychosis. Even then, it is not the case that massively large datasets are necessarily required for biomarker development; smaller studies could suffice, provided that a particular biomarker produces sufficiently high discrimination accuracy for its indication.

Another fundamental challenge for biomarker development in psychiatry is the heterogeneity of the disorders themselves. The diagnostic criteria for psychiatric conditions continue to rely on constellations of symptoms and signs that group patients together even if they exhibit very different illness presentations. For example, there are ~1,500 combinations of symptoms that result in a diagnosis of MDD[419]. Therefore, the cohorts of individuals we study are necessarily heterogeneous, and samples in which biomarkers are developed may not be representative of the larger population of patients who meet criteria for a given diagnosis. While newer diagnostic and classification systems, which are more quantitative and/or biologically-based[420,421], may help address this concern to some degree, a fundamental impediment to progress pertains to our insufficient knowledge of the human brain, and this likely can only be fully addressed with novel technologies that fundamentally increase the precision of measurement. Moreover, biomarkers will still be subject to potential confounds – including medication status, age and gender, among others – which threaten internal validity. For neuroimaging in particular, there are even more factors to consider, such as variability stemming from the processing pipeline[422].

Despite these formidable challenges, several strategies and recommendations – either considered individually or in combination – may improve sensitivity and specificity in the search for biomarkers of pathogenesis, treatment response, and safety in psychiatric disorders. First, adequately powered collaborative (epi)genetic studies are needed, involving mega-samples of patients who are deeply phenotyped for clinical course and treatment response, thereby allowing for the generation of poly(epi)genic risk in combination with poly-environmental scores. PRS have been developed for many forms of psychopathology, but must continue to be updated and refined as more GWAS data become available; other psychopathologies would similarly benefit from the creation and validation of PRS and related tools. Collaborative efforts would also further allow for the inclusion of biosystems beyond genetics and neuroimaging, such as proteomics, metabolomics[423] or blood transcriptomics[424], as well as potentially integrating some or all of these markers together in a multimodal framework to improve personalization and prediction.

Second, as alluded to above, alternate forms of classification and diagnosis may be useful for conceptualizing and testing potential biomarkers. This includes the investigation of intermediate phenotypes, which are related to the disorders but are more narrowly defined and putatively more proximal to the underlying neurobiological mechanisms (e.g., for anxiety disorders, the Research Domain Criteria "negative valence systems" traits[425]).

Third, long-term and cohort study designs are needed in order to evaluate the longitudinal course of disorder and remission/relapse after treatment, which may be more promising for biomarker development than diagnosis, being a clearer and more actionable target. Mechanistic confirmation may be achieved via experimental approaches that can demonstrate causality (by modifying the neural substrates thought to drive the disease states), such as neuromodulation techniques[426] or translational approaches incorporating animal models[427].

Fourth, studies could include online remote acquisition of selected measures in a naturalistic setting using mobile health (mHealth) tools (e.g., ecological momentary assessment of physiological data[428,429]). The identification of multimodal and multivariate signatures can be accomplished by means of mathematical modeling using artificial intelligence (e.g., machine learning, pattern recognition methods) in a systems biology approach[430,431]. Finally, *a priori* stratification approaches may be employed to clinically test preventive and therapeutic strategies individually tailored to the individual person's biological risk factor constellation.

In conclusion, although the general consensus is that we do not yet have clinically actionable biomarkers in psychiatry, considerable efforts and investments have fostered useful developments over the last couple of decades. We have reviewed some substantial advances made during this time, while also describing the additional work and complications that need to be addressed in order to accelerate and finalize the development and eventual roll out of candidate biomarkers into clinical settings. In doing so, some shifts in priorities may be necessary, particularly moving from diagnostic biomarker studies, which are currently overrepresented in the literature[84], to targeting questions for which biomarkers may be most clinically actionable.

Recent examples highlight difficulties yielding highly accurate classifiers even when rich datasets and strong incentives for biomarker development are available[432], and have specifically emphasized issues with external validation and robustness to sample-specific factors. For a biomarker to be actionable, however, it will need to be clinically predictive at the individual-person level. It will also need to be economically viable, which includes non-prohibitive cost and the ability to deliver unique information that cannot be gleaned with traditional, less expensive alternatives.

These needs will evolve in parallel to the development of novel therapeutics and technologies, and so the menu of biomarker possibilities in psychiatry is likely to expand in the future. Even with the current state of affairs, though, suboptimal biomarker-based predictions may still be helpful for high-stakes applications if they improve upon

what is possible when relying on clinical information alone, in ways that substantively decrease the individual and societal burden of mental illness. Setting specific benchmarks for well-defined target applications that can be used today where possible, in conjunction with developing appropriate funding and partnership mechanisms for end-to-end biomarker development into the future, will be critical to ultimately reap the societal benefits of this critical scientific and clinical endeavor.

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Biomarkers for clinical use in psychiatry: where are we and will we ever get there?

Almost all aspects of psychiatric practice currently rely on assessing the presence and change in symptoms to diagnose and manage patients. Psychiatric disorders are diagnosed based on clusters of symptoms occurring together for at least a minimum period of time, as defined in the DSM-5 and ICD-11. The efficacy of new treatments for psychiatric disorders, and the approval of new medications by regulatory authorities, rely only on changes in symptom severity based on rating scales.

However, most treatments for psychiatric disorders are effective only for about half of patients and, without any predictive tools to guide treatment decisions, the interventions offered to any given patient are typically based on clinician and patient preferences. Given this unsatisfactory state of affairs, it is clear that psychiatry, more than any other specialty in medicine, needs clinically useful predictive biomarkers to advance diagnosis and treatment of patients.

So, what are biomarkers and how could they help? The US Food and Drug Administration - National Institutes of Health Biomarker Working Group defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or responses to an exposure or an intervention". Based on the clinical applications, biomarkers can be classified into: diagnostic biomarkers which aid in the detection of a disease; susceptibility/risk biomarkers for predicting the risk of development of a disease; predictive biomarkers which predict response or non-response to an intervention; monitoring biomarkers which indicate the change in the status of a disease; prognostic biomarkers which aid in prediction of remission or recurrence; and safety biomarkers which predict the likelihood of an adverse event following an intervention.

Biomarkers are used widely to aid in the diagnosis and management of diseases in many medical and surgical specialties. For example, before the discovery of biomarkers, Alzheimer's disease (AD) diagnosis was primarily based on the clinical symptom profile, as the definitive diagnosis required post-mortem brain pathology. The diagnostic process was transformed with the discovery of imaging and cerebrospinal fluid biomarkers which can now be used to confirm the diagnosis of AD in living humans[1].

Given the urgent and pressing need for biomarkers to transform psychiatric practice, the state of the field review of candidate biomarkers in psychiatry by Abi-Dargham et al[2] is most timely. They correctly point out that the "litmus test for biomarkers in psychiatric disorders is their ability to change clinical practice". While their review identifies some promising biomarker candidates for further testing, sadly none has gone through all the stages of validation required for biomarker development, and few (if any) hold the promise of meaningful sensitivity and specificity for adoption in clinical practice. Thus, their conclusion that "we do not yet have clinically actionable biomarkers in psychiatry" is fully warranted.

Needless to say, despite decades of significant investments in biomarker research, the lack of progress in discovering clinically useful biomarkers for psychiatry is disappointing. Abi-Dargham et al[2] discuss fundamental barriers to biomarker research in psychiatry, including excessive reliance on case-control study designs, heterogeneity of psychiatric disorders, insufficient knowledge of the brain mechanisms and functioning, and confounding effects of age, sex and medication status.

Indeed, study designs comparing patients with DSM diagnoses vs. healthy controls have yet to find precise neurobiological/neurochemical alterations underlying symptom expression of psychiatric disorders, a major impediment for targeted discovery of biomarkers. This is not surprising, given the heterogeneity of many DSM-defined psychiatric disorders, as one would not expect the same underlying biological alterations in diverse subgroups of patients. The difficulties in defining the "appropriate phenotype" for biomarker discovery and validation are further compounded by the poor inter-rater agreement for various DSM diagnoses[3] and the presence of comorbidities, medication effects and chronicity amongst other factors.

Furthermore, despite rapid advances in imaging to study structure, connectivity, neurochemicals and their receptors, and functioning of brain, methods to explore several processes occurring at cellular and molecular levels in the brain are not yet feasible. While animal models have been developed for many psychiatric disorders, none meets the triad of face validity, construct validity and predictive validity, thus limiting their utility in providing neural insights into these conditions. For these reasons, our ability to gain a full understanding of neurobiological and neurochemical alterations in brains of people with psychiatric disorders remains very limited.

Given these challenges, will we ever see biomarkers that are relevant for clinical use in psychiatry? Abi-Dargham et al[2] offer some suggestions for advancing biomarker discovery, such as focussing on promising biomarker candidates identified in their review, designing studies with an explicit goal of discovering biomarkers for a particular indication, embracing alternate forms of classification for testing potential biomarkers in subgroups of patients based on neurobiological features, adequately powered epi/genetic studies of mega-samples well characterized in clinical course and treatment response, and *a priori* stratification approaches to test preventive and therapeutic approaches. These are all useful avenues to pursue for biomarker research.

In addition, advances in the use of human-induced pluripotent stem cell (iPSC) technology[4], especially the iPSC-based three-dimensional (3D) tissue engineering as an *in vitro* model for diseases[5] and CRISPR-Cas9 gene editing, should be leveraged to interrogate and understand molecular mechanisms underlying psychiatric disorders in order to facilitate biomark-

er discovery. As well, standard data collection protocols should be developed for deep clinical phenotyping, cognitive assessments, biological sampling, and electrophysiological and imaging procedures, to enable pooling of data from centers around the world.

The AD Neuroimaging Initiative (ADNI) is an exemplar of such effort[6]. ADNI began in 2004 with substantial public-private partnership funding that allowed academic centers internationally to standardize data collection and pool data, which led to discovery of biomarkers for AD. Similar initiatives in psychiatry, such as the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression (EMBARC) project, the Canadian Biomarker Integration Network in Depression (CAN-BIND), the Personalized Prognostic Tools for Early Psychosis Management (PRONIA) Consortium, and the planned longitudinal cohort study by the recently launched BD[2] Integrated Network[7], are clearly steps in the right direction.

Moreover, industry-sponsored phase 2/3 clinical trial programs that ascertain the efficacy of new drugs for psychiatric disorders generate vast amounts of treatment data. These data could be a huge resource for biomarker discovery if the trials implement standardized data collection protocols that include deep clinical phenotyping and biological sampling, and the data are made available for pooling with other networks.

Looking to the future, the probability of discovering diagnostic biomarkers that map precisely to specific DSM-5 disorders is very low, given the heterogeneity of the disorders and the symptom overlap among them. However, the emerging evidence reviewed by Abi-Dargham et al and the continuing advances in research methods for biomarker discovery offer a ray of hope that susceptibility markers for disease conversion and predictive biomarkers for treatment response will become a future reality in psychiatry.

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Promising approaches in the search for biomarkers of bipolar disorder

Abi-Dargham et al[1] highlight the critical gaps that exist in the validation of candidate biomarkers of major psychiatric disorders. They point out that one of the problems of several large consortia studies has been the absence of "actionable biomarker targets", as studies have largely been designed to identify between-group differences and/or associations among measures rather than biomarkers for specific purposes such as risk prediction or treatment response. Further problems are the considerable heterogeneity of many of the major psychiatric disorders and the insufficiently precise measurement technologies. The authors make several recommendations regarding approaches that should be taken in future biomarker discovery and validation studies. One such approach is the focus on intermediate phenotypes that reflect underlying pathophysiological mechanisms better than diagnostic categories of illness.

I would like to provide examples of how this approach can be implemented in the study of biomarkers of bipolar disorder. Probably because of the complex clinical presentation of this disorder, it has been especially difficult to identify neurobiological markers that reflect underlying pathophysiological mechanisms. I would argue, however, that it is possible to begin to meet this challenge by focusing on the study of neurobiological mechanisms underlying some key constructs that characterize the defining feature of bipolar disorder, i.e. mania/hypomania.

A well-replicated literature indicates that mania/hypomania is characterized, and its onset and associated functional impairment predicted, by elevated reward sensitivity and goal overvaluation[2], and impulsive decision-making and behavior[3]. These characteristics are closely associated with other clinical features of mania/hypomania, such as increased energy/reduced need for sleep, and exuberant/irritable mood. Focusing on those two characteristics is thus a way to identify the neurobiological mechanisms underlying mania/hypomania.

The above characteristics can be triggered within reward expectancy contexts in individuals with bipolar disorder[2]. Two such reward expectancy contexts that can be modeled in experimental paradigms are: a) uncertain reward expectancy during goal (reward) pursuit, where the probability of an immediate future reward is varied and uncertain, and where potential future rewards will be overvalued by reward sensitive/goal overvaluation prone individuals[2]; and b) intertemporal decision-making, where a choice is made between an immediate smaller vs. a delayed larger reward option, based on the subjective value of these two options, and where reward-driven impulsive decision-making and behavior (i.e., choosing the often more disadvantageous immediate smaller reward) can be triggered in more impulsive individuals. Uncertain reward expectancy and intertemporal decision-making are thus ideal contexts for examining the neurobiological mechanisms underlying reward sensitivity/goal overvaluation and reward-driven impulsive decision-making and behavior.

Dopamine transmission abnormalities likely underlie predisposition to the above key features of mania/hypomania, since amphetamine can induce mania/hypoma-

nia, and antipsychotic medications used to treat or prevent recurrence of mania/hypomania impact dopamine transmission[4]. Moreover, the prefrontal cortical-striatal reward neural network, which has been implicated in bipolar disorder and predisposition to mania/hypomania[5], has extensive dopamine projections: midbrain ventral tegmental area to ventral striatum (mesolimbic), midbrain substantia nigra pars compacta to dorsal striatum (nigrostriatal), and ventral tegmental area to prefrontal cortex (mesocortical) pathways.

Furthermore, amphetamine-induced ventral striatal dopamine release was positively associated with increase in mania/hypomania in adults with bipolar disorder vs. non-psychiatric control participants[6]; and a large rodent literature associates elevated reward network ventral tegmental area dopamine transmission with reward-driven impulsive behavior, as well as other features of mania/hypomania, such as reduced sleep and increased energy[4].

Together, these findings indicate that the combination of specific reward expectancy paradigms and multimodal imaging approaches examining reward expectancy-related neural network activity and underlying dopaminergic modulation is a promising way to identify biomarkers reflecting neurobiological mechanisms predisposing to mania/hypomania.

Bipolar disorder has also been conceptualized as a disorder of energy regulation[7], involving high levels of mitochondrial dysfunction and oxidative stress that might result from elevated dopamine transmission. Elegant translational work in mice and humans has shown that sustained elevated dopamine synthesis results in elevated cytosolic dopamine, which in turn leads to increased metabolism of dopamine by monoamine oxidase[8]. In this process, monoamine oxidase anchors to the outer mitochondrial membrane and transfers electrons generated by dopamine deamination into the mitochondrial inter-membrane space, increasing electron transport chain activity and supporting elevated dopamine synthesis and release. Increased metabolic demand can, however, ultimately lead to impaired mitochondrial function and a toxic cascade in which elevated oxidative stress-induced mitochondrial dysfunction results in cytosolic dopamine oxidation, with elevated cytosolic dopamine further contributing to mitochondrial oxidative stress[9]. Thus, elevated dopamine transmission and associated mitochondrial dysfunction is a putative mechanism underlying the energy regulation dysfunction characterizing mania/hypomania in bipolar disorder.

These examples provide possible approaches that can be adopted by future studies aiming to identify biomarkers reflecting core neurobiological mechanisms underlying key features characterizing and predisposing to mania/hypomania. An important point to note, however, is that these features, especially reward-driven impulsive decision-making and behavior, are associated, at least in part, with other disorders, such as substance use disorders. Thus, these approaches will likely yield biomarkers that are not necessarily specific to a given psychiatric disorder as currently defined by the DSM-5, but instead reflect neurobiological mechanisms underlying constructs that cut across different diagnostic categories.

This transdiagnostic approach accords with the Research Domain Criteria model, where the two reward expectancy contexts described above link with two subconstructs of the Reward Valuation construct of Positive Valence Systems. As Abi-Dargham et al highlight in their paper, a given DSM-5-defined disorder may be associated with several different biomarkers, each reflecting a neurobiological mechanism related to a transdiagnostic construct, which may promote a move toward biologically-based classification systems in psychiatry.

Clearly, there is a need for extensive work replicating findings in independent samples to ultimately provide robust and reliable biomarkers of any given disorder. Yet, I remain hopeful that with increasingly sophisticated neuroimaging methodologies (e.g., higher field strength magnetic resonance imaging), alongside better animal and cellular models, there is now an opportunity to elucidate neurobiological mechanisms of key transdiagnostic constructs and provide robust biomarkers to help shape new classification systems. This will yield targets to aid risk identification and help develop new interventions.

As Abi-Dargham et al note, this is not only a major scientific goal in our field, but is also a critical clinical mission to improve the health and well-being of all of those suffering from these debilitating and yet common illnesses.

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Balancing the beautiful and the good in pursuit of biomarkers for depression

The overview by Abi-Dargham et al[1] offers a perspective on psychiatric biomarker development primarily based on the classical forward translational model. This approach, currently prioritized by the US National Institute of Mental Health, postulates a linear path from first identifying a biological pathological process through to development of an intervention that both engages the

pathophysiologic target and leads to clinical improvement.

This model reflects the beauty of translational neuroscience in its most pure form. When successful, it brings great intellectual satisfaction and has the added benefit of enabling a clear explanation for clinicians to use to bolster their treatment recommendations to patients, thereby building confidence in the intervention for all involved.

The overview outlines several novel areas of biomarker investigation for mood disorders, though all examples still stand far from the essential third (external validation) and fourth (clinical utility) stages of development.

From our vantage point, there are three key clinical questions to prioritize in biomarker development for major depressive disorder (MDD). First, the greatest clinical utility that biomarkers can offer would be to match individuals to the treatment most likely to be efficacious, without harmful effects, commonly characterized as "precision medicine". Precision medicine is driven by the variability of therapeutic outcomes within the context of a specific diagnosis. There is little controversy around this goal, yet the bulk of biomarkers for MDD to date have focused on distinguishing patients with MDD from healthy controls. This distinction has little clinical relevance, given that non-depressed people do not present to the clinic for care.

Second, the primary diagnostic challenge in assessing a patient who presents with a depressed mood is the differential diagnosis of MDD versus bipolar disorder, not versus "non-depressed". A biomarker that could distinguish these two mood disorders would have high clinical utility, as it would directly inform treatment choices that differ and carry different levels of risk. This differential diagnosis is of greatest importance for adolescents and emerging adults, for whom a major depressive episode may be the presenting mood complaint, yet the life history is too short to have experienced hypomania or mania, and for whom the initiation of an antidepressant medication in the absence of a mood stabilizer when needed could result in tragic consequences.

Finally, prognostic biomarkers of MDD course would have great clinical utility for care planning and as targets for intervention. Despite clear clinical evidence of a subset of patients with MDD who have a progressive, deteriorating course of illness that requires treatment with maintenance electroconvulsive therapy or deep brain stimulation, the field has suffered from a severe underinvestment in biologically-informed longitudinal studies of MDD that might identify biomarkers of poorer prognosis and increasing treatment resistance. Furthermore, the majority of mood disorder patients being treated today receive antidepressant medications for much longer durations than in the past, but the potentially adverse impacts on disease course of such open-ended neurochemical modulation is almost entirely unknown. Development of biomarkers that indicate probable MDD recurrence, supplemented by behavioral measures, could inform decision-making regarding maintenance or tapering of treatment, and guide the development of interventions targeting the recurrence-risk biology.

As the primary organ of interest in mood disorders, characterizing the state of the brain as a component of biomarker development cannot be overstated. Blood-based inflammatory and metabolomic markers have been demonstrated to modulate core neurocircuits in MDD[2,3]. Characterizing anatomical and functional neurocircuit states within studies of treatment-selection biomarker development, and linking them to clinical features, may also inform additional strategic reverse translational mechanistic studies, enhancing the likelihood for identifying impactful targets for investigation[4-6].

Given their high potential clinical utility, how should the field approach developing treatment-selection biomarkers for patients with MDD? The classical approach of identifying a pathological target and engineering agents to engage that target is the one that offers the greatest long-term pay-off, as it brings mental disorders into line with medical disorders for which the pathophysiology is more clearly defined. But, should this be the only way forward for identifying treatment-relevant biomarkers[7]? The overview by Abi-Dargham et al suggests that the promised land for the application of forward-translation biomarkers is very far off into the future. What can be done today that could yield more rapidly applicable biomarkers with high clinical utility?

We believe that there is enormous biomarker discovery value that can derive from the highly divergent mechanisms of action of the existing MDD treatments and the heterogeneity of patient responses to those treatments. Patients may do poorly with psychotherapy and wonderfully with a selective serotonin reuptake inhibitor, and vice versa. Previous studies have already demonstrated that such outcomes reflect not two different brain networks but different states of the same network[4,5,8], suggesting that classical forward translation approaches alone may prove inadequate. Further, patients showing no response to one class of medication may achieve remission with switch to an alternative class or after addition of an atypical antipsychotic or lithium, while others only improve after receiving a course of ketamine or a neuromodulatory approach. Mechanistic changes that lead to improvement with each of these treatments likely differ, even if, as hypothesized, they all ultimately lead to a final common pathway of enhanced synaptogenesis or other modes of neuroplasticity at whichever depression "brain state" they are introduced.

Therefore, critical to the ultimate selection of the "right" psychotherapy, pharmacotherapy or neuromodulation therapy is a deeper understanding and characterization of a patient's current brain state and what renders a patient unable to respond to a treatment or to lose response to a treatment that was previously effective. Differential responses to invasive and non-invasive forms of neuromodulation have particular explanatory power. In fact, in addition to identifying brain states of response to the different forms of stimulation, activity within networks contributing to those states can be directly modulated by the intervention, thus informing a mechanistic forward translational approach to biomarker development[9].

This rich mix of a variety of effective treatments with differing biological effects, combined with the individual variability of response to specific treatments, offers great value for revealing biomarkers with high clinical utility. Yet, investment in such approaches has been minimal. We suspect that this under-investment is due to the absence of mechanistic hypothesis testing in exploration-based, association-driven

methods. Applying a reverse engineering approach, working backwards from treatment outcome heterogeneity to identify treatment-selection biomarkers (which may not have any direct causal role in the pathophysiology of disease), has already proven to be valid and potentially productive[4-8]. The clinical utility of such biomarkers rests on their potential to allow practitioners to move beyond the current trial-and-error standard, thus shortening time to remission and minimizing exposure to potential adverse effects. Application of treatment-selection biomarkers would further transcend the concept of "clinical stages" of treatment resistance, enabling patients to proceed immediately to more intensive treatments that, under current care models, are withheld until the patient demonstrates non-response to standard treatments.

Researchers should remain mindful of the seductive nature of the classical forward translational medical models that proceed linearly from a defined pathophysiology to a treatment. There is truth in their beauty, but the day of their emergence for mood disorders remains distant. In the meantime, there are other, perhaps less intellectually satisfying, approaches that may nevertheless lead to significant gains in treatment selection and mitigation of disease course. Explaining variability in clinical outcomes via biomarkers integrated within well-conducted comparative treatment trials has the greatest immediate potential to inform decision making within a precision medicine framework. Neglecting to invest in and recognize the value of these more imminently impactful, clinically actionable biomarker strategies is a disservice to the millions of patients who are suffering now and will continue to suffer into the future.

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The time is now to start evaluating biomarkers in the clinic

Despite considerable investment, no biomarkers are regularly in use to help people with mental health and substance use problems. Yet, there may be opportunities to evaluate biomarkers in the clinic, and potentially change clinical practice and care. Abi-Dargham et al[1] provide a comprehensive account of the current state of candidate biomarkers in psychiatric disorders. Their effort is wide-reaching and impressive, describing promising candidates and gaps in autism spectrum disorder, schizophrenia, anxiety, post-traumatic stress disorder, mood disorders, and substance use disorders.

It is now time for our field to stop letting perfect be the enemy of the good. We are often divided (still sometimes even about whether some of the disorders we take care of have biological underpinnings at all) and highly self-critical. This is often healthy, but at times self-defeating. Prediction of outcomes, events, or treatment response does not need to be perfect. It needs to be better than chance, to provide more benefit than harm, and, where possible, to be cost-effective. Cost-effective where possible, because sometimes certain societal or other benefits, even if more expensive, may be considered worthwhile depending on value systems. Here I propose a path forward for the most promising biomarkers identified by Abi-Dargham et al, using the example of the striatal connectivity index (SCI) in schizophrenia.

The authors identify the SCI as a particularly promising biomarker for evaluating treatment response (and resistance) to antipsychotic medication in first episode psychosis[2,3]. Concerning Step 1 of biomarker development (the targeting of the clinical question), response to antipsychotics is of undebatable importance, because non-response often leads to hospitalization, and sometimes death. As to Step 2 (internal validation), it is clear that this biomarker is targeting the underlying process, due to rigorous study design that utilized algorithmic treatment, participants with limited or no antipsychotic exposure, and testing using different antipsychotics. Step 3 (external validation) was successful, using an even higher bar, testing in a chronic schizophrenia sample. In addition, the original papers examining the SCI showed that it was associated with days of inpatient hospitalization, creating an even stronger argument for its potential, via association with a "high stakes outcome". There are implications with this biomarker for getting first-episode patients to clozapine faster, which can be life-saving for some, given that those who do not respond to conventional antipsychotics could be identified at their first episode of psychosis. So, what is left to do? Evaluate clinical utility, i.e. Step 4.

The time is now to conduct randomized controlled trials that directly assess the utility of promising biomarkers in ordinary clinical practice. Sticking with the SCI example, this could mean conducting a randomized controlled trial of early psychosis patients stratified via their SCI. This trial could explore whether early use of clozapine in those identified by the SCI as likely non-responders to conventional antipsychotics actually has a positive impact in terms of clinical improvement, e.g. by reducing hospitalization days, thus helping understand whether the SCI is clinically useful. That is, does the use of the SCI in clinical practice lead to better outcomes for this group of patients than usual care? While this could be interpreted as a question sim-

ply of earlier clozapine utilization, it is not about earlier utilization for all. Rather, the biomarker would guide earlier utilization by clinicians only for that group of patients with a SCI value that indexes likely non-response to conventional antipsychotics. A trial such as this one, if successful, would have the potential to change prescribing and regulatory guidelines specifically for patients assessed by the SCI as likely not to respond to conventional antipsychotics. This could mean that a biomarker in psychiatry would have real-world impact, when currently there is no such case.

An opportunity could exist in the same trial to incorporate melanocortin 4 receptor genotype, which confers a nearly five-fold increased risk of weight gain in relation to antipsychotic exposure[4]. Similarly, while agranulocytosis is rare, an allele in the HLA-DQB1 gene carries a ~15 fold increased risk of this potentially lethal event[5]. Therefore, one could stratify patients on multiple biomarkers, maximizing potential gains and minimizing potential harms, in the same clinical trial. Cost-effectiveness analyses could further strengthen the case. Saving even one day in hospital would likely offset the costs of the magnetic resonance imaging (MRI) and genetic tests.

If we are serious about getting biomarkers into clinical practice, the biomarker/biological field and the psychiatric services field should work together for successful implementation. Engaging patients and family members with lived experience would be important. A parent who has witnessed his/her teenager or young adult child recovering from early psychosis thanks to the use of a given biomarker would be a powerful advocate, providing a lived experience voice that could help support the scale and spread (i.e., the implementation) of that biomarker into clinical practice. In addition, engaging policy makers who may have a say in health system incentives early in the process, as well as the relevant regulatory agencies, would be wise.

Practice change is notoriously difficult. Even the implementation of measurement-based care in mental health clinics, e.g. using a scale routinely to guide treatment decisions, may be a challenge. If we have the data to bring MRI results or a genetic test into the clinic, the challenge of implementation may be even greater. Fortunately, in relation to the SCI biomarker example in early psychosis, the presence of networks of clinics that are part of a learning health system – e.g. via EPI-NET in the US, as well as similar initiatives in Canada, Australia and elsewhere – could be as good of an environment as we might hope for to propel successful translational efforts into clinical practice. In that sense, the time is now as well, and the broader notion of precision medicine, implementation science, and a learning health care system has been described[6], and could be applied in psychiatry.

Much of the focus of the comprehensive review by Abi-Dhargam et al is on adult psychiatry. However, the peak age of onset of mental illness is 14.5 years of age[7]. When describing or planning for biomarker evaluation in anxiety or depression, where many cases have their onset during adolescence, one could argue that most studies should be conducted at that timepoint in the lifespan. The dynamic evolution of mental illness at that timepoint also offers primary and secondary prevention opportunities. For instance, 75% of all index psychotic episodes have already presented for mental health care earlier in life for other mental illness[8]. Therefore, capitalizing on our knowledge of the windows of brain development that are paired with windows of onset of mental illness (and substance use) could assist in more optimal study design related to timing.

Furthermore, funders might consider investing in "master observational trials", which have been dubbed "a new class of master protocol to advance precision medicine"[9], currently emerging in oncology. The master observational trial is a prospective, observational trial that broadly accepts patients and collects comprehensive data on each. All of the information is tied together in a prospective observational registry using standardized reporting and metrics. The goal of these trials, which would be of tremendous benefit to psychiatry, is to harness the power of real world data to advance biomarker discovery and test the clinical utility of precision-based and personalized medicine.

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Searching for biomarkers in the fluidity of mental ill-health

How close are we to establish biomarkers of psychiatric disorders? Still far, according to Abi-Dargham et al's review of the state of the art in some of the most prevalent and debilitating mental and neurodevelopmental conditions[1]. The authors provide a balanced appraisal of current evidence, which exposes the shortcomings of emerging biomarkers such as problems to capture between-subjects heterogeneity within psychiatric diagnoses, limited sensitivity and specificity, and the hindered transition from in-sample discovery to external and clinical validation stages. To change the landscape, they propose enabling adequately powered studies that are purpose-built for biomarker discovery (versus traditional case-control approaches), prioritizing long-term cohort studies supported by *ad-hoc* mechanistic experiments, and leveraging novel phenotype ontologies and digital tools to refine

a priori stratification (i.e., to parse heterogeneity) and the reliability and validity of measurement. These are bold and sensible solutions, and I will highlight here potential enablers and additional challenges they may entail, drawing from examples stemming mostly from the substance use disorders literature, but also from recent studies on schizophrenia and bipolar disorder.

A point that emerges from Abi-Dargham et al's review is that collaborative, multimodal studies (e.g., omics, multiple neuroimaging modalities, cognitive and psychosocial measures) including flexible prediction workflows are a promising approach to discover biomarkers for psychiatric disorders. There are encouraging examples of this methodology in the context of escalation of substance use. In a large-scale, multi-site European cohort study (the IMAGEN study), machine learning-based structural and functional neuroimaging indices of fronto-parietal executive function network alterations predicted escalation of binge drinking across middle adolescence both in-sample and using cross-validation[2]. This evidence can directly inform the design of time-sensitive and executive function-targeted prevention programs during this critical developmental period.

Although the field of neuroscience-based prevention is still in an early stage, emerging interventions targeting executive control or using neuroscience-informed psychoeducation have shown positive initial results[3]. There is also an increasing effort to incorporate pragmatic, biologically-informed mechanistic measures of treatment response into clinical trials of cognitive training and remediation for substance use disorders. For example, electroencephalography indices of frontal midline theta changes, linked to executive function, have been successfully used as a marker of therapeutic response to mindfulness-based emotion regulation training for opioid misuse[4]. These mechanisms-informed trials have great potential to improve our understanding of the neurobiological signatures of active treatment ingredients, and thus inform development of predictive biomarkers for the treatment of psychiatric disorders.

Emerging biomarker research will likely leverage on rapid technology advance. The neurobiological alterations that underpin several psychiatric conditions – such as schizophrenia, substance use, mood, anxiety, and stress-related disorders – hinge on the interaction between executive function, reward processing and emotion regulation networks. These networks can now be precisely measured and manipulated using human brain connectomics and non-invasive brain stimulation techniques respectively, as well as chemo- and opto-genetic tools for translational animal experiments. Studies using these novel techniques are generating detailed neural and neurochemical maps, and sophisticated insights into the valence and directionality of circuit-level alterations associated with mental disorders severity and progression[5]. This creates an opportunity for targeted, hypothesis-driven studies that investigate common and differential circuit-level alterations across different disorders. This targeted approach can contribute to expedite the efficiency and improve the specificity of brain biomarker discovery.

At the behavioural level, digital technologies and advanced psychometric modelling are also improving the precision, specificity and validity of cognitive measures, which sit at the interface between the pinpointed neural networks and day-to-day behaviour and symptom expression[6]. These cognitive measures are better poised to detect individual differences in the cognitive mechanisms linked to the executive function, reward processing and emotion regulation networks, and thus can be exploited to refine behavioural phenotyping and improve *a priori* stratification approaches for biomarker discovery.

But still, will we be close to the target? Key challenges are likely enduring. Mental disorders are multifactorial and fluid. Taking progression of alcohol use in the IMAGEN study as an example, while multimodal neuroimaging markers were significant contributors and optimized the overall prediction workflow, psychosocial life experiences such as romantic break-ups were the most influential predictor of escalation of consumption[2]. The pre-eminence of psychosocial over biological factors exposes the importance of integrating biomarkers with subjective experiences. In the future, brain computer interfaces could aid this integration by linking biological readouts with subjective reports *in situ*. This may contribute to disentangle between-subjects heterogeneity, as certain readouts could be meaningfully linked to influential psychosocial factors in some people but not others.

In addition to between-subjects differences, there is increasing recognition of the relevance of high intra-individual variability in mental disorders. For example, people with substance use or bipolar disorders show substantial fluctuations in the neural systems and cognitive processes underpinning executive function, which are linked to meaningful clinical outcomes such as reduction of substance use or response to cognitive remediation interventions[7]. This phenomenon speaks to the importance of considering not only static but also dynamic biomarkers sensitive to state-related fluctuations in cognitive and neural networks function. It also suggests that, from a methodological standpoint, we should strategize development and harmonization of protocols that maximize test-retest reliability and enable tracking of dynamic biomarker trajectories that can reliably predict outcomes (and minimize error) across time.

A related aspect of state-related variability is that, despite the scientific and intuitive appeal of mechanisms-driven predictive biomarkers, the efficacy of treatments for mental disorders may often rely on non-specific motivational factors. For example, cognitive bias modification (i.e., redirecting biases away from maladaptive cues) is a validated intervention for alcohol use disorder which has a clear-cut active mechanism involving a reduction of the appetitive value of alcohol-related stimuli. However, general treatment motivation (i.e., treatment seeking status) is a better predictor of the efficacy of the intervention than this specific active mechanism[8].

Another important challenge for establishing biomarkers of psychiatric disorders is the frequent presence of comorbidities. Notably, some of these comorbidities may impact the identification of biomarkers in unexpected ways: instead of amplifying the ability to detect maladaptive markers, they can obscure the detection of these markers. For example, some putative peripheral biomarkers of schizophrenia, such as pro-inflammatory interleukins and elevated levels of anandamide-related endocannabinoids, are not observed in people with schiz-

ophrenia and comorbid cannabis use disorder[9]. This finding highlights the malleable nature of biological markers in the context of highly prevalent comorbidities (i.e., substance use disorders) which co-occur not only with schizophrenia but also with several other neurodevelopmental and mental disorders.

Altogether, the insights from the Abi-Dargham et al's review[1] and the advances, limitations and opportunities discussed here suggest that, along with the excitement that novel approaches and technologies will likely bring to the biomarker discovery field, we need to remain mindful of the inherent challenges, particularly the biopsychosocial nature of psychiatric disorders and the multiple sources of inter- and intra-individual variability influencing clinical outcomes. We also need to work towards research endeavours that are better poised to address these challenges via collaboration between biological and psychosocial scientists, concerted large-scale international efforts to improve and harmonize both biological and behavioural measures (as well as their underpinning ontologies), and incorporation of people's living experiences into our definitions and measurements of biomarkers.

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Discovering informative biomarkers in psychiatry

Arguably, there is not a more important theme in psychiatry today than biomarkers. We don't have many; some would say, none. The panel of authors of Abi-Dargham et al's paper[1] is eminent and broad, and they have been capable to summarize our current needs and advise on developing and using biomarkers in our field.

The authors note a gap in the biomarker validation process, i.e., in demonstrating that each individual biomarker is valid, reliable and useful. They are certainly correct in this respect. For diseases of the cardiovascular and metabolic systems, we have lots of biomarkers. Some of them were identified before they became useful, so that, once ready for validation, the data were already collected to analyze. In psychiatry, we still have a good deal of data collection to do.

An exceptional model for advancing biomarker discovery is represented by the Framingham Heart Study, a project which was motivated by President Roosevelt's untimely death from cardiovascular disease in 1945 and has been ongoing since 1948[2]. We have untold thousands of discoveries, pieces of data and follow-on innovations in cardiology all deriving in part from this rich, longitudinal, trans-generational, deep phenotyping, cohort study. It has been both the scientific organization and the structure of the effective collaborations which has enabled this project to transform knowledge in cardiology. Also, the idea of the learning health care system[3] was introduced to help clinicians conceptualize how to use the health care system to not only deliver care, but to associate clinical facts and biomarkers to outcomes in order to advance knowledge in the field. These are two models useful in anyone's compendium on biomarkers. But, it is the complexity of unexplained neural biology that makes the work harder and slower in psychiatry.

Within this framework, there are certain principles describing biomarker development within our field that seem secure, several of which are articulated in Abi-Dargham et al's paper. In addition, in psychiatry, the field needs to discover and use biomarkers of brain function, not only of psychiatric diagnoses. It needs to be said that we do not even know if the field has its diagnoses correct, with skepticism in this area fueled by polygenicity and pleiotropy across many disease traits[4]. Psychiatric diagnoses are not biologically founded, and can lead to imprecise conclusions.

The field most critically needs brain biomarkers associated with characteristics of disease constructs: their risk factors, mechanisms, treatment, course and outcomes. The idea of a true cohort study is to use the variability in large subject samples to define true patterns of the expression of a biomarker within a brain disorder, rather than cripple the clinical outcomes with biased samples. We may not be accustomed to the necessary large size of such studies[2], and they may be costly. Costly, however, in the short run, with payoff in their application.

It is important to notice and avoid uncritical research on biomarkers which result, not from the illness, but from the chronic effects of drugs used to treat the illness. Biomarkers around dopamine functions in psychosis and noradrenergic functions in depression fall into this category, unless the trial design allows treatment vs. disease to be distinguished. It is true that sometimes the strongest hypotheses develop from therapeutic categories, e.g. research on dopamine in schizophrenia, but their validation must involve the use of strategies such as recruitment of drug-free subjects, animal studies of chronic drug effects and/or testing the biomarker on and off from treatment drugs.

In addition, the idea of applying a biomarker battery, i.e., collecting multiple diverse measures from a target population and clustering them within a single population, is frequently productive. Often, it is too difficult to anticipate or hypothesize which biomarker may really be useful for what, without using a battery of them, as the first step. Application of a full biomarker battery in a particular disorder is informative with respect to what biomarkers cluster with each

other and which cluster with a target outcome, using replication to build confidence in an interpretation.

Indeed, in the Bipolar and Schizophrenia Network for Intermediate Phenotypes (BSNIP) study[5], it was the entire biomarker battery which went into defining the final characteristics of the experimental biomarker-defined entities, which were called "psychosis biotypes". These biotype constructs have provided research with an alternative to phenomenologically defined entities, as a stage in developing final disease categories. Moreover, it is the full biomarker battery which can be applied to distinguishing and understanding defined features of the illness, such as negative symptoms[6].

BSNIP researchers have developed several individual studies, now ongoing, to test the clinical applicability of the above biotype constructs. One such study tests the hypothesis that biotype 1, with its low intrinsic EEG activity, is a biomarker which indicates responsiveness to clozapine; specifically, we test the hypothesis that increasing intrinsic EEG activity with clozapine in biotype 1 will correlate with symptomatological improvement, using the attractor network model[6]. A second study, designed to predict treatment response in early psychosis, hypothesizes that the biotypes will define good (biotype 3), moderate (biotype 2) or poor (biotype 1) response to standard coordinated specialty care (CSC)[6]. In each of these examples, a double-blind trial of the biomarker observation (now ongoing) is necessary, and its application can only be supported if this is done with rigorous design.

There is no doubt that considerable hard work will have to go into the study of biomarkers in psychiatry before we are able to bring them to a clinically useful place. Yet, the validation of biomarkers, as reviewed in Abi-Dargham et al's paper, can be so decisive for the future of our field that these studies need to be conducted. Costs have to be born. Yes, wisely; but urgently.

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The curse and opportunity of heterogeneity in the pursuit of psychiatric biomarkers

Abi-Dargham et al[1] provide a comprehensive overview of the state of biomarker research in psychiatry. Over the past two decades the field has witnessed a remarkable increase in studies aiming to identify biomarkers for mental disorders, facilitated by large-scale funding initiatives (e.g., by the US National Institute of Mental Health) and advancements in acquisition technologies and computational approaches. However, a clinically actionable biomarker is yet to be identified for any mental disorder. This is a timely opportunity to reflect on some of the barriers to and future directions for developing clinically useful biomarkers in psychiatry.

The authors define different stages of development of biomarkers: biomarker identification, internal validation, external validation, and demonstrating clinical utility[1]. Most of the identified biomarkers have not moved beyond the second stage, with few biomarkers externally validated in independent datasets. The few studies that have looked at predictive performance of biomarkers in external validation samples have often used small sample sizes, which may lead to systematically inflated predictive performance estimates[2]. The sparsity of studies with external validation and sufficiently large sample sizes reflects the pilot-study stage of research in this area, where results can be interpreted as promising but still in their infancy.

In line with the authors' conclusions, I believe that the current approach to identifying diagnostic biomarkers (mostly case-control studies within a single mental disorder) is unlikely to lead to a biomarker-based or -assisted diagnostic framework for mental disorders. This judgment is based on the observation that most individual neuroimaging, genetic and peripheral markers have relatively small effect sizes, explaining an insufficient amount of variance of the disease phenotypes. Even when, for instance, multimodal neuroimaging measures are combined with the hope to obtain larger effects, diagnostic accuracy often remains limited[3]. The small effects and limited diagnostic ability of identified biological abnormalities can be explained by the fact that mental disorders are highly multi-factorial in nature, with a broad set of psychological and environmental factors contributing to vulnerability.

An alternative, or perhaps complementary, explanation can be found in the imprecise measurement of our disease phenotypes. Unlike other medical fields such as oncology, that relies on histopathology for diagnosis, psychiatry is plagued with highly complex and heterogeneous presentations within and across diagnostic categories. Current diagnostic classifications incorrectly assume the existence of syndromes with a fixed set of symptoms identical for all patients. However, persons with different symptom profiles within a psychiatric diagnostic category likely differ from each other with respect to their underlying biology, severity or functioning. For example, recent large-scale studies (N>150,000) have identified a specific symptom profile of major depressive disorder (MDD), characterized by atypical energy-related symptoms. This profile is linked to a unique biological signature – most noticeably a dysregulation of the immune system[4]. Indeed, larger effect sizes for associations of immune and metabolic dysregulations with this specific depression symptom profile are observed than when comparing all patients with an MDD diagnosis to healthy individuals[5]. The common practice of aggregating diverse or even opposite symptom profiles has

hampered the development of clinically useful diagnostic biomarkers of mental disorders.

Furthermore, most identified genetic and (neuro)biological abnormalities are not specific to a single mental disorder[6], making them unsuitable for differential diagnosis, which is arguably a more meaningful objective than distinguishing people with a mental disorder from those who are healthy. For example, the above-mentioned atypical energy-related symptom profile of depression linked to immunometabolic dysregulations is likely not unique to MDD, since similar symptoms as well as immune and metabolic disturbances are observed in other disorders (e.g., bipolar disorder). Therefore, incorporating transdiagnostic symptom or behavioural dimensions as the phenotype of interest has the potential to significantly advance biomarker development, albeit not necessarily facilitating a more accurate diagnosis.

It is important to remind ourselves that the value of identifying biological markers of mental disorders is not restricted to whether or not they can represent useful tools for diagnostic purposes; they may also provide important clues for optimization of existing treatments or development of new interventions. For example, abnormal functional connectivity between the dorsal prefrontal cortex and subgenual anterior cingulate cortex has been suggested to be a core functional deficit in MDD. The effect size of this deficit is too small for it to serve as a diagnostic biomarker. Nonetheless, it has proven to be an important target site for repetitive transcranial magnetic stimulation (rTMS). Recent preliminary work suggests that rTMS can be optimized and individualized by targeting dorsolateral prefrontal cortex sites that display stronger negative functional connectivity with the subgenual cingulate cortex[7], thereby reducing heterogeneity of rTMS treatment outcomes.

Despite suggested strategies to improve diagnostic biomarker identification, I agree with the authors that a shift from a focus on diagnostic biomarkers to prognostic or predictive biomarkers would be appropriate. Identifying prognostic biomarkers of relapse/recurrence or treatment response may be a more fruitful endeavour, as they correspond more clearly to processes involved in the outcome in question (e.g., a biological treatment). Indeed, studies have shown that therapeutic outcomes are often related to pre-treatment brain differences, and that the brain changes as a result of the treatment. Moreover, grouping people based on their response to a treatment may result in more homogeneous samples than those based on a DSM diagnosis, further enhancing the likelihood of deriving clinically actionable biomarkers. Some studies are beginning to show promising candidate treatment biomarkers that have been internally and/or externally validated, including, for instance, EEG biomarkers of response to selective serotonin reuptake inhibitors in patients with MDD[8,9].

Nonetheless, heterogeneity may still exist within groups of treatment responders or those who experience recurrent episodes of mental ill-health, since different underlying mechanisms may lead to the same outcome in different people (most treatments have no clear single mechanism of action). Unfortunately, most clinical trials have not been adequately powered to disentangle this within-group heterogeneity, and future larger-scale clinical trials (e.g., through clinical trial networks), data pooling initiatives of existing trial data, or more flexible trial designs are required.

Another important consideration for future development of prognostic and predictive biomarkers is the extension of predictive models with time-varying predictors, facilitated by recent advancements in machine learning (e.g., recurrent neural networks). Including time-varying biomarkers could enhance predictive accuracy, given that treatment response or recurrence of mental ill-health is often not a static but a dynamic process. Very few studies to date have exploited the time-varying nature of predictor variables, although initial studies are starting to show increased prediction accuracy for treatment response when adding early changes in biomarkers to baseline predictors[8].

In conclusion, even though a clinically actionable biomarker is yet to be discovered, several developments – including larger-scale studies and collaborations (enabling independent validation), advances in statistical methods, and more precise phenotyping – have the potential to accelerate progress in psychiatric biomarker research in the coming years. Harnessing heterogeneity within and across our current diagnostic classifications, and within groups of treatment responders, will be key to future success of biomarkers in optimizing care for the next generation of people with mental disorders.

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The non-ergodic nature of mental health and psychiatric disorders: implications for biomarker and diagnostic research

The ultimate goal of both diagnosis and biomarkers in psychiatry – as in all areas of medicine – is to lead to better outcomes through improved management, tailored as necessary to the individual patient. As Abi-Dargham et al show in their magisterial overview of the field[1], despite a massive research effort spanning half a century, no biomarkers have been identified that have

proven useful and valid enough to change the clinical practice of psychiatry (the authors do not cover dementias, a group of psychiatric disorders where biomarkers are in fact relevant for management).

While the complexity of mental illness is such that even now the field may be regarded to be in its early stages, it is perhaps not premature to examine whether there are fundamental implicit assumptions in this search for valid biomarkers that need to be reconsidered or amended. Here I propose that the temporal structure of mental health and psychiatric disorders is insufficiently captured in the way diagnoses and biomarkers are defined and validated in psychiatry. Specifically, I will argue that the non-ergodic nature of the mind limits the usefulness of constructing biomarkers cross-sectionally. I will outline a research program that can help to address this issue in future investigations.

Without going into mathematical details[2], a system is called ergodic if the variation across components is asymptotically equivalent to the variation within components (i.e., across time). If this is true, the time average and the expectation value of an observable will be the same. This formulation comes from statistical mechanics and was meant to capture systems at thermodynamic equilibrium such as gases. However, it has been widely applied throughout science, and even to groups of human beings and their mental processes.

In psychiatry, the ergodicity assumption implies that one can draw inferences on the way a specific person will behave or respond to treatment (the goal of predictive biomarkers) from a cross-sectional statistical analysis across individuals captured at one point in time: the group average will be the most likely outcome for the individual. Even though this assumption is rarely questioned, it is often obviously false: depending on how payouts are defined, one round of Russian roulette in 100 individuals may yield a good average profit, while a game of 100 rounds of Russian roulette in one individual means certain death.

Much of current biomarker research directly hinges on the ability to make inferences from groups to individuals, because many biomarkers are derived from very large samples of participants assessed only once or at few time points. This is especially true for the largest multinational collaborations collecting genetic (e.g., Psychiatric GWAS Consortium) or neuroimaging (e.g., ENIGMA) data. Ergodicity assumptions are also implicit in much of the work to build up diagnostic systems in psychiatry, such as the DSM-5 and ICD-11, because these systems are meant to optimize reliability in cross-sections of clinical samples. What is worse, these two approaches are compounded because many biomarkers aim at cross-sectional predictions of diagnoses (e.g., polygenic risk scores) which are defined in a way that makes only the most rudimentary reference (through duration or exclusion cri teria) to the time course of mental illness. Therefore, even if rarely made explicit, the success of biomarkers so derived hinges on the presence of ergodicity. What is the evidence here?

Unfortunately, a substantial body of work shows that ergodicity assumptions do in fact not hold for mental processes[3]. Cases in point are the so-called ecological fallacies, in which group data predict the opposite of what is found within individuals. For example, across individuals, higher stress is linked to reduced physical activity, whereas the opposite relationship holds for a given person. A systematic study showed that within-person variability of mood scores exceeded that across individuals several fold[3]. This is not surprising, because the human brain and mind clearly operate very far from equilibrium and exhibit a broad repertoire of dynamics. Thus, biomarker research needs to take this problem seriously and aim to address it in future work.

Fortunately, the desired inference from the group to the individual is sometimes possible even in non-ergodic systems, when deviations from the underlying assumptions are addressed through experimental or statistical methods. In this sense, there is less a black-and-white dichotomy than a "non-ergodicity continuum"[4]. The two main deviations from ergodicity to consider are: a) heterogeneity across individuals and b) non-stationarity of the dynamics across time within individuals. Of these two, inter-individual heterogeneity is well recognized in psychiatry and the focus of much biomarker and clinical development work. For example, randomization in clinical studies is performed precisely to account for unobserved heterogeneity of study participants, in order to make observed differences between a treatment and a control condition applicable to individual responses[4]. Similarly, much biomarker work aims to identify relevant variation not captured by current categorical diagnoses[1]. To optimally address (non)ergodicity, further work on heterogeneity should also aim to capture inter-individual variation irrespective of diagnoses, since these are also potentially problematic. For example, we have found that dimensional descriptors of behavior and neuropsychology are linked to neurofunction across and beyond diagnoses[5].

Even greater transformative potential in biomarker research lies in methods and paradigms to address non-stationarity. The ubiquity of smartphones, the sensors that they contain and that are found in wearables, and new analysis methods now allow research to move out of the laboratory and to capture the time course of psychiatrically relevant parameters within individuals at unprecedented detail and scale[6]. This ecological momentary assessment (EMA) approach drives two qualitative advances in the field: a) it makes within-individual variability accessible and thus uncovers a critical and previously inaccessible dimension to future biomarkers related to mental health, and b) it enables characterizing the environmental context (physical, but especially social) that generates changes in mental status. For example, we have seen strong links between intra-individual reactivity to environmental exposures and mental health risk[7].

The ability to capture the course of symptoms and mental states is especially important for psychiatry, because many mental disorders – at least in their early phases – manifest in the context of life events and crises that overwhelm the individual homeostatic capacity. They may thus inherently reflect critical changes in the underlying mental dynamics that can be captured from EMA time series through methods from dynamical systems theory. This makes essential non-stationarities explicit and allows accounting for them in biomarker research. Even potentially more important, inter-individual variation that predicts such changes in dynamics can and should be sought. For example, we and others have found that variations in dopaminergic genes

influence the dynamical repertoire of brain networks[8]. Finally, a life-span perspective on the temporal dimension of mental disorders is afforded by new machine learning approaches to normative modelling, which can characterize an individual's deviation from a normative developmental timeline as a biomarker supporting early intervention and prevention approaches[9].

Several of these methodological recommendations for future research dovetail with the perspective outlined by Abi-Dargham et al[1]. Taken together, they have the potential to generate significant advances in the predictivity and clinical applicability of biomarkers through addressing obstacles from group to individual inference. Patients, their relatives, clinicians and research are likely to benefit from this.

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Prevalence and trends of common mental disorders from 2007-2009 to 2019-2022: results from the Netherlands Mental Health Survey and Incidence Studies (NEMESIS), including comparison of prevalence rates before vs. during the COVID-19 pandemic

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Up-to-date information on the prevalence and trends of common mental disorders is relevant to health care policy and planning, owing to the high burden associated with these disorders. In the first wave of the third Netherlands Mental Health Survey and Incidence Study (NEMESIS-3), a nationally representative sample was interviewed face-to-face from November 2019 to March 2022 (6,194 subjects; 1,576 interviewed before and 4,618 during the COVID-19 pandemic; age range: 18-75 years). A slightly modified version of the Composite International Diagnostic Interview 3.0 was used to assess DSM-IV and DSM-5 diagnoses. Trends in 12-month prevalence rates of DSM-IV mental disorders were examined by comparing these rates between NEMESIS-3 and NEMESIS-2 (6,646 subjects; age range: 18-64 years; interviewed from November 2007 to July 2009). Lifetime DSM-5 prevalence estimates in NEMESIS-3 were 28.6% for anxiety disorders, 27.6% for mood disorders, 16.7% for substance use disorders, and 3.6% for attention-deficit/hyperactivity disorder. Over the last 12 months, prevalence rates were 15.2%, 9.8%, 7.1%, and 3.2%, respectively. No differences in 12-month prevalence rates before vs. during the COVID-19 pandemic were found (26.7% pre-pandemic vs. 25.7% during the pandemic), even after controlling for differences in socio-demographic characteristics of the respondents interviewed in these two periods. This was the case for all four disorder categories. From 2007-2009 to 2019-2022, the 12-month prevalence rate of any DSM-IV disorder significantly increased from 17.4% to 26.1%. A stronger increase in prevalence was found for students, younger adults (18-34 years) and city dwellers. These data suggest that the prevalence of mental disorders has increased in the past decade, but this is not explained by the COVID-19 pandemic. The already high mental disorder risk of young adults has particularly further increased in recent years.

Key words: Common mental disorders, prevalence, trends, young adults, NEMESIS studies, COVID-19 pandemic, anxiety disorders, mood disorders, substance use disorders, attention-deficit/hyperactivity disorder

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In recent decades, it has been suggested that an increasing proportion of the population is developing poorer mental health[1,2]. If there is indeed an increase in the prevalence of mental disorders, this is relevant to health care policy and planning, owing to the high burden associated with these disorders[3].

Mood, anxiety and substance use disorders are common across the world, but studies examining trends in their prevalence in representative samples of the adult population have provided mixed findings. Some studies have found an increase in the prevalence rates of mental disorders or mental health problems over time[4-13], while others have reported stable prevalence rates[14-23]. No study has found evidence for a decrease in prevalence.

The existing trend studies have many limitations. Most of them focused solely on major depressive episodes, while trends in anxiety and substance use disorders were explored far less (in one and four of the 20 studies above, respectively). Only a few studies used fully structured diagnostic interviews to assess mental disorders, while most relied on abbreviated versions of such interviews or self-report symptom questionnaires. Hardly any study investigated socio-demographic differences in time trends. Almost no study examined trends over the past decade.

However, precisely in these more recent years, the prevalence of mental disorders in the general population of Western countries may have changed, due to factors such as the economic crisis that started in 2008[24], the increased income inequality[25], the further individualization of society[26], and the recent COVID-19 pandemic. The reported rise in mental health care use[27,28] might indicate that the prevalence of mental disorders has increased, but this may also be explained by improved accessibility, efficiency and capacity of care.

Since the outbreak of the COVID-19 pandemic, the number of studies examining the mental health status of the general population and of specific groups has increased enormously. Most of these studies were online surveys, based on convenience samples with one-time data collection, suggesting dramatic increases in clinically significant anxiety and depression early in the pandemic[29]. However, a systematic review of general population studies comparing prevalence rates before vs. during the pandemic reported a much more modest increase in the prevalence of depressive and anxiety disorders during the first year of the pandemic[30].

That review was largely based on studies with short-reference symptom scales. It included only three studies that used diagnostic interviews allowing statements about trends in mental disorders. Two of these studies indicated stable levels of depression[31] and mental disorders[32] during the pandemic compared to pre-pandemic levels, while another suggested a large increase in the prevalence of mental disorders[33]. However, all three studies used a different method to collect data before vs. during the pandemic, for example moving from face-to-face or paper-and-pencil to telephone or web interviews.

Our study attempts to avoid these drawbacks of COVID-era

studies by using a strong data source: a standardized diagnostic instrument and the same (face-to-face) interview method were used before and during the first two years of the pandemic, assessing not only major depressive episodes but also anxiety and substance use disorders.

We report prevalence rates of DSM-5 mood disorders, anxiety disorders, substance use disorders, and attention-deficit/hyperactivity disorder (ADHD), and their socio-demographic correlates, based on data from the third Netherlands Mental Health Survey and Incidence Study (NEMESIS-3)[34]. This is a psychiatric epidemiological study of the Dutch general population aged 18-75 years, designed to provide up-to-date information on the prevalence of mental disorders. As the fieldwork for the first wave of NEMESIS-3 was conducted before and during the COVID-19 pandemic, we could investigate the extent to which the pandemic has had an effect on population mental health.

Furthermore, we could assess time trends in the 12-month prevalence rates of DSM-IV mood disorders, anxiety disorders, substance use disorders and ADHD at the baseline wave of NEMESIS-3 vs. NEMESIS-2 (i.e., in 2019-2022 vs. 2007-2009). We could also examine to what extent these trends were similar for different socio-demographic groups, and whether the trends in disorder prevalence paralleled those of service use for mental health problems.

METHODS

Study design

We used a multistage, stratified random sampling procedure. First, a random sample of municipalities was drawn. Second, in NEMESIS-3[34], a random sample of individuals aged 18-75 years was drawn from the Dutch population register (Basisregistratie Personen, BRP). This compares to NEMESIS-2[35], in which a random sample of addresses of private households from postal registers was drawn – each address with the same selection probability. A random individual aged 18-64 years was selected to be asked to participate, based on the most recent birthday at first contact within the household. In both studies, individuals with insufficient command of the Dutch language, as well as institutionalized individuals (i.e., those living in hostels, hospices or prisons), were excluded. Individuals temporarily living in institutions were contacted to be interviewed after returning home.

For NEMESIS-3, the Medical Research Ethics Committee (METC Utrecht) stated that the Dutch Medical Research Involving Human Subjects Act (WMO) did not apply (reference number: WAG/mb/19/017126; May 15, 2019). Therefore, no official approval was required under the WMO. The field procedures, information for respondents and informed consent forms were assessed positively by the local ethical review committee. NEMESIS-2 was approved by a medical ethics committee (the Medical Ethics Review Committee for Institutions on Mental Health Care, METiGG; reference number: CCMO/NL18210.097.07), since it included saliva collection. In both studies, respondents provided written informed consent, after full written and verbal information about the study was given before and at the start of the interview.

Fieldwork and interview characteristics

In NEMESIS-3, the baseline wave was performed from November 2019 to March 2022, and included three fieldwork-free periods owing to the COVID-19 pandemic. In NEMESIS-2, the first wave was performed from November 2007 to July 2009. In both studies, the recruitment methods were intensive, and a relatively long fieldwork period was chosen to have sufficient time to re-contact potential respondents.

In both studies, the face-to-face interviews were laptop computer-assisted, and almost all were held at the respondent's home. In NEMESIS-3, 1,576 participants (25.4%) were interviewed before and 4,618 (74.6%) during the COVID-19 pandemic. A total of 500 interviews (8.1%) were completed via video call. The average interview duration was 91 min in NEMESIS-3 and 95 min in NEMESIS-2.

Response and generalization to the population at large

Thanks to the fieldwork methods, it was possible to achieve relatively high response rates[36-38]: 54.6% (N=6,194) in NEMESIS-3[34], and 65.1% (N=6,646) in NEMESIS-2[35]. In both studies, the following groups were somewhat under-represented: younger people, higher secondary educated people, those not living with a partner, people living in bigger towns, and people of non-Western origin[34,35]. To allow generalization of the data to the Dutch population, based on post-stratification, a weighting factor was constructed for each study. After weighting, the distribution of the socio-demographic characteristics of both study samples was very similar to that of the Dutch population in the particular study period[34,35].

Diagnostic assessment

In both studies, DSM-IV diagnoses of common mental disorders were ascertained using the Composite International Diagnostic Interview (CIDI) 3.0. This is a fully structured diagnostic interview, developed for use in the World Mental Health Survey Initiative[39]. In NEMESIS-3, a slightly modified version of CIDI 3.0 was used to enable both DSM-IV and DSM-5 diagnoses[34].

We assessed the following conditions: mood disorders (major depressive disorder, persistent depressive disorder/dysthymia, bipolar disorder); anxiety disorders (panic disorder, agoraphobia, social anxiety disorder or social phobia, specific phobia, generalized anxiety disorder); substance use disorders (alcohol and drug use disorders); and ADHD. These disorders are assessed with good validity using the CIDI 3.0[40,41].

Most DSM-5 definitions of mental disorders are based on information already available in the CIDI 3.0, and were applied by

making small changes in the algorithms[34]. However, to enable the assessment of ADHD according to DSM-5 criteria, the childhood symptom questions referred to their presence prior to age 12, instead of age 7 as in the DSM-IV. Due to this change, we do not report the trend of ADHD prevalence rates between the studies.

Other variables

Information on sex, age, education, living situation, employment status, household income, country of origin, urbanicity, and service use was collected during the interview.

Household income was calculated based on the income of the respondent and, if applicable, the partner, for various living situations (e.g., living with partner and children, living with partner without children, single parent, living alone), and was then divided into the lowest 25%, the middle 50% and the highest 25% income category per living situation. Country of origin was categorized as Dutch (respondent and both parents born in the Netherlands) or non-Dutch. Service use was defined as at least one contact made in general medical or mental health care for emotional or alcohol or drug problems in the previous 12 months.

In NEMESIS-3, the same questions and measurement methods as in NEMESIS-2 were used, to enable comparisons[34,35].

Statistical analyses

The characteristics of the NEMESIS-3 sample were described using frequency tables. Lifetime and 12-month prevalence rates of DSM-5 disorders (mood disorders, anxiety disorders, substance use disorders, ADHD) were calculated for the total sample and stratified by sex. Additionally, the association of socio-demographic characteristics with the 12-month DSM-5 disorder prevalence rates was explored using logistic regression analysis adjusted for sex and age.

To assess differences before vs. during the COVID-19 pandemic, we calculated the 12-month prevalence rates of DSM-5 disorders separately for individuals interviewed before and during the pandemic. We tested the differences between these rates using logistic regression analysis adjusted for socio-demographic characteristics (sex, age, education, living situation, employment status, urbanicity).

To study trends over time, 12-month DSM-IV disorders (mood disorders, anxiety disorders, substance use disorders) among the same age range of respondents (18-64 years) in NEMESIS-3 and NEMESIS-2 were combined in one dataset, with *study* as independent variable and *socio-demographic variables* as confounders. Trends for these disorders were calculated using descriptive statistics and were analyzed using logistic regression adjusted for differences in socio-demographic characteristics between the samples (sex, age, education, living situation, employment status, urbanicity), because the population structure and therefore the sample composition of the studies had changed over time. To analyze whether the trend was the same for all socio-demographic groups, we estimated additive interaction effects between study and each socio-demographic feature using generalized linear models with a binomial distribution and an identity link function adjusted for socio-demographic characteristics[42,43].

Trends in mental health care use were also examined, to determine to what extent these were comparable to those for mental disorders.

RESULTS

Description of the NEMESIS-3 sample

Table 1 provides a description of the sample. The mean age was 46.2 years (standard error, SE: 0.35). The sample included 50.0% women; 42.2% with higher secondary education; 63.0% living with a partner; 64.0% with paid employment; 56.3% living in a city (i.e., high and very high degree of urbanization) and 81.2% of Dutch origin.

Prevalence of DSM-5 disorders

Table 2 shows the lifetime prevalence rates of DSM-5 disorders in NEMESIS-3. Any lifetime disorder was found in almost half of the respondents (48.4%). Mood and anxiety disorders were the most prevalent disorder categories (27.6% and 28.6%, respectively), followed by substance use disorders (16.7%) and ADHD (3.6%). The most prevalent specific disorders were major depressive disorder (24.9%), social phobia (13.1%), specific phobia (11.8%) and alcohol use disorder (12.8%). Of all respondents, 21.8% had one disorder during their lifetime, 11.8% had two and 14.8% had three or more.

One in four respondents (25.9%) met the criteria for any disorder in the 12 months before the interview. Of those with any lifetime disorder, more than half (53.5%) also had a disorder in the past year. The most prevalent disorder category was anxiety disorders (15.2%), followed by mood disorders (9.8%), substance use disorders (7.1%) and ADHD (3.2%). ADHD was still present in adulthood among the vast majority of cases with that disorder in childhood (88.9%). Of those with a mental disorder in the past 12 months, 42.5% had two or more disorders.

Socio-demographic correlates of DSM-5 disorders in the past 12 months

Women were more likely to have any mental disorder in the past 12 months than men (Table 3). While the prevalence of mood and anxiety disorders was higher in women, that of substance use disorders and ADHD was higher in men. Lower age was associated with higher prevalence of all disorder categories.

Respondents with primary or lower secondary education, and those with a low household income, more often had mood disorders, anxiety disorders and ADHD, but not substance use disor-

Table 1 Description of the NEMESIS-3 sample (2019-2022) of people aged 18-75 years (N=6,194), in unweighted numbers and weighted percentages

	N	%
Sex		
Men	3,071	50.0
Women	3,123	50.0
Age at interview (years)		
18-24	665	12.1
25-34	938	17.5
35-44	1,004	16.2
45-54	1,096	19.4
55-64	1,266	18.6
65-75	1,225	16.3
Education		
Primary or lower secondary	1,367	23.2
Higher secondary	2,259	42.2
Higher vocational or university	2,568	34.6
Living situation		
With partner and children	2,138	33.8
With partner without children	2,025	29.1
Without partner with children (single parent)	260	5.0
Alone	987	17.3
With other(s)	784	14.7
Employment status		
Paid job	3,876	64.0
Homemaker	318	5.1
Student	454	8.1
Unemployed/disabled	479	8.6
Retired	1,067	14.2
Income		
Low	1,584	27.8
Medium	2,892	48.6
High	1,462	23.6
Urbanicity		
Very low	570	7.6
Low	1,414	20.9
Medium	994	15.1
High	1,819	30.4
Very high	1,397	25.9
Country of origin		
Dutch	5,125	81.2
Non-Dutch	1,069	18.8

Data were weighted based on post-stratification to facilitate generalization to Dutch population. Urbanicity: very low, <500 addresses per km^2; low, 500-1,000 addresses per km^2; medium, 1,000-1,500 addresses per km^2; high, 1,500-2,500 addresses per km^2; very high, ≥2,500 addresses per km^2.

ders. Respondents living alone were more likely to have all disorder categories than those living with a partner and children. For all disorder categories, unemployed or disabled subjects were worse off than those in paid employment. While the degree of urbanization of the place of residence was clearly associated with the prevalence of 12-month disorders, country of origin was not.

Prevalence rates before and during the COVID-19 pandemic

Table 4 shows that the prevalence rate of any DSM-5 disorder in the past 12 months assessed before vs. during the COVID-19 pandemic did not differ significantly (26.7% pre-pandemic vs. 25.7% during the pandemic), even after controlling for differences in socio-demographic characteristics of the respondents interviewed in these two periods. This was the case for all four disorder categories.

In a sensitivity analysis, we also assessed differences in 6-month prevalence rates to ensure that the rates of the respondents interviewed after the first lockdown (from September 2020 onwards) were only related to a period during the COVID-19 pandemic. These analyses showed that the prevalence rates of any 6-month DSM-5 disorder before vs. during the COVID-19 pandemic did not differ significantly (21.8% pre-pandemic vs. 19.7% during pandemic). However, after controlling for differences in socio-demographic characteristics, the 6-month prevalence rate of any DSM-5 disorder was significantly lower during the pandemic than pre-pandemic (19.5% vs. 22.5%, respectively; adjusted odds ratio, aOR=0.82, 95% CI: 0.70-0.96). A lower prevalence during the pandemic was also evident in the 6-month prevalence of substance use disorders (aOR=0.70, 95% CI: 0.54-0.91), but not of mood disorders (aOR=0.82, 95% CI: 0.67-1.00) and anxiety disorders (aOR=0.91, 95% CI: 0.75-1.10).

Trends in 12-month prevalence of disorders

Table 5 shows that the 12-month prevalence rate of any DSM-IV mood, anxiety or substance use disorder among 18-64 year olds significantly and substantially increased from 17.4% in NEMESIS-2 to 26.1% in NEMESIS-3, and that this change remained significant after controlling for differences in socio-demographic characteristics between the studies. A similar trend was seen for any mood disorder (from 6.0% to 10.8%) and any anxiety disorder (from 10.1% to 15.6%). The prevalence of any substance use disorder also increased (from 5.5% to 7.1%), but the change was not significant after controlling for differences in socio-demographic characteristics between the two studies. All specific mood, anxiety and substance use disorders assessed in both studies significantly increased in the period between NEMESIS-2 and NEMESIS-3 after controlling for differences in socio-demographic characteristics between the studies, except for alcohol use disorder.

Among those with any 12-month mood, anxiety or substance use disorder, the ratio of those with a mild, moderate or severe dis-

Table 2 Prevalence rates of lifetime and 12-month DSM-5 disorders among people aged 18-75 years, based on NEMESIS-3 (2019-2022; N= 6,194), in weighted percentages with standard error (SE)

	Lifetime prevalence						12-month prevalence					
	Men		Women		Total		Men		Women		Total	
	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE
Any mood disorder	22.1	0.9	33.0	1.2	27.6	0.8	8.1	0.7	11.5	0.7	9.8	0.5
Major depressive disorder	19.2	0.8	30.5	1.2	24.9	0.8	6.7	0.6	10.4	0.7	8.5	0.5
Persistent depressive disorder	6.7	0.5	11.4	0.8	9.1	0.5	2.6	0.4	4.4	0.6	3.5	0.3
Bipolar disorder	2.5	0.3	1.8	0.3	2.1	0.2	1.3	0.2	1.1	0.2	1.2	0.2
Any anxiety disorder	21.8	0.9	35.5	1.3	28.6	1.0	11.0	0.7	19.4	1.0	15.2	0.7
Panic disorder	3.7	0.4	7.5	0.6	5.6	0.4	1.5	0.2	2.9	0.5	2.2	0.3
Agoraphobia	2.4	0.3	5.5	0.4	4.0	0.3	1.1	0.2	2.7	0.4	1.9	0.2
Social phobia	10.8	0.7	15.3	0.8	13.1	0.6	4.6	0.5	6.7	0.6	5.6	0.4
Specific phobia	7.5	0.6	16.1	0.8	11.8	0.6	4.6	0.4	11.0	0.7	7.8	0.4
Generalized anxiety disorder	6.5	0.5	12.6	0.6	9.5	0.5	2.8	0.3	4.8	0.5	3.8	0.3
Any substance use disorder	22.5	1.4	11.0	1.2	16.7	1.2	9.5	1.1	4.8	0.6	7.1	0.7
Alcohol use disorder	17.8	1.2	7.9	0.9	12.8	0.9	7.5	0.8	3.3	0.4	5.4	0.6
Drug use disorder	8.5	1.0	4.7	0.7	6.6	0.7	2.8	0.6	1.7	0.3	2.3	0.4
Cannabis use disorder	5.9	0.7	1.9	0.3	3.9	0.4	1.9	0.3	0.6	0.1	1.3	0.2
ADHD	4.3	0.4	3.0	0.3	3.6	0.3	3.7	0.3	2.7	0.3	3.2	0.3
One mental disorder	22.1	0.8	21.5	0.8	21.8	0.6	14.9	1.0	15.0	0.8	15.0	0.7
Two mental disorders	11.2	0.7	12.5	0.6	11.8	0.5	5.2	0.5	6.0	0.6	5.6	0.4
Three or more mental disorders	11.8	0.8	17.8	1.1	14.8	0.8	4.0	0.5	6.8	0.7	5.4	0.5
Any mental disorder	44.9	1.3	51.8	1.5	48.4	1.2	24.0	1.3	27.8	1.2	25.9	1.1

Data were weighted based on post-stratification to facilitate generalization to Dutch population. ADHD – attention-deficit/hyperactivity disorder.

order remained the same between the two studies (34.8%, 31.4% and 33.9% in NEMESIS-2 vs. 34.6%, 31.3% and 34.1% in NEMESIS-3, respectively). The percentage of those with two or more mental disorders significantly increased (from 32.6% in NEMESIS-2 to 41.3% in NEMESIS-3), and the increase remained significant after controlling for differences in socio-demographic characteristics between the two studies (OR=1.50, 95% CI: 1.21-1.86).

Post-hoc, we assessed differences in 3-year prevalence rates of DSM-IV mood, anxiety and substance use disorders during the three follow-up waves of NEMESIS-2, to guide our interpretation of time trends. Prevalence rates of all categories increased over time after controlling for differences in socio-demographic characteristics. The increases were most evident between the first and the last follow-up waves (i.e., between 2010-2012 and 2016-2018) (see Table 6).

Trends in socio-demographic correlates of 12-month disorders

To study whether the trend was the same for all socio-demographic groups, we estimated additive interaction effects between study and each socio-demographic characteristic adjusted for all other socio-demographic variables. A stronger increase in the 12-month prevalence of any DSM-IV disorder in the period between the two studies was found for younger adults (18-34 years) compared to those aged 35 and older (p<0.001), for students compared to those with a paid job (p<0.001), and for those living in a city compared to non-urban residents (p=0.002). In contrast, retirees showed a less marked increase compared to people with a paid job (p=0.030). No interaction effects were found for sex, education and living situation.

Trends in service use for mental health problems

Parallel to these increasing trends in the prevalence of common mental disorders, general medical and specialized mental health care significantly and substantially increased between the two studies: from 9.0% and 6.2% in NEMESIS-2 to 15.0% and 10.0% in NEMESIS-3, respectively (see Table 7). The same was true for psychotropic medication use, which rose from 5.7% to 6.9%. On the other hand, unmet need for care also increased: from 1.8% to 4.0%. All these trends in service use remained significant after controlling for differences in socio-demographic characteristics between the studies.

Table 3 Association between socio-demographic characteristics and 12-month DSM-5 disorders among people aged 18-75 years, based on NEMESIS-3 (2019-2022; N=6,194), in weighted percentages, adjusted odds ratios (aORs) and 95% confidence intervals (CIs), controlled for sex and age

	Mood disorders		Anxiety disorders		Substance use disorders		ADHD		Any mental disorder	
	%	aOR (95% CI)	%	aOR (95% CI)	%	aOR (95% CI)	%	aOR (95% CI)	%	aOR (95% CI)
Sex										
Men	8.1	1	11.0	1	9.5	1	3.7	1	24.0	1
Women	11.5	**1.50 (1.21-1.86)**	19.4	**1.97 (1.66-2.34)**	4.8	**0.48 (0.38-0.60)**	2.7	**0.73 (0.55-0.96)**	27.8	**1.24 (1.07-1.44)**
Age at interview (years)										
18-24	13.3	**3.04 (1.91-4.83)**	19.9	**2.68 (2.00-3.57)**	15.8	**7.17 (4.45-11.57)**	3.7	**3.67 (1.78-7.59)**	39.6	**4.09 (3.16-5.28)**
25-34	13.1	**2.97 (2.01-4.37)**	19.8	**2.62 (2.05-3.36)**	12.6	**5.56 (3.65-8.48)**	3.9	**3.86 (1.92-7.76)**	35.2	**3.37 (2.76-4.11)**
35-44	11.1	**2.41 (1.46-3.96)**	17.5	**2.20 (1.72-2.83)**	7.4	**3.13 (1.75-5.59)**	5.5	**5.66 (2.68-11.95)**	27.7	**2.35 (1.76-3.14)**
45-54	9.5	**2.05 (1.48-2.85)**	13.3	**1.61 (1.24-2.09)**	4.1	**1.65 (1.05-2.58)**	2.9	**2.90 (1.31-6.41)**	21.8	**1.72 (1.39-2.14)**
55-64	7.9	**1.67 (1.05-2.66)**	13.8	**1.68 (1.31-2.16)**	3.3	1.30 (0.78-2.15)	2.5	**2.44 (1.14-5.20)**	21.4	**1.68 (1.34-2.12)**
65-75	4.9	1	8.7	1	2.6	1	1.0	1	13.9	1
p for linearity		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
Education										
Primary or lower secondary	12.0	**2.21 (1.70-2.87)**	17.0	**1.79 (1.46-2.20)**	6.4	1.16 (0.82-1.64)	5.0	**3.25 (1.99-5.32)**	27.9	**1.77 (1.43-2.20)**
Higher secondary	10.2	**1.37 (1.08-1.74)**	15.9	**1.28 (1.06-1.53)**	6.3	**0.72 (0.57-0.89)**	3.0	1.44 (0.93-2.24)	26.0	1.13 (0.98-1.31)
Higher vocational or university	7.9	1	13.3	1	8.6	1	2.2	1	24.4	1
Living situation										
With partner and children	7.7	1	12.9	1	4.0	1	2.8	1	20.5	1
With partner without children	7.5	1.20 (0.92-1.57)	11.8	1.09 (0.85-1.40)	5.3	**1.85 (1.33-2.57)**	2.5	1.09 (0.67-1.76)	20.6	**1.32 (1.10-1.58)**
Single parent	12.2	1.53 (0.96-2.44)	23.0	**1.75 (1.15-2.66)**	5.0	1.63 (1.00-2.68)	5.2	**2.14 (1.26-3.64)**	31.1	**1.71 (1.18-2.47)**
Alone	14.0	**2.23 (1.68-2.97)**	19.4	**1.86 (1.47-2.36)**	9.9	**2.83 (1.95-4.11)**	3.8	**1.43 (1.00-2.05)**	32.7	**2.23 (1.80-2.75)**
With other(s)	13.6	1.24 (0.89-1.74)	19.9	1.20 (0.90-1.60)	15.4	**1.67 (1.16-2.41)**	4.2	0.87 (0.57-1.33)	39.0	**1.40 (1.11-1.77)**
Employment status										
Paid job	8.1	1	13.2	1	6.7	1	2.7	1	23.3	1
Homemaker	11.2	1.47 (0.97-2.22)	18.9	1.39 (1.00-1.93)	3.9	1.15 (0.60-2.21)	3.3	1.84 (0.99-3.41)	26.8	**1.41 (1.05-1.88)**
Student	13.5	1.06 (0.76-1.47)	20.3	1.03 (0.78-1.37)	17.4	1.27 (0.99-1.64)	3.1	0.74 (0.38-1.47)	41.1	1.21 (0.96-1.52)
Unemployed/disabled	27.6	**4.70 (3.58-6.16)**	35.6	**3.90 (3.08-4.94)**	11.2	**2.30 (1.53-3.46)**	11.3	**5.34 (3.89-7.33)**	52.0	**4.17 (3.27-5.30)**
Retired/other	4.2	0.95 (0.55-1.63)	7.9	1.01 (0.76-1.35)	2.2	1.26 (0.71-2.26)	0.8	0.56 (0.23-1.35)	12.9	1.13 (0.81-1.56)
Income										
Low	13.1	**1.77 (1.34-2.32)**	19.2	**1.45 (1.13-1.86)**	8.0	1.05 (0.75-1.48)	4.4	**1.88 (1.19-2.99)**	30.5	**1.41 (1.13-1.74)**
Medium	9.2	**1.32 (1.01-1.73)**	14.5	1.16 (0.93-1.44)	7.1	1.11 (0.85-1.44)	2.9	1.32 (0.82-2.11)	25.4	**1.23 (1.04-1.44)**
High	6.9	1	12.3	1	6.2	1	2.3	1	21.3	1

Table 3 Association between socio-demographic characteristics and 12-month DSM-5 disorders among people aged 18-75 years, based on NEMESIS-3 (2019-2022; N=6,194), in weighted percentages, adjusted odds ratios (aORs) and 95% confidence intervals (CIs), controlled for sex and age *(continued)*

	Mood disorders		Anxiety disorders		Substance use disorders		ADHD		Any mental disorder	
	%	aOR (95% CI)	%	aOR (95% CI)	%	aOR (95% CI)	%	aOR (95% CI)	%	aOR (95% CI)
Urbanicity										
Very low	6.4	1	10.3	1	3.4	1	1.9	1	16.5	1
Low	7.7	1.20 (0.70-2.06)	10.9	1.04 (0.70-1.55)	5.2	1.54 (0.77-3.09)	2.5	1.27 (0.62-2.58)	20.4	1.27 (0.92-1.74)
Medium	7.5	1.14 (0.62-2.07)	14.4	1.42 (0.91-2.19)	6.5	1.92 (0.95-3.88)	3.3	1.71 (0.85-3.44)	23.2	**1.47 (1.04-2.07)**
High	10.8	**1.73 (1.02-2.93)**	17.3	**1.77 (1.20-2.60)**	6.0	1.81 (0.92-3.54)	3.3	1.69 (0.86-3.30)	27.3	**1.85 (1.38-2.49)**
Very high	12.7	**1.94 (1.17-3.23)**	18.2	**1.78 (1.19-2.66)**	11.6	**3.22 (1.57-6.60)**	4.0	1.95 (0.99-3.84)	33.0	**2.24 (1.63-3.07)**
p for linearity		**<0.001**		**<0.001**		**<0.01**		**<0.05**		**<0.001**
Country of origin										
Dutch	9.3	1	14.5	1	7.0	1	3.1	1	24.9	1
Non-Dutch	12.3	1.23 (0.92-1.65)	18.7	1.21 (0.98-1.50)	7.8	0.99 (0.78-1.25)	3.9	1.19 (0.75-1.90)	30.2	1.15 (0.96-1.38)

Data were weighted based on post-stratification to facilitate generalization to Dutch population. Significant values of aOR or p for linearity (<0.05) are highlighted in bold prints. Urbanicity: very low, <500 addresses per km^2; low, 500-1,000 addresses per km^2; medium, 1,000-1,500 addresses per km^2; high, 1,500-2,500 addresses per km^2; very high, ≥2,500 addresses per km^2. ADHD – attention-deficit/hyperactivity disorder.

Table 4 Prevalence rates of 12-month DSM-5 disorders before vs. during the COVID pandemic in NEMESIS-3 (2019-2022; N=6,194), in weighted percentages, odds ratios (ORs) or adjusted odd ratios (aORs), and 95% confidence intervals (CIs)

	Pre-pandemic (N=1,576)		During pandemic (N=4,618)		Unadjusted model	Adjusted model
	%	95% CI	%	95% CI	OR (95% CI)	aOR (95% CI)
Mood disorders	10.2	8.5-11.9	9.7	8.6-10.9	0.95 (0.79-1.14)	0.91 (0.75-1.11)
Anxiety disorders	15.7	13.4-18.1	15.1	13.6-16.6	0.95 (0.80-1.14)	0.92 (0.77-1.09)
Substance use disorders	7.8	5.8-9.8	7.0	5.5-8.4	0.89 (0.71-1.11)	0.80 (0.63-1.00)
ADHD	3.4	2.5-4.4	3.2	2.6-3.8	0.94 (0.66-1.33)	0.91 (0.65-1.27)
Any mental disorder	26.7	23.5-29.9	25.7	23.5-27.8	0.95 (0.82-1.09)	0.89 (0.77-1.02)

Data were weighted based on post-stratification to facilitate generalization to Dutch population. Unadjusted model: OR and p not controlled for socio-demographic differences between respondents interviewed before and during the pandemic. Adjusted model: aOR and p controlled for socio-demographic differences (sex, age, education, living situation, employment status, urbanicity) between respondents interviewed before and during the pandemic. ADHD – attention-deficit/hyperactivity disorder.

DISCUSSION

This study presents prevalence rates of DSM-5 disorders in a sample representative of the general population; examines the effect of the COVID-19 pandemic on population mental health using a structured face-to-face diagnostic interview before and during the pandemic; and explores trends in DSM-IV disorders over more than a decade between two highly comparable samples randomly drawn from the general population.

Nearly half of the NEMESIS-3 respondents (48.4%) had a DSM-5 mood disorder, anxiety disorder, substance use disorder or ADHD during their lifetime, and one in four (25.9%) in the 12 months prior to the interview. There were no significant differences in the 12-month prevalence of mental disorders before vs. during the COVID-19 pandemic. The 12-month prevalence of any DSM-IV mood, anxiety or substance use disorder substantially increased over time (from 17.4% in 2007-2009 to 26.1% in 2019-2022), and this was paralleled by a marked increase in the use of specialized mental health care (from 6.2% to 10.0%). At the same time, unmet need for care rose from 1.8% to 4.0%.

The prevalence rates of any mental disorder in the lifetime and in the past 12 months in this sample from the Netherlands are similar to those reported in the US, but higher than those found in other European countries, based on studies dating back to the turn of the century[45]. The most recent population study performed in the US showed similar rates of DSM-5 mood and anxiety disorders, but higher rates of substance use disorders[46]. These findings show that mental disorders are quite common in the general population. It is important to recognize, though, that not all mental disorders are severe[47]. Mild and moderate cases are nonetheless meaningful, because even mild disorders can be impairing and often evolve into severe mental disorders over time[48].

The socio-demographic correlates of having 12-month DSM-5 disorders in NEMESIS-3 are broadly consistent with previous surveys that mostly used DSM-IV criteria: lower age[49,50]; sex (being female for any anxiety and mood disorder, and being male for substance use disorder and ADHD[40,49]); living alone[16,51]; being unemployed[16,49,51]; a low education level or having a low income[16,40,51]; and a higher degree of urbanization[49,51].

We found that the prevalence rates of mental disorders before vs. during the COVID-19 pandemic did not differ significantly. This finding is in line with two studies that used diagnostic interviews before and during the pandemic[31,32], but in contrast with a study that found an increase in the prevalence of mental disorders[33]. However, this latter study used market research quota sampling, a design that likely overestimates the increase in disorder prevalence[30]. In contrast, a fourth study found a decrease in the prevalence of major depressive and generalized anxiety disorder relative to pre-pandemic levels[52]. Other studies that used short-reference symptom scales instead of diagnostic interviews

Table 5 Trends in prevalence rates of 12-month DSM-IV disorders in people aged 18-64 years (N=11,615), based on NEMESIS-2 (2007-2009) and NEMESIS-3 (2019-2022), in weighted percentages, odds ratios (ORs) or adjusted odds ratios (aORs), and 95% confidence intervals (CIs)

	NEMESIS-2		NEMESIS-3		Unadjusted model	Adjusted model
	%	95% CI	%	95% CI	OR (95% CI)	aOR (95% CI)
Mood disorders	6.0	5.3-6.8	10.8	9.7-11.9	**1.89 (1.59-2.24)**	**2.04 (1.71-2.42)**
Anxiety disorders	10.1	9.2-11.0	15.6	14.3-16.9	**1.64 (1.44-1.87)**	**1.76 (1.56-1.99)**
Substance use disorders	5.5	4.5-6.5	7.1	6.1-8.2	**1.32 (1.04-1.68)**	1.27 (0.99-1.63)
Any mental disorder	17.4	16.0-18.7	26.1	24.2-28.0	**1.68 (1.48-1.90)**	**1.78 (1.59-2.00)**

Data were weighted to be representative of the adult population in the particular study period. Unadjusted model: OR and p not controlled for socio-demographic differences between the studies. Adjusted model: aOR and p controlled for socio-demographic differences (sex, age, education, living situation, employment status, urbanicity) between the studies. Significant values of OR or aOR (<0.05) are highlighted in bold prints.

Table 6 Prevalence rates of 3-year DSM-IV disorders during the follow-up waves of NEMESIS-2 (2010-2018; N=12,021), in weighted percentages, adjusted odds ratios (aORs) and 95% confidence intervals (CIs)

	Wave 2 (2010-2012)		Wave 3 (2013-2015)		Wave 4 (2016-2018)		Adjusted model (reference: wave 2)	
							Wave 3	Wave 4
	%	95% CI	%	95% CI	%	95% CI	aOR (95% CI)	aOR (95% CI)
Mood disorders	7.4	6.4-8.5	7.5	6.3-8.8	10.7	9.0-12.3	1.01 (0.81-1.27)	**1.51 (1.22-1.86)**
Anxiety disorders	6.8	5.7-8.0	8.1	6.8-9.5	9.6	7.7-11.5	1.21 (1.00-1.47)	**1.47 (1.15-1.88)**
Substance use disorders	4.8	3.8-5.8	6.1	4.5-7.6	6.5	4.8-8.1	**1.31 (1.02-1.68)**	**1.42 (1.09-1.85)**
Any mental disorder	15.3	13.5-17.1	17.3	15.1-19.4	20.2	17.7-22.7	**1.17 (1.02-1.33)**	**1.44 (1.23-1.68)**

The trend is shown on the follow-up waves, because at baseline no 3-year prevalence rates were assessed. Data were weighted based on post-stratification to facilitate generalization to Dutch population. The analyses are based on the respondents who participated at all follow-up waves. Similar results were found when we included all respondents in the analyses. Adjusted model: % with 95% CI, aOR and p controlled for socio-demographic differences (sex, age, education, living situation, employment status) between respondents interviewed at the different follow-up waves. Significant values of aOR (<0.05) are highlighted in bold prints.

generally showed an increase in the prevalence of depression and anxiety during the pandemic compared to pre-pandemic levels[30]. These differences in findings of COVID studies indicate that symptom ratings do not equate to the presence of mental disorders[53].

We found a substantial increase in the prevalence of all main categories of common mental disorders between 2007-2009 and 2019-2022. *Post-hoc* analyses of NEMESIS-2 data showed that the increase in prevalence started before the initiation of NEMESIS-3. Previous trend studies reported mixed findings (i.e., suggesting an increase or stabilization, but not a decrease), but those studies did not examine trends in the past decade.

Although our study was not designed to provide explanations for the trends between 2007-2009 and 2019-2022, we cautiously suggest possible reasons. We found that students and those aged 18-34 years showed a stronger increase in the prevalence of any 12-month disorder compared to people with a paid job and those aged 35 and older, respectively. In recent decades, young adults may have been more adversely affected by the further individualization of society[26], the rise of social media[54,55], and the increasing pressure to succeed[56]. They may also be more adversely affected by current social problems (e.g., shortage of affordable housing, climate change concerns), or have more difficulty coping with setbacks, such as not immediately having a successful job or owner-occupied home.

A stronger increase in the prevalence of any 12-month disorder was also seen among those living in a city, which was not explained by differences in socio-demographic characteristics between the two studies. Living in a city may come with more disadvantages today than before.

Among retired people, a smaller increase in disorder prevalence was found, perhaps because they have been less affected by the long-term consequences of the economic crisis that started in 2008[24], or are less adversely affected by current social problems than the employed.

While we can only speculate about the reasons for the trends, we can rule out some explanations. The significant increase in the prevalence rates of mental disorders over time cannot be attributed to the small difference in clinical assessment instrument between NEMESIS-3 and NEMESIS-2, as in both studies the DSM-IV diagnoses were based on the same questions using the same algorithms. The increase is also not caused by the fact that 500 interviews (8.1%) were conducted via video calling in NEMESIS-3, as those interviewed via video calling did not differ in 12-month and lifetime prevalence rates from those interviewed face-to-face, after adjustment for socio-demographic differences between the two groups[34]. Change in the population structure, such as relatively more highly educated people and more people with a paid job, also does not explain the sharp increase in prevalence of mood and anxiety disorders, but it may have played a limited role in explaining the increase in substance use disorders.

The increase in mood and anxiety disorders could be due to people being more likely to recognize and admit mental health prob-

Table 7 Trends in 12-month service use for mental health problems in people aged 18-64 years (N=11,615), based on NEMESIS-2 (2007-2009) and NEMESIS-3 (2019-2022), in weighted percentages, odds ratios (ORs) or adjusted odds ratios (aORs), and 95% confidence intervals (CIs)

	NEMESIS-2		NEMESIS-3		Unadjusted model	Adjusted model
	%	95% CI	%	95% CI	OR (95% CI)	aOR (95% CI)
General medical care	9.0	8.3-9.7	15.0	13.8-16.1	**1.77 (1.57-2.00)**	**1.85 (1.64-2.08)**
Mental health care	6.2	5.4-6.9	10.0	8.7-11.3	**1.69 (1.42-2.02)**	**1.71 (1.44-2.04)**
Psychotropic medication use	5.7	5.2-6.3	6.9	6.1-7.7	**1.22 (1.04-1.44)**	**1.27 (1.07-1.50)**
Unmet care need	1.8	1.5-2.2	4.0	3.3-4.7	**2.22 (1.70-2.91)**	**2.14 (1.60-2.84)**

Data were weighted to be representative of the adult population in the particular study period. Unadjusted model: OR and p not controlled for socio-demographic differences between the studies. Adjusted model: aOR and p controlled for socio-demographic differences (sex, age, education, living situation, employment status, urbanicity) between the studies. Significant ORs and aORs are highlighted in bold prints.

lems today than in the past. However, we believe that these factors explain the substantial increase in disorder prevalence only to a limited extent, as we have used a clinical assessment instrument that asks about symptoms of a disorder and not about the disorder itself, which is less subject to feelings of shame and taboo.

Finally, the increase cannot be attributed to the COVID-19 pandemic, as we found that the pandemic was not associated with a higher prevalence of mental disorders in the general population. The only clinically relevant effect of the COVID-19 pandemic on population mental health was a significant decrease in the 6-month prevalence of substance use disorder, which mainly includes mild alcohol use disorder, during the pandemic. One explanation for this could be that the social restrictions during the pandemic reduced the possibility of drinking alcohol with others or in bars and restaurants, thus reducing alcohol consumption and its consequences.

Some limitations of the study should be mentioned. First, while the CIDI 3.0 assesses DSM-IV mood, anxiety and substance use disorders with generally good validity[41], the validity and reliability of our slightly modified CIDI 3.0 to assess DSM-5 diagnoses have not been formally investigated. Second, our prevalence rates are based on retrospective recall: diagnosing disorders in the lifetime, rather than within the past 12 months, often results in underreporting[44]. Third, survey non-response could lead to bias in prevalence estimates: in line with an international trend towards declining response rates in all types of surveys[37], the non-response in NEMESIS-3 was larger than in NEMESIS-2; however, similar to NEMESIS-2, we found that hard-to-reach respondents – who might most resemble non-responders – did not differ in the prevalence of mood, anxiety and substance use disorders compared to easier-to-recruit respondents[34]. Fourth, although the sample was representative of the Dutch population on most parameters, those with insufficient mastery of Dutch, those with no permanent residential address, and those who were long-term institutionalized were excluded from participation.

To conclude, the present study shows that the mental state of a population is subject to gradual changes, probably related to long-term sociocultural developments, and that youngsters and city dwellers seem to be more sensitive to these developments. The study also shows that adversities of shorter duration (such as the COVID-19 pandemic) have little or no effect on that mental state. This could suggest effective resilience and adaptation, although time-lag effects of the pandemic may yet be felt[53]. These findings reaffirm the role of social determinants as risk factors for common mental disorders, and the need to develop and implement effective mental health promotion programmes, and to ensure timely access to mental health care, especially for young people[57].

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The status of psychodynamic psychotherapy as an empirically supported treatment for common mental disorders – an umbrella review based on updated criteria

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To assess the current status of psychodynamic therapy (PDT) as an empirically supported treatment (EST), we carried out a pre-registered systematic umbrella review addressing the evidence for PDT in common mental disorders in adults, based on an updated model for ESTs. Following this model, we focused on meta-analyses of randomized controlled trials (RCTs) published in the past two years to assess efficacy. In addition, we reviewed the evidence on effectiveness, cost-effectiveness and mechanisms of change. Meta-analyses were evaluated by at least two raters using the proposed updated criteria, i.e. effect sizes, risk of bias, inconsistency, indirectness, imprecision, publication bias, treatment fidelity, and their quality as well as that of primary studies. To assess the quality of evidence we applied the GRADE system. A systematic search identified recent meta-analyses on the efficacy of PDT in depressive, anxiety, personality and somatic symptom disorders. High quality evidence in depressive and somatic symptom disorders and moderate quality evidence in anxiety and personality disorders showed that PDT is superior to (inactive and active) control conditions in reducing target symptoms with clinically meaningful effect sizes. Moderate quality evidence suggests that PDT is as efficacious as other active therapies in these disorders. The benefits of PDT outweigh its costs and harms. Furthermore, evidence was found for long-term effects, improving functioning, effectiveness, cost-effectiveness and mechanisms of change in the aforementioned disorders. Some limitations in specific research areas exist, such as risk of bias and imprecision, which are, however, comparable to those of other evidence-based psychotherapies. Thus, according to the updated EST model, PDT proved to be an empirically-supported treatment for common mental disorders. Of the three options for recommendation provided by the updated model (i.e., "very strong", "strong" or "weak"), the new EST criteria suggest that a strong recommendation for treating the aforementioned mental disorders with PDT is the most appropriate option. In conclusion, PDT represents an evidence-based psychotherapy. This is clinically important since no single therapeutic approach fits all psychiatric patients, as shown by the limited success rates across all evidence-based treatments.

Key words: Psychodynamic therapy, psychotherapies, empirically supported treatments, evidence-based medicine, depressive disorders, anxiety disorders, personality disorders, somatic symptom disorders

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More than 20 years ago, criteria for empirically supported psychotherapeutic treatments (ESTs) were first proposed[1,2]. These criteria suggested that at least two randomized controlled trials (RCTs) from independent research groups were required to demonstrate that a manual-guided treatment was superior to control conditions, or as efficacious as an already established treatment, in a specific mental disorder[1].

However, concerns were raised about those criteria. They included the exclusive focus on symptom improvement while neglecting psychosocial functioning, the limited generalizability of results from research settings to clinical practice, the neglect of design flaws and researcher allegiance, and the fact that only two RCTs were required to demonstrate efficacy[3]. Furthermore, an independent empirical re-evaluation of the studies included in the American Psychological Association's database of ESTs found replicability and power estimates to be low across almost all ESTs[4]. Some ESTs rated as having "strong" evidence according to the model failed to outperform their "modest" counterparts with regard to efficacy[4].

As a result, a new model for ESTs has been proposed, taking these concerns into account[3]. This model requires a focus on: a) systematic (quantitative) reviews (meta-analyses) rather than individual studies, b) study quality, c) clinical significance in addition to statistical significance, d) long-term outcomes in addition to short-term efficacy, e) functional or other health-related outcomes in addition to symptom improvement, f) generalization to non-research settings, g) de-emphasizing categorical diagnoses and emphasizing syndromes and diagnostically complex patients, and h) mechanisms of psychopathology and therapeutic change[3].

For candidate treatments, the new EST model suggests the use of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system by an expert committee, to assess the quality of evidence and the degree to which benefits exceed potential harms[5-8]. The original GRADE system allows to rate the evidence as "high quality", "moderate quality", "low quality" or "very low quality"[5-9]. If there are differences in ratings of evidence between primary (critical) outcomes and other outcomes (e.g., side effects or costs), GRADE regards efficacy outcomes as the most important on most occasions, and suggests that guideline panels can base their rating of the quality of evidence exclusively on data on efficacy[7].

For high quality evidence, the new EST model requires a wide range of studies with no major limitations, small heterogeneity and narrow confidence intervals (CIs)[3]. These recommendations differ considerably from the original approach of the GRADE

group, which considered "one or more well-designed RCTs yielding consistent directly applicable results" as required for high quality evidence[7]. Moderate quality evidence is defined by the updated EST model as "a few" studies, of which some have limitations, but no major flaws, with some variation between studies or a wide CI for the summary estimate[3]. Again, this recommendation differs from the original approach of the GRADE group, which defined moderate quality evidence for RCTs in terms of "important" limitations[7]. Low quality evidence was originally restricted by the GRADE group as referring to observational studies and only occasionally to RCTs with multiple serious limitations[7], whereas the newly proposed EST criteria define low quality evidence as referring to "studies" (no specification if RCTs or observational studies) with major flaws, or where there are important variations between studies and very wide CIs for the summary estimate[3].

In a next step, the original GRADE system results in "strong" or "weak" recommendations for a treatment[5-7]. In the new EST model, a third category was introduced, i.e. a "very strong" recommendation[3]. Additional contextual factors may increase or decrease the GRADE recommendations (e.g., comparative efficacy to other treatments, evidence for mechanisms of change, evidence for efficacy in minorities or across various patient sub-populations)[3].

Based on the original EST criteria[1], the empirical status of psychodynamic therapy (PDT) has been assessed in several reviews[10-14]. The revised EST criteria, however, have not yet been applied to studies available for PDT. Nevertheless, as pointed out by the Task Force on Promotion and Dissemination of Psychological Procedures, it is critical to investigate whether PDT fulfills the updated criteria, "if this clinically verified treatment is to survive in today's market"[15]. For this reason, we carried out an umbrella review of meta-analyses of PDT in common mental disorders in adults applying the revised EST criteria.

METHODS

Details of the procedures were described in a study protocol[16], which was also pre-registered (PROSPERO: CRD42022342350).

The authors of this review fulfil the criteria proposed by the new EST model[3], that is: a) a broad range of documented expertise, b) disclosure of actual and potential conflicts of interest (see supplementary information), c) maintaining a climate of openness, d) using clearly defined procedures and methods as described in the study protocol.

Definition of psychodynamic psychotherapy

PDT includes a family of psychotherapeutic approaches having in common a focus on the identification of recurring patterns of relating to the self and others (including the therapeutic relationship) and of expression of emotion, the exploration of defensive patterns, and the discussion of past experiences that have an impact on the person's present experiences[17].

PDT operates on a supportive-interpretive continuum[17]. The use of more interpretive or supportive interventions depends on the person's needs and mental capacities[17-19]. While interpretive interventions enhance the person's insight about repetitive conflicts sustaining his/her problems, supportive interventions aim to strengthen psychosocial abilities ("ego-functions") that are currently not accessible to the person.

Similarity

The treatments included in a meta-analysis are required to show sufficient similarity[20], a criterion adopted by the new EST model[3]. For many variants of PDT, the commonalities in techniques have been shown to outweigh the differences, allowing for the development of unified protocols[21-25]. Unified psychodynamic protocols focus on shared ingredients or mechanisms, representing a "mechanism-oriented approach"[21-23]. An analogous approach has been developed in the area of cognitive behavior therapy (CBT)[26,27]. Indeed, the updated EST model encourages a focus on core dimensions of pathology and treatments which may reduce "the EST movement's reliance on a large number of treatment manuals" and lead to a much simpler and "more practitioner-friendly system"[3]. For each mental disorder included in this umbrella review, we tested whether the applied PDT techniques showed sufficient similarity.

Conditions being studied

The following mental disorders in adults, defined according to the ICD or DSM, were eligible for inclusion in this umbrella review: depressive disorders, anxiety disorders, trauma- and stressor-related disorders, dissociative disorders, obsessive-compulsive disorder, eating disorders, somatic symptom disorders, attention-deficit/hyperactivity disorder, substance related disorders, personality disorders, bipolar disorder, schizophrenia spectrum disorders. In addition, complex mental disorders – defined as chronic disorders, highly comorbid disorders, and disorders associated with personality disorders – were also included.

Inclusion criteria

Following the revised EST criteria[3], when evaluating PDT efficacy, we focused on meta-analyses of RCTs in common mental disorders in adults published in the past two years. Older reviews were only included if they provided data not available in more recent reviews, e.g. results on specific domains such as functioning.

Meta-analyses were included which tested PDT against a control condition (e.g., waiting list, treatment-as-usual, TAU; pill or psychological placebo), or against pharmacotherapy or another form of psychotherapy[3]. Results were evaluated per comparison condition, divided into all controls, active controls (e.g., TAU, enhanced

TAU, low intensity therapy), and active therapies (e.g., pharmacotherapy or another form of psychotherapy). If several meta-analyses for one disorder were available, we included the largest, that is the one encompassing most RCTs.

Furthermore, systematic reviews focusing on mechanisms of change of PDT were evaluated, including both RCTs and open studies if they showed all characteristics of RCTs (e.g., treatment manuals, valid assessment of disorder and outcome) with the exception of not including a control condition. In addition, as suggested by the new EST model, effectiveness studies carried out under real-world conditions, as well as cost-effectiveness studies, were evaluated[3]. We included individual studies if no systematic reviews were available for a specific area of research, or if a recent study was not included in available systematic reviews.

Outcomes

As primary (critical) outcome, we used effect sizes in disorder-specific target symptoms post-therapy assessed by validated scales. In addition to statistical significance, clinical significance of effect sizes was assessed. If presented by the authors of the included meta-analyses, data of high-quality studies and data corrected for publication bias or outliers were preferably included. Through this paper, a negative effect size indicates superiority of PDT.

Secondary (important but not critical) outcomes assessed, if available, were adverse events, improvement in functioning, effectiveness under real-world conditions, cost-effectiveness, and impact on minorities.

Search for studies

We searched PubMed and PsycINFO and individual records of the Cochrane Library for systematic reviews, meta-analyses and individual RCTs on the efficacy of PDT in common mental disorders in adults published between 2012 and December 2022. We aimed to focus on meta-analyses published in the past two years, as required by the new EST criteria. However, we allowed inclusion of older reviews providing results not included in more recent ones.

Search terms were (meta-analy* or metaanaly*) and ("psychodynamic therapy" or "dynamic therapy" or "psychoanalytic therapy" or "psychodynamic psychotherapy" or "dynamic psychotherapy" or "psychoanalytic psychotherapy"). Additionally, a regularly updated comprehensive list containing RCTs of psychodynamic treatments was consulted (researchgatenet/publication/317335876) and a hand search in journal papers and textbooks was carried out. Studies on face-to-face and Internet PDT were included, as well as studies on individual and group therapy.

Furthermore, we searched for systematic reviews and individual studies on mechanisms of change in PDT, for effectiveness studies carried out under real-world conditions, and for studies on cost-effectiveness of PDT[3]. For these purposes, additional search terms were "mechanisms of change", "curative factors", "process-outcome", "cost-effectiveness", and "health economic analysis".

At least two reviewers independently screened the results of the database search for relevant meta-analyses and individual studies. If the title and abstract of a paper contained sufficient information to determine that it did not meet the inclusion criteria specified above, the paper was excluded. In a next step, full texts of all studies possibly relevant for inclusion were retrieved. Disagreements about the inclusion of a meta-analysis or study were solved by consensus or by consulting a third expert. The search results for meta-analyses were documented in a PRISMA flow chart (see Figure 1).

Data extraction

A data extraction form was used to retrieve details of included meta-analyses. A similar form was used for individual studies. At least two authors independently extracted the results: type of disorder, number of included RCTs, number of participants, risk of bias, effect sizes, 95% CI, heterogeneity, and adverse events. Discrepancies were solved by consensus. These procedures were applied to all ratings, including assessment of risk of bias, treatment fidelity, quality of meta-analyses and GRADE. We contacted the authors of the included meta-analyses for additional information.

Quality of meta-analyses and primary studies

For rating the quality of included meta-analyses, we applied the Joanna Briggs Institute Critical Appraisal Checklist for Systematic Reviews and Research Syntheses[28]. We used the first nine items which refer to quality, complemented by item 12 of AMSTAR 2 ("Was the impact of risk of bias in individual studies on results of the meta-analysis taken into account?")[29] and an additional item addressing whether the meta-analysis was preregistered.

If data on risk of bias were not reported in the included meta-analyses, we rated this risk for the included studies using the four criteria of the Cochrane Risk of Bias Tool[30] (adequate random sequence generation, allocation concealment, blinding of assessors and/or use of self-report measures only, and use of intent-to-treat analysis).

As to the quality of primary studies, we used ratings based on the Randomized Controlled Trial Psychotherapy Quality Rating Scale (RCT-PQRS)[31]. Treatment fidelity was assessed following criteria proposed by the new EST model[3] (i.e., use of treatment manuals, experienced/qualified therapists, monitoring of treatment during the trial, and empirical assessment of treatment integrity). The quality of studies on mechanisms of change was evaluated as proposed by Crits-Christoph and Connolly Gibbons[32].

Data synthesis

We used the criteria of the new EST model[3] to evaluate the empirical status of PDT in each of the mental disorders. Following

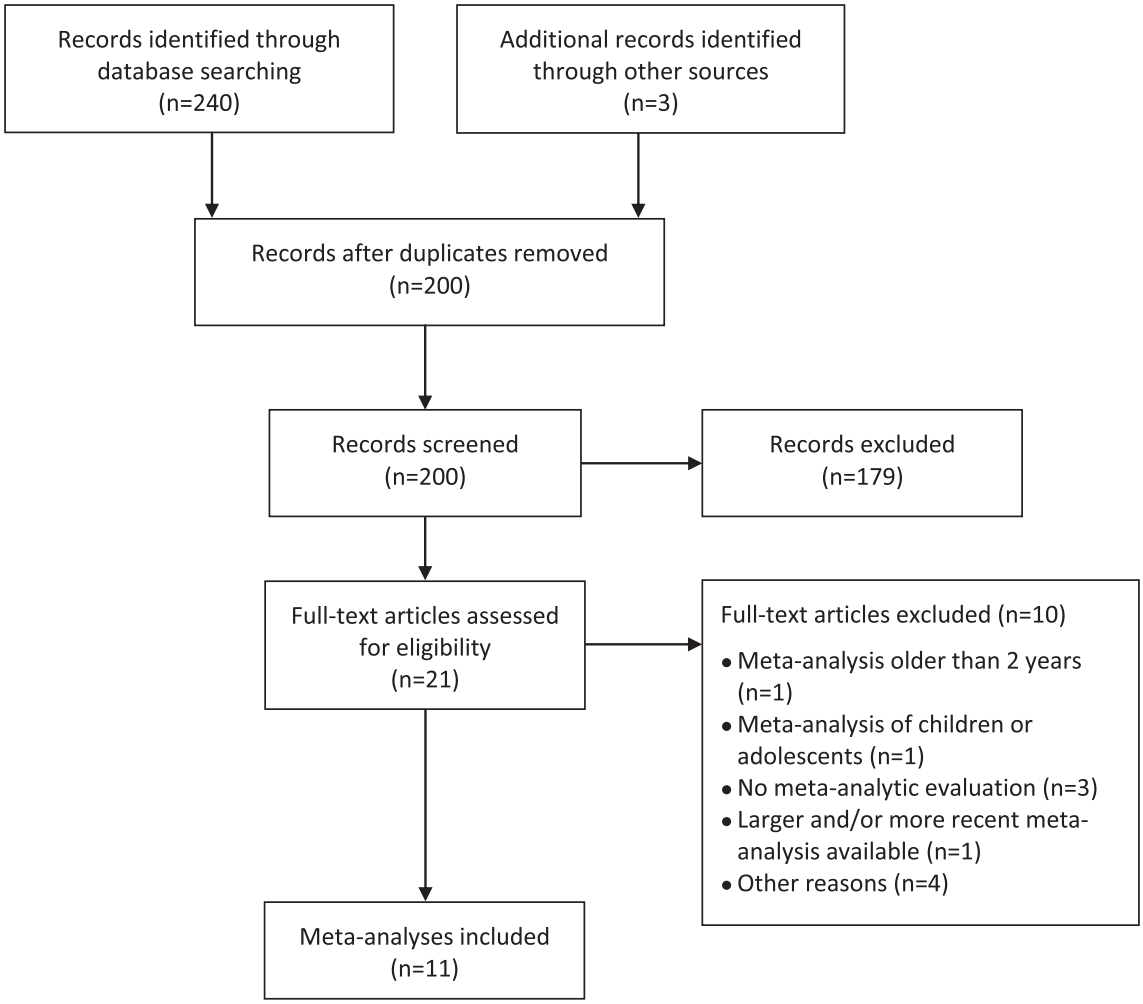

Figure 1 PRISMA flow chart

GRADE, we first identified critical (primary) and important (secondary) outcomes[33]. As critical outcomes, we defined disorder-specific symptom severity at treatment termination in comparison to control conditions or to active therapies. As important outcomes, we defined treatment effects at follow-ups, improvements in functioning, costs, frequency of adverse events, and data on mechanisms of change.

In a second step, following GRADE, we rated the quality of evidence for each outcome, taking risk of bias, inconsistency, imprecision, indirectness and publication bias into account[7]. As to inconsistency, we regarded I^2 values of 25%, 50% and 75% as indicating low, moderate or high heterogeneity[34], and took low and moderate heterogeneity as indicating no serious inconsistency. Indirectness encompassed deviations in patients, outcomes or treatments from those of interest, as well as indirect comparisons (e.g., comparing A and B with placebo without directly comparing A and B)[7,35]. As to risk of bias, a GRADE rating of high quality evidence could only be achieved if more than 50% of the studies were at low risk with regard to random sequence generation, allocation concealment, blinding of assessors (or use of self-report instruments only) and completeness of data (intention-to-treat analysis)[35]. For imprecision, we followed the GRADE guidelines, which suggest that the effect size needs to be statistically significant and the total sample size has to exceed the "optimal information size" (OIS), that is the sample size required to detect a clinically meaningful effect size with a power of 0.80 at α=0.05[36,37]. We also tested whether the recommendations would differ if the upper or lower boundaries of the CIs represented the truth.

We finally graded the evidence and assessed the strengths of treatment recommendations[3,8].

RESULTS

The initial search yielded 243 hits (see Figure 1). In total, eleven meta-analyses were included. Four recent meta-analyses addressing the efficacy of PDT fulfilled the inclusion criteria, referring to depressive, anxiety, personality and somatic symptom disorders[38-40]. Two older reviews fulfilling inclusion criteria which assessed the efficacy of PDT were also included[41,42]. Further included meta-analyses ad-

dressed the efficacy of Internet-delivered PDT[43], the efficacy of adding short-term PDT to antidepressants in depression[44], the effectiveness of PDT under real-world conditions[45], the mechanisms of change[46], and the quality of RCTs of PDT and CBT[47].

Depressive disorders

The eligible recent meta-analysis assessing the efficacy of PDT for depressive disorders, in comparison with control conditions or active therapies, included 27 RCTs (N=3,163 patients)[38]. There was sufficient similarity in the applied techniques to assume that the different studies tested the same essential treatment[21,22].

Efficacy of PDT vs. control conditions

PDT was found to be superior to all control conditions in improving depressive symptoms, with a medium effect size (g=–0.58, 95% CI: –0.33 to –0.83, n=12, I^2=63%, N=1,017) and no evidence for publication bias (see Table 1). Compared to waiting list controls only, the effect size was large (g=–1.14, 95% CI: –1.66 to –0.62, n=3, N=115), while it was medium compared to active controls (g=–0.51, 95% CI: –0.68 to –0.35, I^2=26%, n=9, N=945).

The effect size of –0.58 in comparison to all control conditions corresponds to a difference in success rates of about 33%, or a number needed to treat of about 3[48], clearly exceeding the threshold of a clinically significant effect size of d=±0.24 proposed by Cuijpers et al[49]. This is also true for the effect size of –0.51 achieved in comparison to active controls, which also compares favorably to those found in the largest meta-analyses of psychotherapy (0.31) and pharmacotherapy (0.30) for depressive disorders in comparison to TAU or placebo[50-52].

The above-mentioned threshold of a clinically significant effect (d=±0.24)[49] resulted in an OIS of 432[53]. For PDT vs. all control conditions, the effect size was significant and the sample size exceeded the OIS (N=1,017 > 432), thus indicating no serious imprecision. The lower boundary of the CI (–0.83) represents a large effect size, and the upper boundary (–0.33) exceeds –0.24, thus representing a small but still clinically meaningful effect size. For PDT vs. active controls, there was no serious imprecision (N=945 > 432), the lower boundary of the CI (–0.68) representing a medium to large effect size, while the upper boundary (–0.35) exceeded –0.24, thus representing a small but still clinically meaningful effect size. The width of the CI for comparison with controls is similar to other active therapies, such as CBT vs. TAU (see supplementary information).

There were no indications of serious indirectness with regard to patients, treatment outcomes, or comparisons.

Efficacy of PDT vs. active therapies

Compared to other active therapies, PDT did not differ significantly on the primary outcome, i.e., severity of depression (g=–0.01, 95% CI: –0.34 to 0.32, n=20, N=2,335). Heterogeneity was high (I^2=90%), due to one outlier[54]. When this was removed, heterogeneity was reduced to a moderate level (g=0.10, 95% CI: –0.06 to 0.26, I^2=62%, n=19, N=2,154). Correction for publication bias in the reduced sample did not affect the results (g=–0.03, 95% CI: –0.23 to 0.17, I^2=73%) (see Table 1).

The corrected effect size was not significant, and the sample size exceeded the OIS (N=2,154 > 432), thus indicating no serious imprecision. The CI of the corrected effect size did not exceed ±0.24, indicating no clinically meaningful difference in efficacy compared to other active therapies. Both the upper and the lower boundary of the CI represent small, clinically not meaningful effect sizes. Heterogeneity was moderate.

In follow-ups ranging from 2 to 55 months, the difference between PDT and active therapies remained insignificant (g=–0.01, 95% CI: –0.31 to 0.29, n=10, I^2=71%). After removing one outlier[55], heterogeneity was reduced (g=0.08, 95% CI: –0.14 to 0.30, I^2=50%, n=9, N=1,096). The effect size was below 0.24 and the sample size exceeded the OIS (N=693 > 432), thus indicating no serious imprecision. Both the upper and the lower boundary of the CI represent a small effect size. The upper boundary, however, exceeded 0.24.

Quality measures

The quality of the eligible meta-analysis was found to be good, with 10 out of the 11 relevant items fulfilled. The quality of primary studies, as assessed by the RCT-PQRS, was sufficient (total score ≥ 24) for most studies (74%).

As to treatment fidelity, most of the 27 included studies used a treatment manual (87%), included experienced/qualified therapists (91%), monitored the treatment during the trial by supervision (59%), and assessed treatment integrity empirically (57%).

Adequate random sequence generation, allocation concealment, blinding of assessors (or use of only self-report measures) and intention-to-treat analysis were applied in 56%, 48%, 74% and 67% of the studies, respectively, indicating that most studies showed a low risk of bias (see also supplementary information). The corresponding values for the comparison with all control conditions were 54%, 54%, 54%, and 85%; those for the comparison with active controls only were 67%, 78%, 78% and 100%; and those for the comparison with active therapies were 50%, 40%, 75% and 55%, respectively.

Secondary outcomes

Several studies covered in the recent included meta-analysis[38] reported data on tolerability, detecting no or only a few adverse events.

Improvement in functioning was not assessed in that meta-analysis. An earlier meta-analysis[42] found PDT to be superior to control conditions with regard to improving quality of life, with a medium effect size (d=–0.49, 95% CI: –0.73 to –0.24, n=3, I^2=0%, N=293), while there was no difference compared to other psychotherapies in improving interpersonal functioning, either post-

Table 1 Synthesis of evidence profiles for psychodynamic therapy (PDT) in depressive disorders

Outcomes	Quality assessment								Summary of findings		Quality of evidence
	Quality of systematic review (QSR)	Quality of studies (QS) (RCT-PQRS ≥ 24)	Treatment fidelity (FI)	GRADE				Publication bias	N patients (both arms)	Effect size (95% CI)	GRADE QSR, QS, FI Total rating
				Risk of bias	Inconsistency	Indirectness	Imprecision				
PDT vs. all controls											
Severity of depressive symptoms (critical) 12 RCTs	10/11	74%	+	No	No	No	No	Undetected	1,017	–0.58 (–0.33, –0.83) I^2=63%	++++ +++ High
PDT vs. active controls											
Severity of depressive symptoms (critical) 9 RCTs	10/11	100%	+	No	No	No	No	Undetected	945	–0.51 (–0.68, –0.35) I^2=26%	++++ +++ High
Functioning (important) 3 RCTs	9/11	100%	+	No	No	No	Yes	Not assessed	293	–0.49 (–0.73, –0.24) I^2=0%	+++– +++ Moderate
PDT vs. active therapies											
Severity of depressive symptoms (critical) 19 RCTs (1 outlier excluded)	9/11	68%	+	Yes	No	No	No	Corrected	2,154	–0.03 (–0.23, 0.17) I^2=73%	–+++ +++ Moderate
Follow-up depressive symptoms (important) 9 RCTs	9/11	82%	+	Yes	No	No	No	Undetected	1,096	0.08 (–0.14, 0.30) I^2=50%	–+++ +++ Moderate
Functioning (important) 5 RCTs	9/11	60%	+	Yes	No	No	Yes	Not assessed	408	0.05 (–0.23, 0.34) I^2=40%	–++– +++ Low
Follow-up functioning (important) 4 RCTs	9/11	75%	+	Yes	No	No	Yes	Not assessed	288	–0.15 (–0.70, 0.40) I^2=74%	–++– +++ Low

RCTs – randomized controlled trials; RCT-PQRS – Randomized Controlled Trial Psychotherapy Quality Rating Scale; GRADE – Grading of Recommendations Assessment, Development, and Evaluation

therapy (d=0.05, 95% CI: –0.23 to 0.34, n=5, I^2=40%, N=408) or at follow-up (d=–0.15, 95% CI: –0.70 to 0.40, n=4, I^2=74%, N=288). Using d=±0.24 and N=432 as an OIS resulted in rating of some imprecision in these estimates (N=293, 408, 288 < 432). Risk of bias was low for random sequence generation (100% of studies), allocation concealment (100%), blinding of outcomes (67%) and completeness of data (100%) (see Table 1).

A recent meta-analysis on effectiveness of routinely delivered psychotherapies[45] found large pre-post effect sizes in depression outcomes (d=0.96, 95% CI: 0.88-1.04), with no differences between CBT and PDT (d=–0.07 in favor of PDT). These results were corroborated by a recent effectiveness study on PDT in chronic depression, which found a large effect size (d=–0.90) in comparison to a waiting list condition[56]. As suggested by one RCT, PDT may be a cost-effective intervention in treatment-resistant depressive disorders as compared to TAU[57].

One RCT found gender and racial/ethnic minority status to moderate outcome, with PDT being more efficacious in minority men (primarily African-American) compared to pharmacotherapy and pill placebo[58]. Another RCT conducted in a community setting, including about 50% of patients who identified as a racial/ethnic minority, found PDT to be as efficacious as CBT[59].

Further results

A meta-analysis found PDT combined with antidepressants to be more efficacious than antidepressants with or without brief supportive therapy, with a significant but small effect size post-therapy (g=–0.26; standard error, SE=0.10, p=0.01) and a medium effect size at follow-up (g=–0.50, SE=0.10, p=0.001)[44]. Adequate random sequence generation, allocation concealment, blinding of assessors (or use of only self-report measures) and intention-to-treat analysis were applied in 100%, 100%, 71% and 86% of the studies, respectively.

A meta-analysis of Internet-delivered PDT[43] reported a medium effect size compared to controls in depression outcomes (g= –0.46, 95% CI: –0.73 to –0.19, I^2=23%, n=5, N=359), with two outliers excluded. Risk of bias was low for most studies, and no publication bias was found.

GRADE

According to the results presented above, PTD achieved medium effect sizes compared to both all control conditions (g= –0.58) and active controls (g=–0.51) in the reduction of depressive symptoms, and a small clinically not meaningful effect size compared to other active therapies (g=–0.03). There were no serious indications of inconsistency, indirectness, imprecision or publication bias in critical outcomes (see Table 1). Most studies (74%) showed acceptable quality as assessed by the RCT-PQRS. Treatment fidelity was sufficient for most studies. The quality of the meta-analysis was rated as good. Furthermore, there was a relatively wide range of studies (n=27), with moderate heterogeneity and CIs indicating enough precision. The benefits outweighed the costs and harms, as required by GRADE[6,60].

For comparisons with all controls and active controls, most studies showed a low risk of bias, suggesting high quality evidence (see also supplementary information). For the comparison with active therapies, risk of bias was low in most studies for masking and completeness of data, but not for random sequence generation and allocation concealment (see Table 1 and supplementary information). The GRADE guidelines recommend to be conservative with regard to rating down the quality of evidence[61]. Thus, the review panel decided to downgrade the evidence for PDT vs. active therapies by one level, rating the evidence as moderate, whereas the quality of evidence for PDT vs. all controls and active controls only in depression was rated as high for critical outcomes (see Table 1).

Anxiety disorders

The eligible recent meta-analysis assessing the efficacy of PDT for anxiety disorders, in comparison with control conditions or active therapies, comprised 17 RCTs (N=1,798), including agoraphobia with and without panic disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and post-traumatic stress disorder (PTSD)[38]. There was sufficient similarity in the applied techniques to assume that the different studies tested the same essential treatment[21,23,24].

Efficacy of PDT vs. control conditions

PDT was found to be superior to all control conditions in reducing anxiety symptoms, with a large effect size (g=–0.94, 95% CI: –1.55 to –0.33, n=7, I^2=78%, N=565). Removing one outlier[62] reduced heterogeneity to a moderate level (g=–0.72, 95% CI: –1.06 to –0.37, n=6, I^2=43%, N=479) (see Table 2). There was no evidence for publication bias. Effect sizes did not significantly differ if control conditions included an active element vs. waiting list alone (p=0.401). For comparison with active controls, only three small RCTs were available; PDT yielded a medium effect size, but the CI was wide (g=–0.64, 95% CI: –1.14 to –0.14, n=3, N=86).

The reported effect size of –0.72 in comparison to all control conditions corresponds to a difference in success rates of 38% or a number needed to treat of 2.6[48]. Thus, it can be considered as clinically meaningful. This is also true for the effect size of –0.64 achieved in comparison to active controls.

We used d=±0.25 as a conservative estimate for a minimum clinically meaningful effect size, similar to the proposed effect size of d=±0.24 for depression, resulting in an OIS of 398[53]. The effect size achieved by PDT in comparison to controls was statistically significant, and the sample size exceeded the OIS (479 > 398), indicating no serious imprecision. The lower boundary of the CI represented a large effect size, while the upper boundary exceeded –0.25, a still clinically meaningful effect size. The width of the CI for comparison with controls is similar to other active therapies, such as CBT vs. TAU or placebo (see supplementary information).

Table 2 Synthesis of evidence profiles for psychodynamic therapy (PDT) in anxiety disorders

Outcomes	Quality assessment								Summary of findings		Quality of evidence
	Quality of systematic review (QSR)	Quality of studies (QS) (RCT-PQRS ≥ 24)	Treatment fidelity (FI)	GRADE				Publication bias	N patients (both arms)	Effect size (95% CI)	GRADE QSR, QS, FI Total rating
				Risk of bias	Inconsistency	Indirectness	Imprecision				
PDT vs. all controls											
Anxiety symptoms (critical) 6 RCTs (1 outlier excluded)	10/11	33%	+	Yes	No	No	No	Undetected	479	–0.72 (–1.06, –0.37) I^2=43%	–+++ +–+ Moderate
PDT vs. active controls											
Anxiety symptoms (critical) 3 RCTs	10/11	33%	–	Yes	No	No	Yes	Not assessed	86	–0.64 (–1.14, –0.14) I^2=0%	–++– +–– Low
PDT vs. active therapies											
Anxiety symptoms (critical) 14 RCTs (1 outlier excluded)	10/11	64%	+	Yes	No	No	No	Undetected	1,196	0.06 (–0.11, 0.23) I^2=45%	–+++ +++ Moderate
Interpersonal functioning (important) 3 RCTs	8/11	100%	+	No	Yes	No	Yes	Not assessed	512	–0.03 (–1.19, 1.14) I^2=77%	+–+– +++ Low
Short-term follow-up anxiety symptoms (important) 9 RCTs (1 outlier excluded)	10/11	56%	+	Yes	No	No	No	Corrected	914	–0.03 (–0.25, 0.19) I^2=46%	–+++ +++ Moderate
Long-term follow-up anxiety symptoms (important) 4 RCTs (1 outlier excluded)	10/11	100%	+	No	No	No	No	Not assessed	617	0.00 (–0.20, 0.20) I^2=17%	++++ +++ High

RCTs – randomized controlled trials; RCT-PQRS – Randomized Controlled Trial Psychotherapy Quality Rating Scale; GRADE – Grading of Recommendations Assessment, Development, and Evaluation

There were no indications of serious indirectness with regard to patients, treatment outcomes, or comparisons.

Efficacy of PDT vs. active therapies

Compared to other active therapies, PDT was not significantly different in anxiety outcomes (g=–0.01, 95% CI: –0.21 to 0.20, n=15, I^2=60%, N=1,242). Excluding one potential outlier[63] reduced heterogeneity (g=0.06, 95% CI: –0.11 to 0.23, n=14, I^2=45%, N=1,196). Evidence for publication bias was not found. There were no significant differences in effect sizes achieved by PDT vs. active therapies in generalized anxiety disorder compared to other anxiety disorders (p=0.181), panic disorder (p=0.356), or social anxiety disorder (p=0.977).

The effect size was not significant and the sample size exceeded the OIS (N=1,196 > 398), indicating no serious imprecision. The corrected effect size and its CI did not exceed ±0.25, indicating no clinically meaningful difference in efficacy compared to other active therapies.

Remission rates for anxiety disorders did not differ significantly between PDT and other active therapies (log odds ratio = 0.12, 95% CI: –0.76 to 0.99, p=0.761).

At follow-up of up to one year after termination, outcomes of PDT did not differ from other active therapies (g=0.08, 95% CI: –0.25 to 0.42, n=10, I^2=73%). Excluding one outlier[64] reduced heterogeneity to a moderate level (g=–0.03, 95% CI: –0.25 to 0.19; n=9, I^2=46%, N=914). At follow-up over more than one year after termination, PDT did not differ from other active therapies either (g=0.21, 95% CI: –0.45 to 0.87, n=5, I^2=85%). When removing one outlier[64], heterogeneity was considerably reduced (g=0.00, 95% CI: –0.20 to 0.20; n=4, I^2=17%, N=617). Both corrected effect sizes were not statistically significant and the sample sizes exceed the OIS, indicating no serious imprecision (914, 617 > 398).

Quality measures

The quality of the eligible meta-analysis was found to be good, with 10 out of the 11 relevant items fulfilled. The quality of primary studies, as assessed by the RCT-PQRS, was sufficient (total score ≥ 24) for most studies (65%). However, for the comparison with all control conditions, only 33% of studies scored ≥ 24, due to inclusion of several older studies. For comparisons with active therapies, the majority of RCTs (64%) were of sufficient quality.

As to treatment fidelity, most of the 17 included studies used a treatment manual (89%), included experienced/qualified therapists (89%), and monitored the treatment during the trial by supervision (72%). Treatment integrity was empirically studied in 33% of studies.

Adequate random sequence generation, allocation concealment, blinding of assessors (or use of only self-report measures) and intention-to-treat analysis were reported in 47%, 41%, 71% and 59% of the studies, respectively (see also supplementary information). The corresponding values for the comparison with all controls were 29%, 29%, 57% and 43%; those for the comparison with active therapies were 47%, 40%, 67% and 60%, respectively.

Secondary outcomes

Several studies covered in the recent included meta-analysis[38] reported data on tolerability, detecting no or only a few adverse events.

Improvement in functioning was not assessed in that meta-analysis. An earlier meta-analysis[41] found no differences between PDT and other psychotherapies in improving interpersonal functioning (g=–0.03, 95% CI: –1.19 to 1.14, n=3, N=512). The number of patients exceeded the OIS (512 > 398), but the CI was wide.

A recent meta-analysis on effectiveness of routinely delivered psychotherapies[45] found large pre-post effect sizes in anxiety outcomes (d=–0.80, 95% CI: 0.71-0.09), with no differences between PDT and CBT (d=0.00). One RCT found no differences in cost-effectiveness between PDT and solution-focused therapy in anxiety disorders[65].

Further results

A meta-analysis on Internet-delivered PDT[43] reported a small effect size compared to control conditions in anxiety outcomes (g=–0.32, 95% CI: –0.55 to –0.09; I^2=0%, n=5, N=359). Risk of bias was low for most studies, and publication bias was not found, although the number of studies was small. An RCT found no differences in outcome between PDT and CBT applied via the Internet in generalized anxiety disorder (0.14, 95% CI: –0.50 to 0.78)[66].

GRADE

According to the results presented above, PDT achieved a medium to large effect size (g=–0.72) compared to all control conditions in the reduction of anxiety symptoms, and a small effect size compared to other active therapies (g=0.06). There were no serious indications of inconsistency, indirectness, imprecision or publication bias in critical outcomes (see Table 2). Most studies (65%) showed acceptable quality as assessed by the RCT-PQRS, except for the comparison with (active and inactive) controls, due to the inclusion of several older studies. Treatment fidelity was sufficient for most studies, except for comparisons with active controls. The quality of the meta-analysis was rated as good. Furthermore, there was a relatively wide range of studies (n=17), with moderate heterogeneity and CIs indicating enough precision, except for comparisons with active controls. The benefits outweighed the costs and harms, as required by GRADE[6,60].

For comparisons with all controls, most studies showed an unclear or high risk of bias in critical outcomes for random sequence generation, allocation concealment and completeness, but not for blinding (see also supplementary information). For the comparison with active therapies, risk of bias was low in most studies for masking and completeness of data, while it was unclear or high for random sequence generation and allocation concealment. As noted above, the GRADE guidelines recommend to be conservative with regard to rating down the quality of evidence[61]. Thus, the review panel decided to downgrade the evidence for PDT in

anxiety disorders by one level, rating the evidence as moderate for critical outcomes. For the comparison with active controls, since the evidence was based on only three small old RCTs of low quality, the review panel rated the quality as low (see Table 2).

Personality disorders

The eligible recent meta-analysis assessing the efficacy of PDT for personality disorders, in comparison with control conditions or active therapies, included 16 RCTs, dealing with borderline or Cluster C personality disorders[38,39]. Although there was more heterogeneity between PDT methods used to treat these disorders compared to depressive and anxiety disorders, they are all based on psychodynamic theory and technique and have core dimensions in common[17,25,67].

Efficacy of PDT vs. control conditions

For core personality disorder symptoms, PDT achieved a medium effect size in comparison to all control conditions (g=–0.63, 95% CI: –0.87 to –0.41, n=5, I^2=11%, N=239) (see Table 3). Compared to active controls, PDT achieved a medium effect size (g=–0.65, 95% CI: –0.99 to –0.32, I^2=15%, n=4, N=200). The number of studies was too small to determine any effect of publication bias.

We used a standardized mean difference (SMD) = ±0.43 as a conservative estimate for a minimum clinically meaningful effect size[72], resulting in an OIS of 136[53]. The effect size of PDT in the reduction of personality disorder symptoms compared to all controls was statistically significant, and the sample size exceeded the OIS (N=239 > 136). Thus, there was no serious imprecision. The lower boundary of the CI represents a large effect size, while the upper boundary is close to –0.43, thus still representing a clinically meaningful effect size. For the comparison with active controls, the sample size (N=200) exceeds the OIS as well, but the lower boundary of the CI is below –0.43.

For suicidality, PDT was superior to active control groups, with a large effect size (g=–0.79, 95% CI: –1.38 to –0.20, n=5, I^2=72%). Removing one outlier[71] reduced heterogeneity to a moderate level and the effect size to medium (g=–0.67, 95% CI: –1.13 to –0.20, n=4, I^2=40%, N=239). We used an SMD of ±0.53 as a minimal clinically meaningful effect size, resulting in an OIS of 90[53]. The sample size exceeds the OIS (N=239 > 90). The effect size and the lower boundary of the CI can be regarded as clinically meaningful, but the upper boundary falls below the margin.

There were no indications of serious indirectness with regard to patients, treatments outcomes, or comparisons.

Efficacy of PDT vs. active therapies

No significant differences between PDT and other active therapies with regard to core personality disorder symptoms were found (g=0.05, 95% CI: –0.25 to 0.35, n=7, I^2=54%, N=473). Removing one possible outlier[69] reduced heterogeneity (g=–0.04, 95% CI: –0.31 to 0.22, n=6, I^2=38%, N=473). There was no evidence for publication bias, but the number of studies was small. There were no differences in effect sizes between trials for borderline and Cluster C personality disorders (p=0.953).

Differences to other active therapies with regard to core personality disorder symptoms were insignificant. The sample size exceeded the OIS (N=473 >136). Thus, precision was adequate. The corrected effect size is small and its CI does not exceed ±0.43, implying no clinically significant difference in efficacy compared to other active therapies.

There were no significant differences in follow-up studies comparing PDT with active therapies with regard to core personality disorder symptoms (g=0.00, 95% CI: –0.48 to 0.49, I^2=64%, N=370). Removing one outlier[70] reduced heterogeneity (g=–0.18, 95% CI: –0.38 to 0.03, n=4, I^2=5%). The corrected effect size was neither statistically nor clinically significant, and the sample size exceeds the OIS (N=370 > 136), indicating no serious imprecision.

Quality measures

The quality of the eligible meta-analysis was found to be very good, with 11/11 relevant items fulfilled. The quality of primary studies, as assessed by the RCT-PQRS, was sufficient (total score ≥ 24) for most studies (81%).

As to treatment fidelity, all the 16 included studies used a treatment manual (100%); most studies described adequate qualification of therapists (87.5%) and monitored the treatment during the trial by supervision (94.5%). A smaller percentage empirically assessed treatment integrity (50%).

Adequate random sequence generation, allocation concealment, blinding of assessors (or use of only self-report measures) and intention-to-treat analysis were reported in 50%, 44%, 69% and 50% of the studies, respectively (see also supplementary information). The corresponding values for the comparison with all controls were 60%, 40%, 80% and 40%; those for the comparison with active controls only were 75%, 50%, 75% and 50%; those for the comparison with active therapies were 43%, 43%, 71% and 47%, respectively.

Secondary outcomes

For improvement of functioning, PDT yielded a medium effect size compared to all controls (g=–0.66, 95% CI: –1.01 to –0.32, n=7, I^2=57%). When a potential outlier was removed[73], heterogeneity was reduced (g=–0.72, 95% CI: –1.04 to –0.41, n=6, I^2=42%, N=431). We used an SMD of ±0.45 as a minimal clinically meaningful effect size[72], resulting in an OIS of 124[53]. The sample size exceeds the OIS (N=431 > 124). The effect size and the lower boundary of the CI can be regarded as clinically meaningful, but the upper boundary falls below the margin.

For interpersonal problems (g=–0.05, 95% CI: –0.20 to 0.12; n=4, I^2=2%, N=394) and functioning (g=0.12, 95% CI: –0.12 to 0.36, n=4, I^2=2%, N=394), there were no significant differences between

Table 3 Synthesis of evidence profiles for psychodynamic therapy (PDT) in personality disorders

Outcomes	Quality assessment								Summary of findings		Quality of evidence
	Quality of systematic review (QSR)	Quality of studies (QS) (RCT-PQRS ≥ 24)	Treatment fidelity (FI)	GRADE				Publication bias	N patients (both arms)	Effect size (95% CI)	GRADE QSR, QS, FI Total rating
				Risk of bias	Inconsistency	Indirectness	Imprecision				
PDT vs. all controls											
Personality disorder symptoms (critical) 5 RCTs	11/11	81%	+	Yes	No	No	No	Undetected	239	–0.63 (–0.87, –0.41) I^2=11%	–+++ +++ Moderate
Functioning (important) 6 RCTs (1 outlier excluded)	11/11	67%	+	Yes	No	No	No	Not assessed	431	–0.72 (–1.04, –0.41) I^2=42%	–+++ +++ Moderate
Suicidality (important) 4 RCTs (1 outlier excluded)	11/11	75%	+	Yes	No	No	Yes	Not assessed	239	–0.67 (–1.13, –0.20) I^2=40%	–++– +++ Low
PDT vs. active controls											
Personality disorder symptoms (critical) 4 RCTs	11/11	75%	+	Yes	No	No	No	Not assessed	200	–0.65 (–0.99, –0.32) I^2=15%	–+++ +++ Moderate
PDT vs. active therapies											
Personality disorder symptoms (critical) 6 RCTs (1 outlier excluded)	11/11	83%	+	Yes	No	No	No	Not detected	473	–0.04 (–0.31, 0.22) I^2=38%	–+++ +++ Moderate
Personality disorder symptoms follow-up (important) 4 RCTs (1 outlier excluded)	11/11	100%	+	Yes	No	No	No	Not assessed	370	–0.18 (–0.38, 0.03) I^2=5%	–+++ +++ Moderate
Functioning (important) 4 RCTs	11/11	100%	+	No	No	No	No	Not assessed	394	0.12 (–0.12, 0.36) I^2=2%	++++ +++ High
Interpersonal problems (important) 4 RCTs	11/11	100%	+	No	No	No	No	Not assessed	394	–0.05 (–0.20, 0.12) I^2=2%	++++ +++ High
Follow-up interpersonal problems (important) 4 RCTs (1 outlier excluded)	11/11	100%	+	Yes	No	No	No	Not assessed	370	–0.23 (–0.28, 0.17) I^2=0%	–+++ +++ Moderate

RCTs – randomized controlled trials; RCT-PQRS – Randomized Controlled Trial Psychotherapy Quality Rating Scale; GRADE – Grading of Recommendations Assessment, Development, and Evaluation

PDT and other active therapies. The sample sizes exceeded the OIS (N=62) determined for functioning.

An RCT found PDT to be superior to dialectical behavior therapy and supportive therapy in improving reflective functioning and attachment in borderline personality disorder, thus showing an additional gain[74]. For improving reflective functioning, the effect size in favour of PDT was large (d=–0.84) compared to supportive therapy and medium (d=–0.55) compared to dialectical behavior therapy[74].

Two RCTs suggest that PDT is a cost-effective treatment in personality disorders and high utilizers of psychiatric services[75,76]. The efficacy of PDT for personality disorders has not been specifically tested in minorities. In one RCT of PDT, non-occurrence of any adverse events was explicitly reported[75].

GRADE

According to the results presented above, there is a relatively wide range of studies of PDT in personality disorders (n=16). PDT achieved a clinically meaningful medium effect size compared to all controls (g=–0.63) and active controls (g=–0.65) in the reduction of core personality disorder symptoms. No differences in efficacy compared to other active therapies were detected (g=–0.04). We did not find serious indications of inconsistency, indirectness, imprecision or publication bias (see Table 3). The CIs were relatively wide, but comparable to those of other active therapies[72]. Most studies showed a sufficient quality (81%) as assessed by the RCT-PQRS, and sufficient treatment fidelity. The quality of the meta-analysis was rated as very good.

For comparisons with all controls and active controls in personality disorders, most studies showed a low risk of bias for random sequence generation and blinding, and an unclear or high risk for allocation concealment and completeness (see also supplementary information). For comparisons with active therapies, most studies showed a low risk of bias for blinding, but an unclear or high risk for all other dimensions. As noted above, the GRADE guidelines recommend to be conservative in rating down the quality of evidence. Thus, taking all results into account, the review panel decided to downgrade the evidence for PDT in personality disorders by one level due to risk of bias, rating the evidence for critical outcomes as moderate (see Table 3).

Somatic symptom disorders

The eligible recent meta-analysis assessing the efficacy of PDT for somatic symptom disorders, in comparison with control conditions or active therapies, included 17 RCTs (N=2,106)[40]. There was some heterogeneity between the PDT methods, but they were all based on psychodynamic theory and technique[17].

Efficacy of PDT vs. control conditions and active therapies

PDT was significantly superior to control conditions in improving somatic symptoms, with a large effect size (SMD=–0.84, 95% CI: –1.35 to –0.33, n=11, N=895). There was evidence for possible publication bias (Egger's regression asymmetry test = –3.49, 95% CI: –5.65 to –1.33, p=0.047). Excluding one outlier[77] reduced heterogeneity to a moderate level, resulting in a medium effect size (SMD=–0.47, 95% CI: –0.70 to –0.23, n=10, I^2=55%, N=776).

Compared to active controls, PDT achieved a moderate effect size (SMD=–0.41; 95% CI: –0.74 to –0.09, n=7, N=644, I^2 = 70%).

PDT was significantly superior to control conditions in 3-6 month follow-ups (SMD=–0.45, 95% CI: –0.69 to –0.20, n=4, I^2=30%, N=479). At >6 month follow-up, the effect size was large (SMD= –1.17, 95% CI: –2.07 to 0.27, n=6, N=801), but I^2 was also large at 97%. When removing one outlier[77], the effect size was significant but small (SMD=–0.17, 95% CI: –0.32 to –0.02, n=5, I^2=26%, N=702). Compared to active controls 3-6 months after end of therapy, PDT achieved a medium effect size (SMD=–0.45, 95% CI: –0.69 to –0.20, n=4, I^2=30%, N=479).

We used d=±0.25 as a conservative estimate for a minimum clinically meaningful effect size, resulting in an OIS of 398[53]. The effect size in the reduction of somatic symptoms was significant and the sample size exceeded the OIS (N=776 > 398) for PDT vs. control conditions. The lower boundary of the CI represents a medium to large effect size; the upper boundary is slightly below –0.25 and may still represent a clinically meaningful effect size. The width of the CI is comparable to psychotherapy in somatic symptom disorders in general (see supplementary information). Five RCTs suggest that PDT is at least as efficacious as other therapies, including CBT[40].

There were no indications of serious indirectness with regard to patients, treatments outcomes, or comparisons in any of the analyses.

Quality measures

The quality of the eligible meta-analysis was found to be very good, with 11/11 relevant items fulfilled. The quality of primary studies was assessed according to the criteria defined by Guidi et al[78]: of the 17 studies, 94% described the longitudinal development of the somatic condition, 100% described treatment components, 76.4% reported past/current medication use, 64.7% described weakness of controls, 41.1% used observer and self-rated instruments, while only 17.6% described adverse effects beyond dropout rates, and 24% reported rates of deterioration after treatment beyond dropout rates.

As to treatment fidelity, all but one study used a treatment manual or manual-like guideline (94%), 53% of studies monitored treatments by video or audio recordings, and 53% checked treatment integrity by adherence ratings.

Adequate random sequence generation, allocation concealment, blinding of assessors (or use of only self-report measures) and report of complete outcome data were found in 59%, 53%, 59% and 76% of all studies; in 70%, 70%, 80% and 80% of the studies including all controls, and in 71%, 71%, 86% and 86% of studies including active controls only, respectively.

Secondary outcomes

PDT achieved a medium effect size compared to control conditions in improving functioning at short-term (SMD=–0.58, 95% CI: –1.16 to –0.01, n=5, I^2=88%, N=641). In the follow-up >6 months after end of therapy, a non-significant effect size was achieved compared to all controls (SMD=–0.05, 95% CI: –0.63 to 0.73, n=3, I^2=89%, N=641) (see Table 4).

One RCT suggests that PDT is a cost-effective treatment in somatic symptom disorders[79]. No studies have addressed the efficacy of PDT in minorities. No or only a few adverse events were reported in studies of PDT in somatic symptom disorders.

GRADE

There is a relatively wide range of RCTs of PDT in somatic symptom disorders (n=17). PDT was significantly superior to all controls with a medium effect size (SMD=–0.47). In addition, there is preliminary evidence from individual RCTs that PDT is at least as efficacious as other empirically-supported therapies. Treatment effects were found to be stable at follow-ups. There is evidence to suggest that the benefits outweigh the costs and harms, as required by GRADE[6,60]. We did not find serious inconsistency, indirectness or imprecision. There seems to be some publication bias.

Most studies showed a sufficient quality and treatment fidelity, and the quality of the meta-analysis was rated as good. For comparisons of PDT with all controls and active controls, most studies showed a low risk of bias in critical outcomes for random sequence generation, allocation concealment, blinding and completeness. Taking these results into account, the review panel decided to rate the evidence for PDT in somatic symptom disorders as high for critical outcomes (see Table 4).

Mechanisms of change in PDT

Our systematic search yielded one recent meta-analysis reporting a significant moderate correlation (r=0.31) between insight and outcome across a variety of psychotherapeutic approaches, including PDT[46]. Studies in depressive disorders, anxiety disorders and Cluster C personality disorders found that gains in insight preceded improvements in outcome of PDT[80-82]. These effects were found to be specific to PDT[80-82]. In personality disorders, the effect of transference work in patients with more severe interpersonal difficulties was found to be mediated by both improvements in insight and affect awareness[83].

A recent meta-analysis found a significant moderate correlation of 0.28 between alliance and outcome across different psychotherapies, with no significant differences between approaches[84]. For PDT, the correlation was 0.24[84]. With regard to diagnoses, associations were similar in anxiety, depressive and personality disorders[84]. There is preliminary evidence from studies examining within-patient effects that the alliance may have a causal role in improving outcomes[32], including studies of PDT (in depressive disorders)[85]. Specifically for PDT, it has been documented that the temporal precedence of alliance predicting symptom change becomes stronger with time over the course of long-term therapy[86].

Change in defense mechanisms was found to be related to outcome in studies of PDT in patients with depressive, anxiety and personality disorders, with correlations between 0.28 and 0.64[87,88]. The largest correlations were found for improvements in depression and functioning (0.64, 0.60)[87,88]. However, only a few studies of defense mechanisms examined temporal precedence[32].

A recent study found that PDT outcome in patients with borderline personality disorder was strongly related to improvements in reflective functioning (r=0.89)[89]. However, this study did not examine whether change in reflective functioning preceded change in outcome.

There is some evidence that emotion processing plays a role in PDT of somatic symptom disorders[90]. Furthermore, recent studies highlight the importance of both insight and emotional experiencing as mechanisms of change in PDT for depressive, anxiety and personality disorders[83,91].

Summary and recommendations

A synthesis of the most recent evidence for PDT in depressive, anxiety, personality and somatic symptom disorders as reviewed above is given in Tables 1-4, while a summary for quality of evidence and recommendations is provided in Table 5.

According to the revised EST criteria[3], there is evidence for the efficacy of PDT in these disorders based on recent systematic quantitative reviews, covering a relatively wide range of studies, showing a sufficient conceptual homogeneity between treatments, with sufficient quality of most individual studies (except for anxiety disorders comparing PDT with active controls), sufficient quality of meta-analyses, and sufficient treatment fidelity. No serious indirectness, imprecision, inconsistency or publication bias concerning critical outcomes was found, with the possible exception of publication bias in somatic symptom disorders. Clinically meaningful effects in target symptom improvement compared to (active) controls were found, with moderate heterogeneity after removing outliers, as well as stable effects in longer-term follow-ups, and low risk of adverse events. Clinically meaningful effect sizes in functioning were found in all disorders with the exception of anxiety disorders. Differences in comparison to other active therapies were small and not clinically significant, suggesting equivalence in efficacy. Furthermore, for PDT in the aforementioned disorders, there is some evidence for presumed mechanisms of change. There is also some preliminary evidence that PDT is cost-effective, effective under conditions of routine clinical practice, and efficacious in some sub-populations of the above disorders, which represent contextual factors as listed in the new EST model[3]. A positive balance between benefits, costs and harms exists.

In sum, the results for PDT in the examined disorders fulfill several criteria for high quality evidence according to the new EST model[3]. Some limitations exist as well. There is room for further

Table 4 Synthesis of evidence profiles for psychodynamic therapy (PDT) in somatic symptom disorders

Outcomes	Quality assessment								Summary of findings		Quality of evidence
	Quality of systematic review (QSR)	Quality of studies (QS)	Treatment fidelity (FI)	GRADE				Publication bias	N patients (both arms)	Effect size (95% CI)	GRADE QSR, QS, FI Total rating
				Risk of bias	Inconsistency	Indirectness	Imprecision				
PDT vs. all controls											
Somatic symptoms (critical) 10 RCTs (1 outlier excluded)	11/11	+	+	No	No	No	No	Possible	776	–0.47 (–0.70, –0.23) I^2=55%	++++ +++ High
3-6 month follow-up somatic symptoms (important) 4 RCTs	11/11	+	+	Yes	No	No	No	Not assessed	479	–0.45 (–0.69, –0.20) I^2=30%	–+++ +++ Moderate
>6 month follow-up somatic symptoms (important) 6 RCTs (1 outlier excluded)	11/11	+	+	Yes	No	No	No	Not assessed	702	–0.17 (–0.32, –0.02) I^2=26%	–+++ +++ Moderate
Functioning (important) 5 RCTs	11/11	+	+	No	Yes	No	Yes	Not assessed	641	–0.58 (–1.16, –0.01) I^2=88%	+–+– +++ Low
>6 month follow-up functioning (important) 3 RCTs	11/11	+	+	No	Yes	No	Yes	Not assessed	377	–0.05 (–0.63, 0.73) I^2=89%	+–+– +++ Low
PDT vs. active controls											
0-3 month follow-up somatic symptoms (critical) 7 RCTs (1 outlier excluded)	11/11	+	+	No	No	No	No	Not assessed	644	–0.41 (–0.74, –0.09) I^2=70%	++++ +++ High
3-6 month follow-up somatic symptoms (important) 4 RCTs	11/11	+	+	Yes	No	No	No	Not assessed	479	–0.45 (–0.69, –0.20) I^2=30%	–+++ +++ Moderate

Table 4 Synthesis of evidence profiles for psychodynamic therapy (PDT) in somatic symptom disorders *(continued)*

	Quality assessment								Summary of findings		Quality of evidence
				GRADE							
Outcomes	Quality of systematic review (QSR)	Quality of studies (QS)	Treatment fidelity (FI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	N patients (both arms)	Effect size (95% CI)	GRADE QSR, QS, FI Total rating
>6 month follow-up somatic symptoms (important) 6 RCTs (1 outlier excluded)	11/11	+	+	Yes	No	No	No	Not assessed	702	–0.17 (–0.32, –0.02) I^2=26%	–+++ +++ Moderate
0-3 month follow-up functioning (important) 4 RCTs	11/11	+	+	No	Yes	No	Yes	Not assessed	504	–0.57 (–1.22, 0.09) I^2=91%	+–+– +++ Low
>6 month follow-up functioning (important) 3 RCTs	11/11	+	+	No	Yes	No	Yes	Not assessed	378	–0.16 (–0.70, 0.38) I^2=82%	+–+– +++ Low

RCTs – randomized controlled trials; GRADE – Grading of Recommendations Assessment, Development, and Evaluation

Table 5 Summary of the status of psychodynamic therapy (PTD) as an empirically supported treatment for common mental disorders

	Comparison (critical outcome)	Effect size (95% CI)	GRADE	Quality of evidence	Efficacy demonstrated across several patient sub-populations	Evidence for mechanisms of change	Recommendation
Depressive disorders	PDT vs. all controls	–0.58 (–0.33, –0.83)	++++	High		Yes	Strong
	PDT vs. active controls	–0.51 (–0.68, –0.35)	++++	High	Yes		
	PDT vs. active therapies	–0.03 (–0.23, 0.17)	–+++	Moderate			
Anxiety disorders	PDT vs. all controls	–0.72 (–1.06, –0.37)	–+++	Moderate	Yes	Yes	Strong
	PDT vs. active controls	–0.64 (–1.14, –0.14)	–++–	Low			
	PDT vs. active therapies	0.06 (–0.11, 0.23)	–+++	Moderate			
Personality disorders	PDT vs. all controls	–0.63 (–0.87, –0.41)	–+++	Moderate	Yes	Yes	Strong
	PDT vs. active controls	–0.65 (–0.99, –0.32)	–+++	Moderate			
	PDT vs. active therapies	–0.04 (–0.31, 0.22)	–+++	Moderate			
Somatic symptom disorders	PDT vs. all controls	–0.47 (–0.70, –0.23)	++++	High	Yes	Yes	Strong
	PDT vs. active controls	–0.41 (–0.74, –0.09)	++++	High			

GRADE – Grading of Recommendations Assessment, Development, and Evaluation

research on mechanisms of change in PDT, controlling for temporal precedence. In addition, further studies in minorities and on cost-effectiveness of PDT are needed. With regard to improvements in functioning, the quality of evidence was low in anxiety and somatic symptom disorders.

The new EST model provides three options of recommendation: "very strong", "strong" or "weak"[3]. According to the results presented above, there is high quality evidence for depressive disorders and somatic symptom disorders, and moderate quality evidence for anxiety and personality disorders, that PDT achieves clinically meaningful effects in target symptoms and functioning compared to controls and is associated with low risk of harms and reasonable costs[3]. In addition, there is moderate quality evidence that there are no meaningful differences in efficacy between PDT and other active therapies. Thus, the criteria of the new EST model suggest that a "strong" recommendation for PDT in depressive, anxiety, personality and somatic symptom disorders is most appropriate (see Table 5).

DISCUSSION

This umbrella review suggests that PDT represents an evidence-based psychotherapy for depressive, anxiety, personality and somatic symptom disorders. Limitations of research on PDT were identified as well. For some analyses, our review relied on a limited number of RCTs. Some of these RCTs were old and of poor quality. The included meta-analyses aggregated different categorical diagnoses – such as different forms of depressive, anxiety, personality or somatic symptom disorders – due to the limited number of RCTs per condition. However, this is consistent with the transdiagnostic approach of the new EST model, demonstrating efficacy of PDT across several patient populations.

On the other hand, our review has several strengths. We applied several criteria specified by the new EST model not used in some other recent reviews using that model[92-94], including all the assessments required by GRADE guidelines (risk of bias of individual studies; rating of inconsistency, indirectness and imprecision via the OIS) as well as the assessment of the quality and treatment fidelity of individual studies, and of clinical significance of effect sizes. Furthermore, we primarily included only recent meta-analyses published in the past two years, reviewed cost-effectiveness and mechanisms of change, and systematically reported effect sizes for the different comparison conditions.

Across all evidence-based treatments, the rates of response and remission are limited[30,95]. Thus, a focus of future research on PDT should be on helping the considerable proportion of patients not responding to the available treatments. As a related issue, it is important to find out which patients benefit from which therapy, taking possible moderators into account such as disorder severity, comorbid disorders, personality features, staging of disorder and previous treatment failures/resistance, and family history of mental illness, aiming at a personalized treatment approach[96-99].

Another focus should be on treatment dose, addressing for which patients which number of sessions, session frequency or treatment duration is required. Further individual RCTs of PDT are required in those areas where only a few or old RCTs are available, as well as for specific mental disorders such as bipolar or psychotic disorders. A focus on unified transdiagnostic protocols addressing syndromes rather than categorical diagnoses represents another promising approach which is in accordance with both the transdiagnostic nature of PDT and the new model for EST[21-25]. Focusing on transdiagnostic features such as work-related problems, including perfectionism and procrastination, is another understudied area[100]. More studies are required in which PDT is tailored to minorities and underserved groups. Finally, available treatments may be improved by process-outcome research identifying empirically-supported mechanisms of change[101].

Psychotherapy is a field of rivalry between different approaches. However, patients should be offered a variety of research-supported treatments. The limited rates of remission and response for evidence-based treatments show that no single approach fits all patients. Further studies are needed to identify treatment moderators showing who benefits from which treatment.

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Therapist-supported Internet-based cognitive behaviour therapy yields similar effects as face-to-face therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis

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Providing therapist-guided cognitive behaviour therapy via the Internet (ICBT) has advantages, but a central research question is to what extent similar clinical effects can be obtained as with gold-standard face-to-face cognitive behaviour therapy (CBT). In a previous meta-analysis published in this journal, which was updated in 2018, we found evidence that the pooled effects for the two formats were equivalent in the treatment of psychiatric and somatic disorders, but the number of published randomized trials was relatively low (n=20). As this is a field that moves rapidly, the aim of the current study was to conduct an update of our systematic review and meta-analysis of the clinical effects of ICBT vs. face-to-face CBT for psychiatric and somatic disorders in adults. We searched the PubMed database for relevant studies published from 2016 to 2022. The main inclusion criteria were that studies had to compare ICBT to face-to-face CBT using a randomized controlled design and targeting adult populations. Quality assessment was made using the Cochrane risk of bias criteria (Version 1), and the main outcome estimate was the pooled standardized effect size (Hedges' g) using a random effects model. We screened 5,601 records and included 11 new randomized trials, adding them to the 20 previously identified ones (total n=31). Sixteen different clinical conditions were targeted in the included studies. Half of the trials were in the fields of depression/depressive symptoms or some form of anxiety disorder. The pooled effect size across all disorders was g=0.02 (95% CI: –0.09 to 0.14) and the quality of the included studies was acceptable. This meta-analysis further supports the notion that therapist-supported ICBT yields similar effects as face-to-face CBT.

Key words: Cognitive behaviour therapy, Internet-based cognitive-behaviour therapy, face-to-face therapy, depression, anxiety disorders, online psychotherapy, meta-analysis

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One of the most central challenges for health care services is dissemination of evidence-based psychological treatments[1,2]. This is especially relevant for psychiatric services, but, with a growing number of somatic disorders for which psychological treatment is providing promising results (e.g., tinnitus and irritable bowel syndrome[3,4]), the challenge is also relevant to the broader health care context.

Cognitive behaviour therapy (CBT) is the psychological treatment with the strongest empirical support, and is often the recommended first-line treatment for a range of common mental disorders[5,6]. One way to increase the availability of CBT is to use an Internet-based intervention (ICBT) with minimal clinician support. This treatment format typically means that the individual has access to a secure digital platform where treatment materials in form of texts, video and audio clips, and structured assignments to promote behaviour change, are provided[7].

In the present paper, we define ICBT as online CBT where there is some form of therapist guidance, typically through asynchronous text messages where the therapist provides feedback on assignments, encouragement, and general support. Key advantages of ICBT are that it requires substantially less therapist time per treated patient, and that no scheduled therapist-patient appointments at the clinic or via video are needed.

As conventional face-to-face CBT is arguably the gold-standard psychological treatment for many common clinical conditions, an important question is to what extent therapist-guided ICBT can produce similar effects as face-to-face CBT in terms of symptomatic improvement. In an early systematic review and meta-analysis published in this journal[8], we identified 13 randomized controlled trials comparing ICBT to face-to-face CBT and estimated the pooled post-treatment effect size as g=–0.01 (95% CI: –0.13 to 0.12). In an updated meta-analysis four years later[9], the total number of included randomized trials had increased to 20 and the pooled effect size (g=0.05; 95% CI: –0.09 to 0.20) again suggested that the two formats yield equivalent outcomes.

In both the above reviews we found that, for each specific disorder, there were relatively few randomized trials comparing ICBT to face-to-face CBT. The tendency of the field seemed to be to develop and test ICBT for new indications rather than building a firm evidence base for a specific disorder by comparing that treatment against face-to-face CBT. As ICBT is a field that moves rapidly, and five years have passed since the latest review, we considered it timely to update the systematic review and meta-analysis of randomized controlled trials comparing ICBT to face-to-face CBT for adults with psychiatric and somatic disorders.

METHODS

Design, search strategy and selection of studies

This is a systematic review and meta-analysis building on and updating the two previously published reviews[8,9] (i.e., studies included in the previous reviews were retained, and studies published since then were added), and using the same statistical methods and criteria for study eligibility and quality assessment.

We searched the PubMed database for studies comparing ICBT to face-to-face CBT published from January 1, 2016 to September 13, 2022, using search terms relating to randomized controlled trial designs in combination with a range of clinical conditions and the Internet. The full search string is available in the supplementary information.

Following the same procedures as in our previous systematic reviews, the main inclusion criteria were that, in order for a study to be included, it had to: a) compare therapist-guided ICBT with face-to-face CBT; b) use a randomized controlled design; c) target an adult population; d) test interventions that aimed to treat a manifest clinical condition (in contrast to, for example, preventive care); e) use an online intervention in which ICBT was the main component; and f) use a full-length face-to-face treatment.

We did not search "grey literature", such as dissertations or conference abstracts, and only included studies published in English.

Quality assessment

In order to evaluate the quality of the included studies, we used the Cochrane assessment of bias criteria (Version 1)[10]. This meant that we assessed, for each study, selection bias related to the generation of the randomized sequence, selection bias related to allocation concealment, detection bias (i.e., integrity of masked clinician-assessment, where applicable), attrition bias related to incomplete data, and reporting bias related to the selective reporting of results. Each of the variables was rated as "low risk", "high risk", or "unclear".

Statistical methods

The main unit of analysis was the between-group (ICBT vs. face-to-face CBT) difference at post-treatment. We estimated the pooled standardized effect size across all studies (Hedges' g) using a linear random effects model as implemented in Review Manager (RevMan) Version 5.1. In these analyses, we used the primary outcome (provided it was continuous) as reported in the original study. If no such primary outcome was reported, we used the first reported validated outcome measure of the core symptom domain targeted by the treatment (i.e., if a treatment was designed to treat depression and no primary outcome was reported, we used the first reported measure of depressive symptoms). In studies where both intent-to-treat and per-protocol outcome data were reported, we used the former in the analyses.

To quantify heterogeneity across studies we used the I^2 test, which estimates how much of the total variance in the effect is due to between-study variability rather than chance[11]. This was complemented with X^2 tests for significance of heterogeneity. Analyses were conducted to assess how robust the pooled effect estimate was after exclusion of two studies that contributed substantially to the overall heterogeneity.

We also conducted sensitivity analyses by comparing subgroups of studies where individual treatment was used in the face-to-face arms to those which used group treatment, and by comparing studies that were rated as having high quality on all assessment of bias criteria to those which were not.

To estimate the risk of publication bias, we used a funnel plot where effect sizes of the studies were related to their respective standard errors. A symmetrical distribution around the mean would be indicative of low risk of bias.

As this was an updated meta-analysis in which we did not control trial recruitment, the study was not conducted contingent on a power analysis. However, as a reference, if we had found just one additional study with a number of participants corresponding to the mean one in our most recent meta-analysis, the statistical power to detect a small standardized mean difference of 0.2 in a random effects model analysis, given an alpha-level of 0.05 and a moderate heterogeneity (I^2=50%), would have been approximately 77% (Metapower for R application).

RESULTS

Overall description of study inclusion

Figure 1 provides the flow chart for the inclusion of studies. After removal of duplicates, we screened 5,601 records and included 11 new studies that met all inclusion criteria, which were added to the 20 studies previously identified. Thus, the total number of studies in this review was 31.

These studies included 3,053 participants in the ICBT and face-to-face CBT arms, rendering a mean number of participants per study of 98.5 (standard deviation, SD = 60.6) and a median of 80 (interquartile range, IQR = 49-163). The trials were conducted in Australia, China, Finland, Germany, Sweden, The Netherlands, the UK, the US and Switzerland.

In the 11 new studies, the clinical conditions targeted (one study each) were binge eating disorder[12], bulimia nervosa[13], health anxiety[14], insomnia[15], obsessive-compulsive disorder[16], postnatal depression[17], post-traumatic stress disorder[18], psychological distress in cancer patients[19], serious mental illness[20], social anxiety disorder[21], and subthreshold depression[22].

Table 1 provides a description of selected characteristics of all studies included in the review[12-42]. In the 31 studies, the clinical conditions targeted were depression/depressive symptoms (n=5), social anxiety disorder (n=4), panic disorder (n=3), insomnia (n=3), tinnitus (n=2), animal phobia (n=2), body dissatisfaction (n=2), binge eating disorder (n=1), bulimia nervosa (n=1), health anxiety (n=1), obsessive-compulsive disorder (n=1), postnatal depression (n=1), post-traumatic stress disorder (n=1), psychological distress in cancer patients (n=1), serious mental illness (n=1), fibromyalgia (n=1), and male sexual dysfunction (n=1).

Analysis of treatment effects

Throughout the results presentation, negative effect size (g) estimates reflect larger treatment effects for ICBT, and positive estimates reflect effects in favour of face-to-face CBT. The pooled

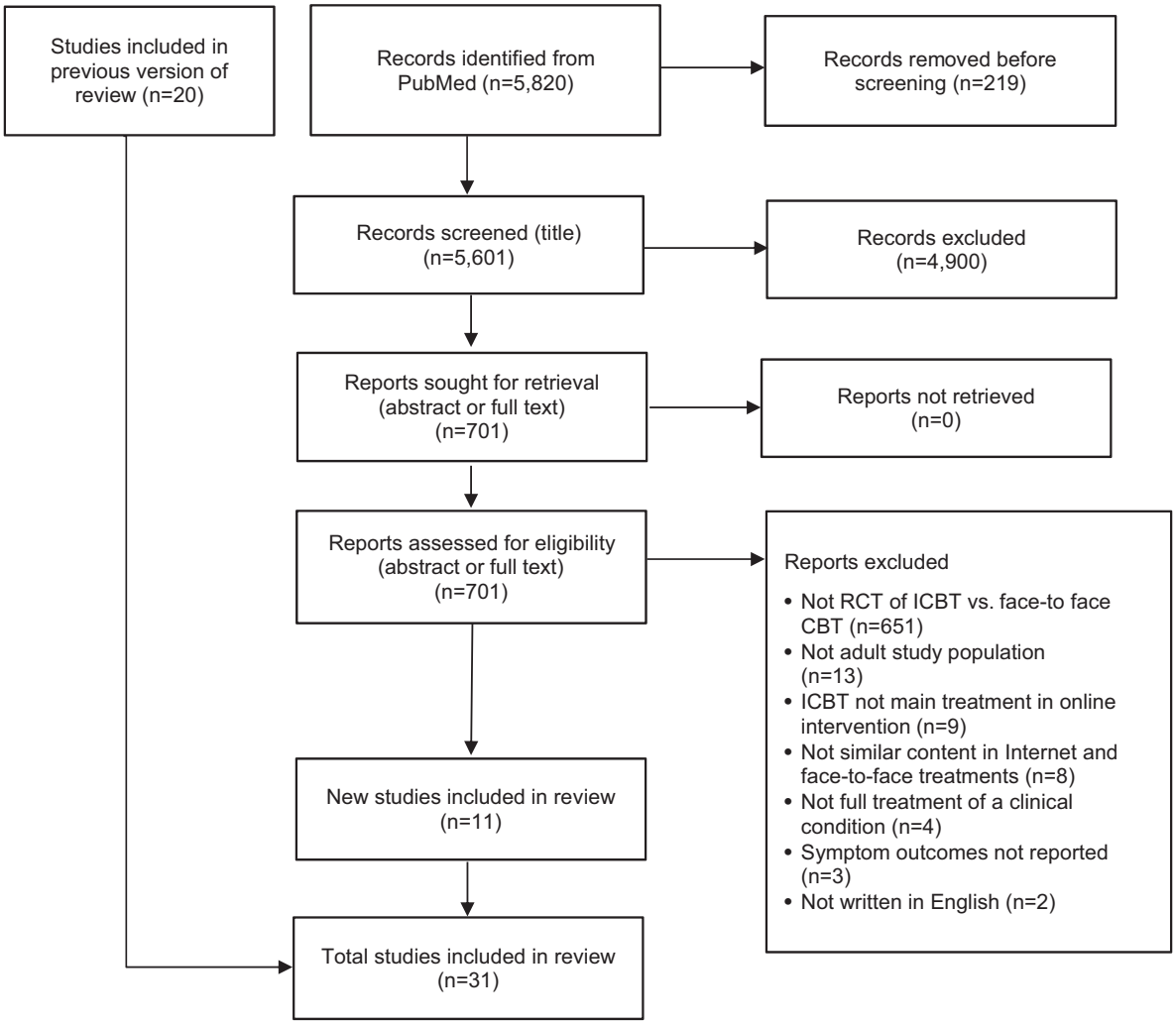

Figure 1 Flow chart of inclusion of studies. RCT – randomized controlled trial, CBT – cognitive behaviour therapy, ICBT – Internet-based cognitive behaviour therapy

standardized effect size post-treatment was g=0.02 (95% CI: –0.09 to 0.14), suggesting similar effects for ICBT and face-to-face CBT in terms of symptomatic improvement across all studies.

Figure 2 presents a forest plot showing the effects of the individual studies as well as the effects according to clinical subgroups. The I^2 test indicated the presence of moderate heterogeneity (54%), also reflected in significant X^2 test results (X^2=65.43, df=30, p=0.0002). We ran a sensitivity analysis after removal of two studies that were clear outliers (large effect sizes with CIs that did not overlap with those of the pooled effect size)[17,41], which reduced the heterogeneity to 23% (X^2=36.13, df=28, p=0.14) and yielded a similar pooled effect size of g=0.01 (95% CI: –0.07 to 0.10).

As one study[20] used a form of face-to-face treatment where we were uncertain as to whether it should be classified as CBT, we also conducted a sensitivity analysis with that study removed, which did not affect the pooled effect size (g=0.02; 95 % CI: –0.10 to 0.14).

Of the 31 randomized trials, 12 used face-to-face treatment in a group format and 19 used an individual format. We explored the potential role of type of format (individual vs. group) in a subgroup analysis, which indicated that the effect estimate was g=0.09 (95% CI: –0.07 to 0.25) in trials using individual treatment as compared to g=–0.08 (95% CI: –0.23 to 0.07) in those using group treatment. Despite the slight differences in observed effect sizes, there was no significant difference in pooled treatment effect between those subgroups (X^2=2.32, df=1, p=0.13), suggesting that the type of format in the face-to-face arms did not significantly affect the main outcome.

Quality of included studies

Figure 3 displays the results of the assessment of study quality based on the Cochrane risk of bias criteria. The criterion related to blinding of outcome assessors (detection bias) was not applicable in most studies, due to the use of self-report measures as outcome. We ran a subgroup analysis comparing studies rated as having a low risk of bias on all applicable criteria (n=17) to those which did not (n=14), and found a pooled effect size of g=–0.03

Table 1 Description of the studies included in the review – Internet-based treatment (INT) vs. face-to-face treatment (FTF)

Study	Disorder	N INT	N FTF	Outcome	Mean (SD) INT pre	Mean (SD) INT post	Mean (SD) FTF pre	Mean (SD) FTF post	Quality	Dropout rate	ITT	Sample
New studies included in current review												
de Zwaan et al[12]	Binge eating disorder	89	89	OBE days	14.1 (7.8)	3.9 (5.5)	13.5 (7.5)	2.0 (4.1)	Low risk of bias on all criteria	10%	Yes	Clinical
Zerwas et al[13]	Bulimia nervosa	98	98	Binge eating frequency	27.8 (22.5)	9.6 (10.6)	24.3 (17.1)	9.0 (10.2)	Unclear/high risk on at least one criterion	33%	Yes	Clinical
Axelsson et al[14]	Illness anxiety or somatic symptom disorder	102	102	HAI	33.9 (6.5)	21.0 (8.8)	34.2 (6.4)	20.4 (8.7)	Low risk of bias on all criteria	5%	Yes	Mixed
Gieselmann & Pietrowsky[15]	Insomnia	23	27	PSQI	12.0 (2.7)	6.8 (2.5)	11.4 (3.6)	7.7 (3.7)	Unclear/high risk on at least one criterion	8%	Yes	Self-referred
Lundström et al[16]	Obsessive-compulsive disorder	38	42	Y-BOCS	22.5 (3.9)	13.93 (4.9)	22.6 (3.8)	12.2 (5.8)	Low risk of bias on all criteria	8%	Yes	Mixed
Milgrom et al[17]	Postnatal depression	39	39	BDI-II	28.1 (7.9)	11.6 (9.0)	27.2 (10.0)	21.4 (12.2)	Low risk of bias on all criteria	13%	Yes	Mixed
Bisson et al[18]	Post-traumatic stress disorder	97	99	CAPS-5	34.6 (6.8)	13.1 (11.7)	35.6 (6.7)	13.0 (11.1)	Low risk of bias on all criteria	18%	Yes	Clinical
Compen et al[19]	Psychological distress in cancer patients	90	77	HADS	17.2 (7.1)	11.9 (6.2)	18.8 (6.7)	13.3 (6.3)	Low risk of bias on all criteria	17%	Yes	Mixed
Ben-Zeev et al[20]	Schizophrenia, schizoaffective disorder, bipolar disorder or depression	82	81	SCL-9	12.71 (7.2)	10.0 (6.5)	11.9 (8.1)	9.5 (7.3)	Low risk of bias on all criteria	9%	Yes	Clinical
Clark et al[21]	Social anxiety disorder	49	50	SAC	0.80 (0.7)	−1.27 (0.9)	0.71 (0.9)	−1.60 (1.0)	Low risk of bias on all criteria	1%	Yes	Clinical
Ying et al[22]	Subthreshold depression	110	110	CES-D	25.1 (2.5)	14.2 (4.7)	24.8 (4.7)	15.8 (2.7)	Low risk of bias on all criteria	27%	No	Self-referred
Studies retained from previous versions of the review												
Hedman et al[23]	Social anxiety disorder	64	62	LSAS	68.4 (21.0)	39.4 (19.9)	71.9 (22.9)	48.5 (25.0)	Low risk of bias on all criteria	12%	Yes	Mixed
Andrews et al[24]	Social anxiety disorder	23	14	SIAS	54.5 (12.4)	44.0 (15.9)	57.8 (43.9)	43.9 (18.7)	Unclear/high risk on at least one criterion	32%	Yes	Clinical
Botella et al[25]	Social anxiety disorder	62	36	FPSQ	53.3 (14.3)	39.7 (15.5)	50.5 (11.9)	39.3 (13.0)	Unclear/high risk on at least one criterion	55%	Yes	Mixed
Carlbring et al[26]	Panic disorder	25	24	BSQ	48.7 (11.7)	31.8 (11.6)	52.6 (10.8)	31.3 (9.1)	Low risk of bias on all criteria	12%	Yes	Self-referred
Bergström et al[27]	Panic disorder	53	60	PDSS	14.1 (4.3)	6.3 (4.7)	14.2 (4.0)	6.3 (5.6)	Low risk of bias on all criteria	18%	Yes	Mixed

Table 1 Description of the studies included in the review – Internet-based treatment (INT) vs. face-to-face treatment (FTF) *(continued)*

Study	Disorder	N INT	N FTF	Outcome	Mean (SD) INT pre	Mean (SD) INT post	Mean (SD) FTF pre	Mean (SD) FTF post	Quality	Dropout rate	ITT	Sample
Kiropoulos et al[28]	Panic disorder	46	40	PDSS	14.9 (4.4)	9.9 (5.9)	14.8 (4.0)	9.2 (5.7)	Low risk of bias on all criteria	0%	Yes	Self-referred
Spek et al[29]	Depressive symptoms in elderly	102	99	BDI	19.2 (7.2)	12.0 (8.1)	17.9 (10.0)	11.4 (9.4)	Unclear/high risk on at least one criterion	39%	Yes	Self-referred
Wagner et al[30]	Depressive symptoms	32	30	BDI	23.0 (6.1)	12.4 (10.0)	23.4 (7.6)	12.3 (8.8)	Unclear/high risk on at least one criterion	15%	Yes	Self-referred
Andersson et al[31]	Depressive symptoms	33	36	MADRS-S	23.6 (4.8)	13.6 (9.8)	24.1 (5.0)	17.1 (5.0)	Low risk of bias on all criteria	6%	Yes	Self-referred
Lappalainen et al[32]	Depressive symptoms	19	19	BDI-II	20.8 (9.3)	10.3 (8.2)	23.1 (6.4)	9.2 (5.2)	Unclear/high risk on at least one criterion	3%	No	Self-referred
Gollings & Paxton[33]	Body dissatisfaction	21	19	BSQ*	129.1 (27.3)	98.4 (35.6)	140.8 (37.2)	109.6 (47.7)	Unclear/high risk on at least one criterion	17.5%	Yes	Self-referred
Paxton et al[34]	Body dissatisfaction, disordered eating	42	37	BSQ*	134.3 (22.5)	116.8 (35.9)	143.3 (28.9)	105.8 (34.0)	Low risk of bias on all criteria	26%	Yes	Self-referred
Kaldo et al[35]	Tinnitus	26	25	TRQ	26.4 (15.6)	18.0 (16.2)	30.0 (18.0)	18.6 (17.0)	Unclear/high risk on at least one criterion	14%	Yes	Mixed
Jasper et al[36]	Tinnitus	41	43	Mini-TQ	12.2 (4.6)	7.4 (5.3)	14.2 (4.5)	8.1 (4.9)	Low risk of bias on all criteria	7%	Yes	Mixed
Schover et al[37]	Male sexual dysfunction	41	40	IIEF	27.4 (17.3)	31.3 (20.4)	26.4 (18.2)	34.4 (22.2)	Unclear/high risk on at least one criterion	20%	Yes	Mixed
Vallejo et al[38]	Fibromyalgia	20	20	FIQ	56.6 (19.8)	57.0 (18.2)	68.4 (19.5)	58.2 (18.6)	Unclear/high risk on at least one criterion	0%	Yes	Clinical
Andersson et al[39]	Spider phobia	15	15	BAT	6.2 (2.6)	10.5 (1.5)	7.3 (1.6)	11.1 (1.2)	Unclear/high risk on at least one criterion	10%	No	Self-referred
Andersson et al[40]	Snake phobia	15	15	BAT	4.1 (3.3)	9.6 (2.6)	3.0 (3.1)	11.2 (2.1)	Unclear/high risk on at least one criterion	13%	No	Self-referred
Lancee et al[41]	Insomnia	30	30	ISI	18.2 (2.9)	12.4 (4.8)	17.3 (2.9)	7.1 (4.2)	Unclear/high risk on at least one criterion	8%	Yes	Self-referred
Blom et al[42]	Insomnia	24	24	ISI	18.7 (4.4)	9.7 (5.3)	17.9 (3.9)	8.4 (4.9)	Low risk of bias on all criteria	6%	Yes	Self-referred

ITT – intention-to-treat, OBE – Objective Binge Eating, HAI – Health Anxiety Inventory, PSQI – Pittsburgh Sleep Quality Index, Y-BOCS – Yale-Brown Obsessive Compulsive Scale, CAPS-5 – Clinician Administered PTSD Scale for DSM-5, HADS – Hospital Anxiety and Depression Scale, SCL – Symptom Check List, SAC – Social anxiety composite, CES-D – Center for Epidemiological Studies Depression Scale, LSAS – Liebowitz Social Anxiety Scale, SIAS – Social Interaction Anxiety Scale, FPSQ – Fear of Public Speaking Questionnaire, BSQ – Body Sensation Questionnaire, BSQ* – Body Shape Questionnaire, PDSS – Panic Disorder Severity Scale, BDI – Beck Depression Inventory, MADRS-S – Montgomery Åsberg Depression Rating Scale - Self-rated, TRQ – Tinnitus Reaction Questionnaire, Mini-TQ – Mini Tinnitus Questionnaire, IIEF – International Index of Erectile Function, FIQ – Fibromyalgia Impact Questionnaire, BAT – Behavioural Approach Test, ISI – Insomnia Severity Index.

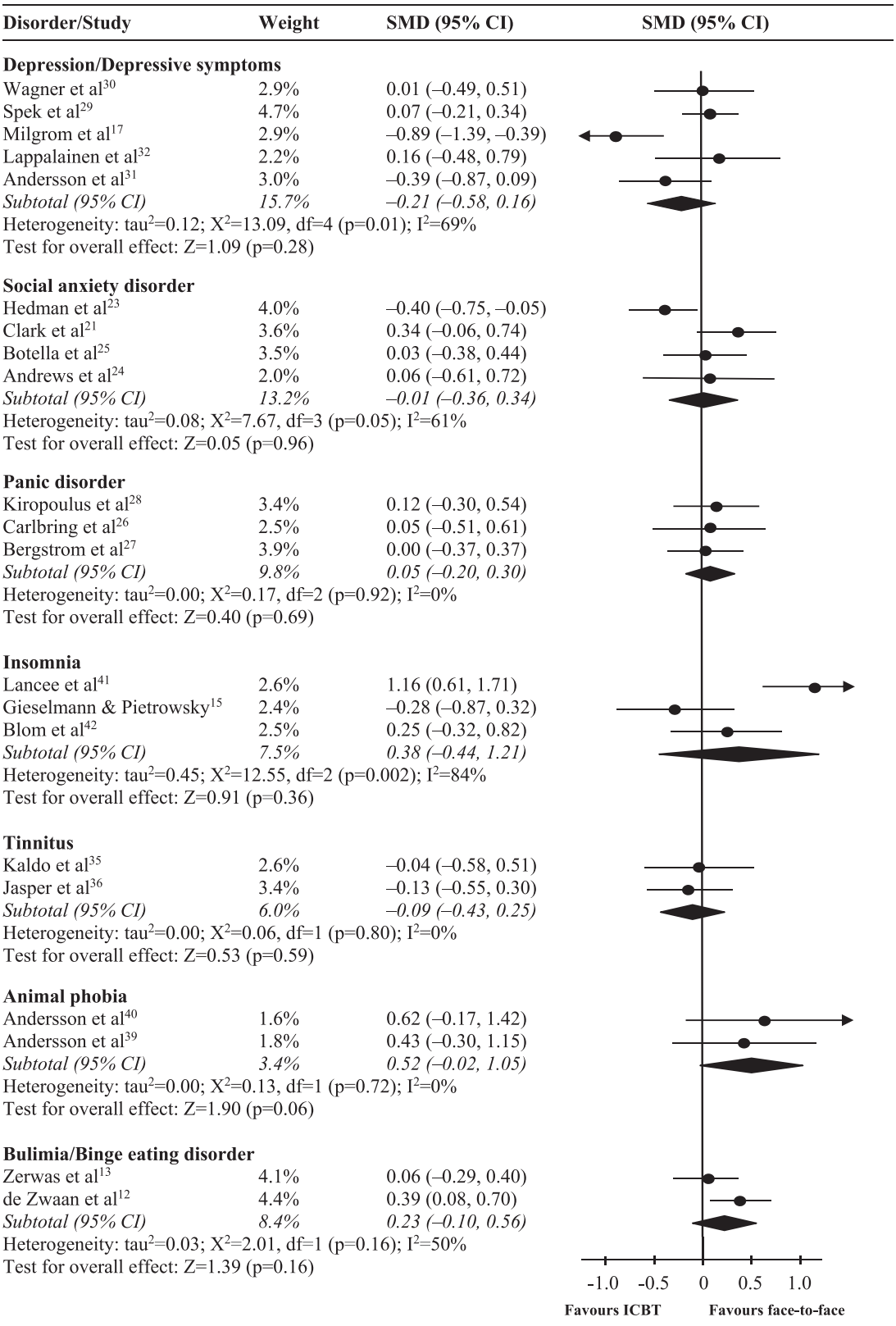

Figure 2 Forest plot of standardized effect size (g) for Internet-based cognitive behaviour therapy (ICBT) vs. face-to-face therapy (CBT). SMD – standard mean difference

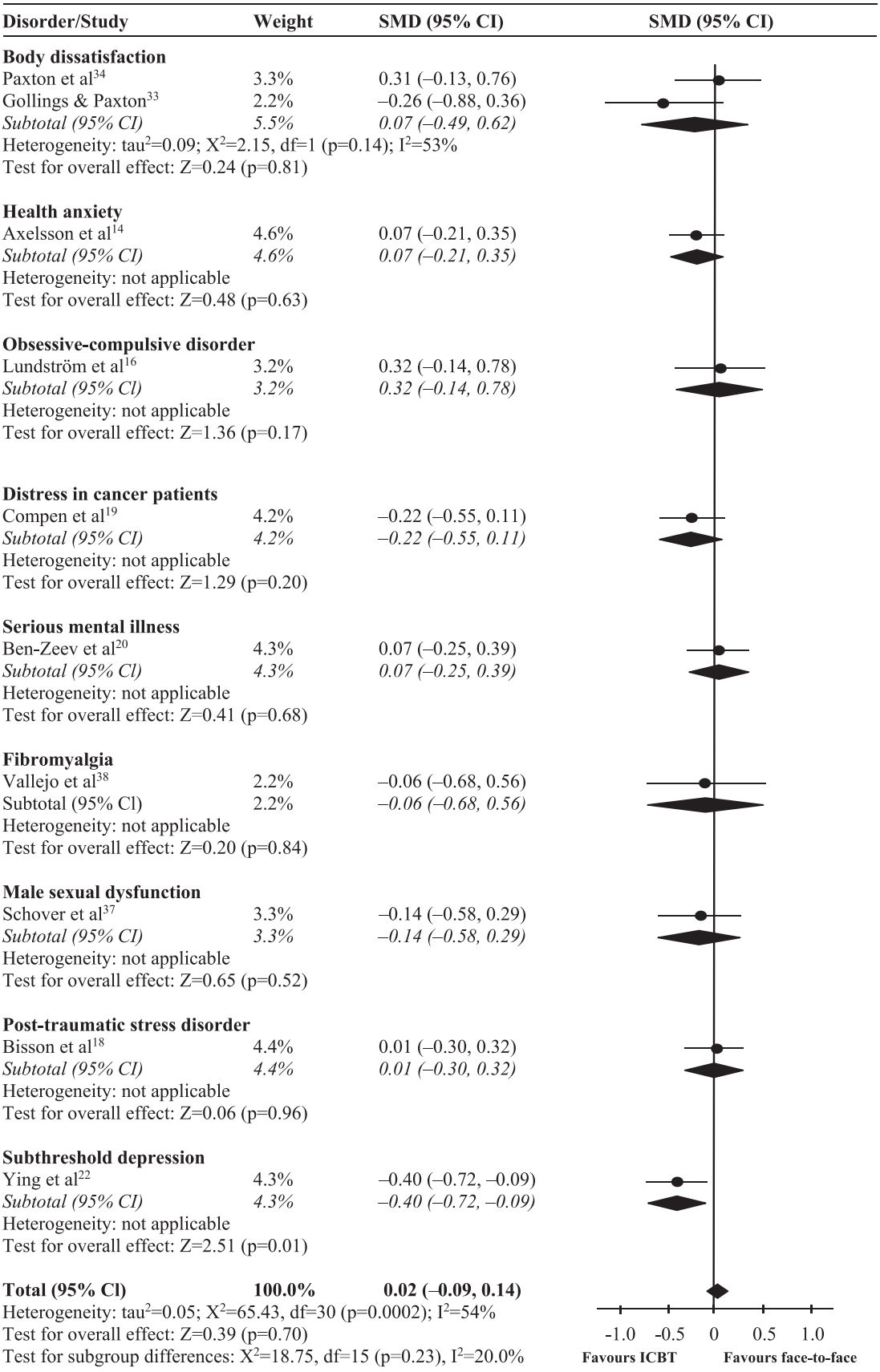

Figure 2 Forest plot of standardized effect size (g) for Internet-based cognitive behaviour therapy (ICBT) vs. face-to-face therapy (CBT). SMD – standard mean difference *(continued)*

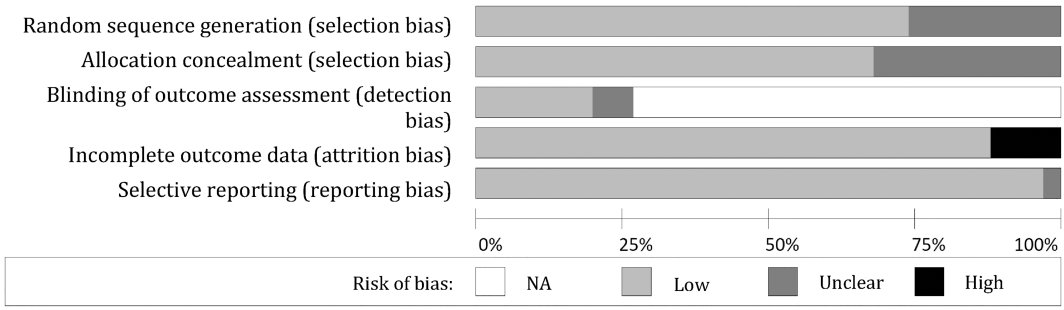

Figure 3 Results from risk of bias assessment. NA – not applicable. The white part of the blinding of outcome assessment bar is due to omission of studies that used self-reported outcomes only.

(95% CI: –0.18 to 0.12) in the former group and of g=0.10 (95% CI: –0.07 to 0.28) in the latter. The test for difference in effect between subgroups was non-significant (X^2=1.19, df=1, p=0.28), suggesting that study quality was not related to outcome.

Publication bias

Figure 4 presents a funnel plot relating the effect sizes of studies to the precision of estimates (i.e., the magnitude of standard errors). The distribution of the effect sizes was largely symmetrical, suggesting that publication bias did not skew the results substantially.

DISCUSSION

This is an updated systematic review and meta-analysis of studies comparing ICBT to face-to-face CBT for adults with psychiatric or somatic disorders, based on 31 randomized trials, conducted in nine different countries with a total of 3,053 participants. The results indicate that the two treatment formats yield similar symptomatic improvement across all study populations. The small pooled effect size and the fairly narrow confidence interval of the estimate (g=0.02; 95% CI: –0.09 to 0.14) suggest that the true effect difference between ICBT and face-to-face CBT is probably minimal.

We identified 11 new randomized controlled trials since the last update, of which most targeted disorders or patient populations for which there were no previously published randomized trials of ICBT vs. face-to-face CBT. Overall, this review reveals that there are just few clinical conditions, albeit all common mental disorders, for which ICBT has been directly compared to face-to-face CBT in at least three randomized controlled trials conducted by at least two independent research groups.

Since our first meta-analysis of ICBT vs. face-to-face CBT[8], there has been a rapid development in the field of ICBT. A search in PubMed using the search term "cognitive behavioural therapy AND Internet" with "randomized controlled trial" as search filter

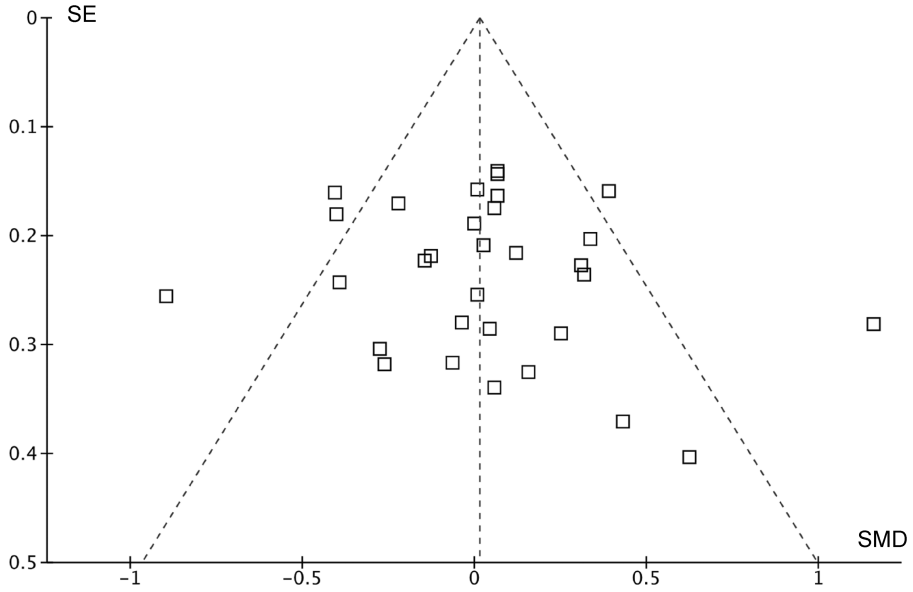

Figure 4 Funnel plot presenting the relation between effect sizes and standard errors (SE) in the included studies. SMD – standardized mean difference

yielded 885 hits published between 2014 and 2022. This massive increase in accumulated knowledge is reflected in this updated meta-analysis: the number of 13 randomized controlled trials (total N=1,053) comparing the two delivery formats in 2014 has now increased to 31 trials with more than 3,000 participants in total. The pooled effect size estimate has remained stable since the original meta-analysis (from g=–0.01 to g=0.02), and the emerging picture is that we have reached a point where the addition of new trials does not alter the estimated (lack of) overall effect difference between ICBT and face-to-face CBT.

It is important to underscore that the research question that this meta-analysis addresses is to what extent ICBT and face-to-face CBT produce similar effects for a person with a psychiatric or somatic disorder who is suitable for both treatment formats. Although independent research groups have conducted several randomized trials comparing ICBT to face-to-face CBT for some of the most common psychiatric conditions (i.e., depression, social anxiety disorder, panic disorder, insomnia), and recently published network meta-analyses showed comparable effects across CBT formats in the treatment of depression and panic disorder[43,44], for most indications we found only one or two trials. Moreover, for a range of fairly common mental disorders (e.g., generalized anxiety disorder, borderline personality disorder), we did not find any study making the ICBT vs. face-to-face CBT comparison. This means that, for several of the individual clinical conditions, the confidence interval around the effect size estimate is considerably wider compared to that for the overall pooled effect size, or, even worse, there are no empirical data from which an effect size can be calculated. So, while the overall pooled effect size estimate can be viewed as robust, it is uncertain that the effect of ICBT vs. face-to-face CBT is comparable for individual clinical conditions.

However, since the first published trial of ICBT vs. face-to-face CBT, we have waited in vain to see for what clinical problem the online format is clearly inferior. In fact, this meta-analysis included trials that recruited participants with problems typically considered fairly severe (such as post-traumatic stress disorder, obsessive-compulsive disorder, schizophrenia and bipolar disorder[16,18,20]), but the results showed no marked differences between therapeutic formats. Against this backdrop, and in combination with our results indicating that the effect size of ICBT vs. face-to-face CBT has remained stable, and by and large around zero, despite a rapidly growing number of indications for which this comparison has been made, our assessment is that, if conventional face-to-face CBT works, then ICBT works. In other terms, for clinical problems where CBT has been demonstrated to be effective in a conventional face-to-face format (i.e., where the individual sees a therapist on a weekly basis for typically 8 to 15 weeks, learns about the clinical problem, and is given concrete homework assignments in accordance with a CBT model), the format (Internet vs. face-to-face) has minimal effect on the outcome in terms of symptomatic improvement.

Notwithstanding the foregoing, there are several unanswered research questions in this field. One is about the moderators of the treatment effect, that is, what treatment works best for whom. Even if the treatment effect is similar on average across formats, it is possible that face-to-face CBT is more suitable for some individuals and ICBT for others. Identifying such moderators would be important, as it has the potential of increasing the overall response rate to CBT. Since an inherent limitation of randomized trials is that all participants must be willing to accept randomization to either of the two treatment modalities, it might not suffice to conduct analyses of effect moderators based on data from such trials, but such analyses should be conducted also in samples collected from routine care. Other avenues for future research are the investigation of implementation strategies, and the potential benefits of using so-called blended treatments[45], in which the patient receives treatment both online and via face-to-face sessions.

Among the strengths of the current meta-analysis are the broad scope and the wide search terms, which rendered screening of 5,601 publications; the inclusion of randomized controlled trials; the high statistical power of the main analysis; and the assessment of the study quality using the Cochrane risk of bias criteria.

One limitation is that we relied on the PubMed database to identify studies. However, we do not believe that this affected our results substantially, given previous research suggesting that the additive effect of using databases other than PubMed is modest in the therapeutic field[46]. Also, in a recently conducted meta-analysis of ICBT vs. face-to-face CBT for anxiety disorders – in which the authors used Scopus, Emerald, ProQuest, and Science Direct in addition to PubMed to identify studies – no additional studies compared to our meta-analysis were included[47].

Another limitation is that we did not contact authors of the original studies to obtain individual patient data, which would have enabled more detailed statistical modelling of outcomes. Finally, we regarded it as beyond the scope of this paper to assess effects on secondary outcomes or long-term outcomes. This is another potential avenue for future research.

Based on the results of this updated systematic review and meta-analysis, including 31 randomized trials, we conclude that overall clinician-supported ICBT yields similar effects compared to face-to-face CBT. Although more studies are needed to reduce the uncertainty of effect estimates for individual clinical conditions, we regard it as unlikely that the addition of new randomized trials will change our confidence in the overall conclusion.

ACKNOWLEDGEMENT

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Long-term efficacy of antipsychotic drugs in initially acutely ill adults with schizophrenia: systematic review and network meta-analysis

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Most acute phase antipsychotic drug trials in schizophrenia last only a few weeks, but patients must usually take these drugs much longer. We examined the long-term efficacy of antipsychotic drugs in acutely ill patients using network meta-analysis. We searched the Cochrane Schizophrenia Group register up to March 6, 2022 for randomized, blinded trials of at least 6-month duration on all second-generation and 18 first-generation antipsychotics. The primary outcome was change in overall symptoms of schizophrenia; secondary outcomes were all-cause discontinuation; change in positive, negative and depressive symptoms; quality of life, social functioning, weight gain, antiparkinson medication use, akathisia, serum prolactin level, QTc prolongation, and sedation. Confidence in the results was assessed by the CINeMA (Confidence in Network Meta-Analysis) framework. We included 45 studies with 11,238 participants. In terms of overall symptoms, olanzapine was on average more efficacious than ziprasidone (standardized mean difference, SMD=0.37, 95% CI: 0.26-0.49), asenapine (SMD=0.33, 95% CI: 0.21-0.45), iloperidone (SMD=0.32, 95% CI: 0.15-0.49), paliperidone (SMD=0.28, 95% CI: 0.11-0.44), haloperidol (SMD=0.27, 95% CI: 0.14-0.39), quetiapine (SMD=0.25, 95% CI: 0.12-0.38), aripiprazole (SMD=0.16, 95% CI: 0.04-0.28) and risperidone (SMD=0.12, 95% CI: 0.03-0.21). The 95% CIs for olanzapine versus aripiprazole and risperidone included the possibility of trivial effects. The differences between olanzapine and lurasidone, amisulpride, perphenazine, clozapine and zotepine were either small or uncertain. These results were robust in sensitivity analyses and in line with other efficacy outcomes and all-cause discontinuation. Concerning weight gain, the impact of olanzapine was higher than all other antipsychotics, with a mean difference ranging from –4.58 kg (95% CI: –5.33 to –3.83) compared to ziprasidone to –2.30 kg (95% CI: –3.35 to –1.25) compared to amisulpride. Our data suggest that olanzapine is more efficacious than a number of other antipsychotic drugs in the longer term, but its efficacy must be weighed against its side effect profile.

Key words: Antipsychotics, schizophrenia, long-term efficacy, olanzapine, positive symptoms, negative symptoms, all-cause discontinuation, weight gain

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Schizophrenia is a mental disorder which ranks among the 20 top causes of disability according to the World Health Organization[1], and affects about 1% of the population. Antipsychotic drugs are the mainstay of its treatment. Although acute episodes must often be treated with antipsychotics for several months (and these drugs are frequently continued as maintenance treatment thereafter), most antipsychotic drug trials are short-term. Indeed, the median study duration in a recent network meta-analysis on acute schizophrenia was only 6 weeks, and the maximum duration was restricted to 13 weeks[2].

This discrepancy between the usual course of the disorder and the duration of trials of its main treatment has rightly been criticized[3]. Some side effects of antipsychotics, such as weight gain, may accumulate over time and can therefore be adequately assessed only in longer-term studies. The efficacy findings of meta-analyses based on short-term trials can be biased as well. Some drugs – e.g., olanzapine, quetiapine and clozapine – have a strong affinity for histamine receptors, whose blockage leads to sedation[4]. This may confound assessment of actual antipsychotic efficacy. As initial sedation often subsides when patients get used to their medication, longer-term studies in initially acutely ill patients are likely to better reflect the true efficacy of antipsychotics.

Long-term relapse prevention studies which have been summarized in other network meta-analyses[5,6] cannot really fill the above gap, because they include patients stabilized on antipsychotics for several months before randomization. Side effects may have already reached a plateau at study start, and the outcome assessed in such studies is re-exacerbation of symptoms (relapse) rather than reduction of symptoms.

Thus, the missing link is to examine improvement of symptoms and side effects in longer-term randomized controlled trials (RCTs) conducted in acutely ill patients with schizophrenia. In the current report, we filled this gap by a network meta-analysis of the efficacy and tolerability of antipsychotics including only RCTs of at least 6-month duration in patients with an acute episode of the illness.

METHODS

We report our results following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was registered at PROSPERO (CRD42014014919).

Participants

We included studies on adults with initially acute symptoms of schizophrenia or related disorders (i.e., schizophreniform or schizoaffective disorder). To comply with the transitivity requirement of network meta-analysis, we excluded studies which by

their inclusion criteria were restricted to the following patient subgroups: initially stable patients (relapse prevention studies), children and adolescents, elderly, first-episode patients, treatment-resistant patients, and patients with predominant negative or depressive symptoms, or concomitant substance abuse, or concomitant medical illness.

Interventions

We included all second-generation antipsychotics (SGAs) available in Europe or the US, and a selection of first-generation antipsychotics (FGAs) guided by a survey among international schizophrenia experts[7,8] (i.e., benperidol, chlorpromazine, clopenthixol, flupenthixol, fluphenazine, haloperidol, levomepromazine, loxapine, molindone, penfluridol, perazine, perphenazine, pimozide, sulpiride, thioridazine, thiothixene, trifluoperazine and zuclopenthixol). We considered all formulations (including long-acting injectables, LAIs), except short-acting intramuscular ones (because they are primarily used in emergency situations).

We included all flexible-dose studies, because the investigators can titrate to the optimum dose for the individual patient. In fixed-dose studies, we included target-to-maximum doses according to the International Consensus Study of Antipsychotic Dosing[9]. If studies used several doses, we averaged the results of the individual arms with appropriate methods[10].

Outcomes

The primary outcome was change in overall symptoms of schizophrenia, as measured by rating scales such as the Positive and Negative Syndrome Scale (PANSS)[11], the Brief Psychiatric Rating Scale (BPRS)[12], or any other published scale.

Secondary outcomes were all-cause discontinuation; change in positive, negative and depressive symptoms; quality of life, social functioning, weight gain, antiparkinson medication use, akathisia, serum prolactin level, QTc prolongation, and sedation.

Study design

We included published and unpublished RCTs reported to be single-blind or double-blind. The minimum study duration was 6 months (following the criteria of the Cochrane Schizophrenia Group[10] to define long-term studies). Studies with a high risk of bias in sequence generation, according to the Cochrane Collaboration risk of bias tool Version 1[13], were excluded.

We excluded studies from mainland China due to serious quality concerns[8]; trials in which antipsychotics were used in combination; those in which patients could change the antipsychotic during the trial[e.g.,14], or long-term extensions in which only acute-phase responders were followed up (since this design corrupts randomization). We included RCT extensions in which all patients could be followed up.

Search strategy

We started from the searches of previous meta-analyses by our group[15,16], and made update searches of the Cochrane Schizophrenia Group specialized register on June 14, 2021, on September 21, 2021, and until March 6, 2022 (see supplementary information).

Study selection and data extraction

At least two reviewers screened the update search results independently, retrieved full text articles, and checked inclusion criteria. In case of doubt, a third reviewer was involved. Two reviewers independently extracted data and entered them in electronic forms in Microsoft Access 2010. An algorithm checked for conflicting data entries. Differences were discussed and, if consensus was not reached, a third reviewer was involved. Study authors were contacted in case of important missing or unclear information.

For extracting data on the outcomes, we preferred results based on mixed models of repeated measurements or multiple imputation rather than last-observation-carried-forward or completer-only analyses. Missing standard deviations were estimated from test statistics or imputed as the mean standard deviation of the included studies. We also extracted data on age, sex, baseline severity (PANSS total score), publication year, study duration, pharmaceutical sponsor, and whether only a completer analysis was conducted. Risk of bias was independently assessed using the Cochrane Collaboration's risk of bias tool Version 1[13].

Data analysis

We conducted a network meta-analysis in a frequentist framework with the netmeta R package[17]. The effect size for continuous, scale-derived outcomes was the standardized mean difference (SMD). Mean differences (MDs) were used for weight gain, serum prolactin level and QTc prolongation. Odds ratios (ORs) were used for dichotomous outcomes. All values are presented with 95% confidence intervals (CIs).

All relative treatment effects were estimated against the drug with most trials (olanzapine). We present and interpret treatment effects considering the mean estimate and the width of the 95% CIs, avoiding terms such as "statistically significant" and other ways of dichotomizing results based on p values. To enhance interpretability, the final estimated ORs have been transformed to relative risks (RRs) using the event rate of the outcome in the olanzapine arms (see also supplementary information).

The plausibility of the transitivity assumption was evaluated by comparing the distribution of potential effect modifiers of the primary outcome across studies grouped by comparison. We assumed a common heterogeneity parameter across all treatment comparisons, and presented the between-study variance (τ^2) for each outcome. We characterized the amount of heterogene-

ity as low, moderate or high using the first and third quantiles of their empirical distributions[18,19]. To check the network for inconsistency, we performed the SIDE-test[20] for each comparison (more than 10% of tests with p<0.1 considered important) and the design-by-treatment interaction test for the overall network (p<0.1 considered important)[21].

We undertook sensitivity analyses by excluding studies with high risk of bias[2], studies with completer-only analyses, placebo-controlled trials, studies with unfair dose comparisons, sponsored trials, studies with duration shorter than one year, and studies with imputed standard deviations. In *post-hoc* sensitivity analyses, we excluded single-blind studies, long-term extensions of RCTs, and the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study[22]; and we analyzed LAIs and oral drugs separately. To investigate the presence of small-study effects (potentially associated with publication bias), we examined the comparison-adjusted funnel plot for the primary outcome, ordering the treatments from the newest to the oldest.

The certainty of evidence for the primary outcome was evaluated using the CINeMA (Confidence in Network Meta-Analysis) framework, which allows to grade the confidence in the results into high, moderate, low and very low[23]. We set the minimum relevant SMD to ±0.1 for this purpose.

RESULTS

We screened 2,432 records and included 45 studies with 11,238 participants (see supplementary information). Forty-one studies were double-blind, and four rater-blind. The mean study duration was 42 weeks (interquartile range, IQR: 26 to 52). The participants' mean age was 37.2 years (IQR: 35.2 to 39.1); 40% were women.

The RCTs examined amisulpride, aripiprazole, asenapine, chlorpromazine, clozapine, fluphenazine, fluspirilene, haloperidol, iloperidone, loxapine, lurasidone, olanzapine, paliperidone, penfluridol, perphenazine, pimozide, quetiapine, risperidone, thioridazine, tiotixene, trifluoperazine, ziprasidone, zotepine, and placebo. Very few participants were available for FGAs, except haloperidol and perphenazine (all others had fewer than 100 participants, except tiotixene which contributed 105 participants to all-cause discontinuation). The characteristics of individual studies and the risk of bias assessment are presented in the supplementary information.

Primary outcome: change in overall symptoms

A total of 23 studies with 9,814 participants on 14 antipsychotics were available for the network meta-analysis of the primary outcome: change in overall symptoms. The comparisons were reasonably transitive (see supplementary information).

Figure 1 presents the network plot, and Figure 2 the results of the network meta-analysis. Olanzapine was on average more efficacious than ziprasidone (SMD=0.37, 95% CI: 0.26-0.49), asenapine (SMD=0.33, 95% CI: 0.21-0.45), iloperidone (SMD=0.32, 95% CI: 0.15-0.49), paliperidone (SMD=0.28, 95% CI: 0.11-0.44), haloperidol (SMD=0.27, 95% CI: 0.14-0.39), quetiapine (SMD=0.25, 95% CI: 0.12-0.38), aripiprazole (SMD=0.16, 95% CI: 0.04-0.28), and risperidone (SMD=0.12, 95% CI: 0.03-0.21). The 95% CIs for olanzapine versus aripiprazole and risperidone included the possibility of trivial effects. The differences between olanzapine and

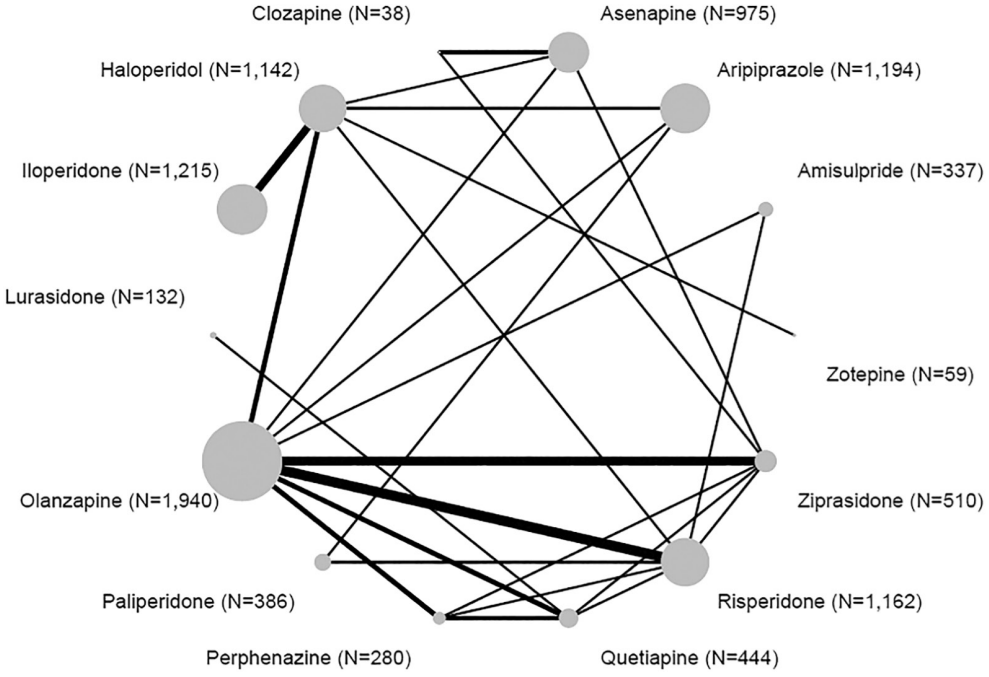

Figure 1 Network plot for change in overall symptoms (primary outcome). The numbers in parentheses are those of participants in the trials.

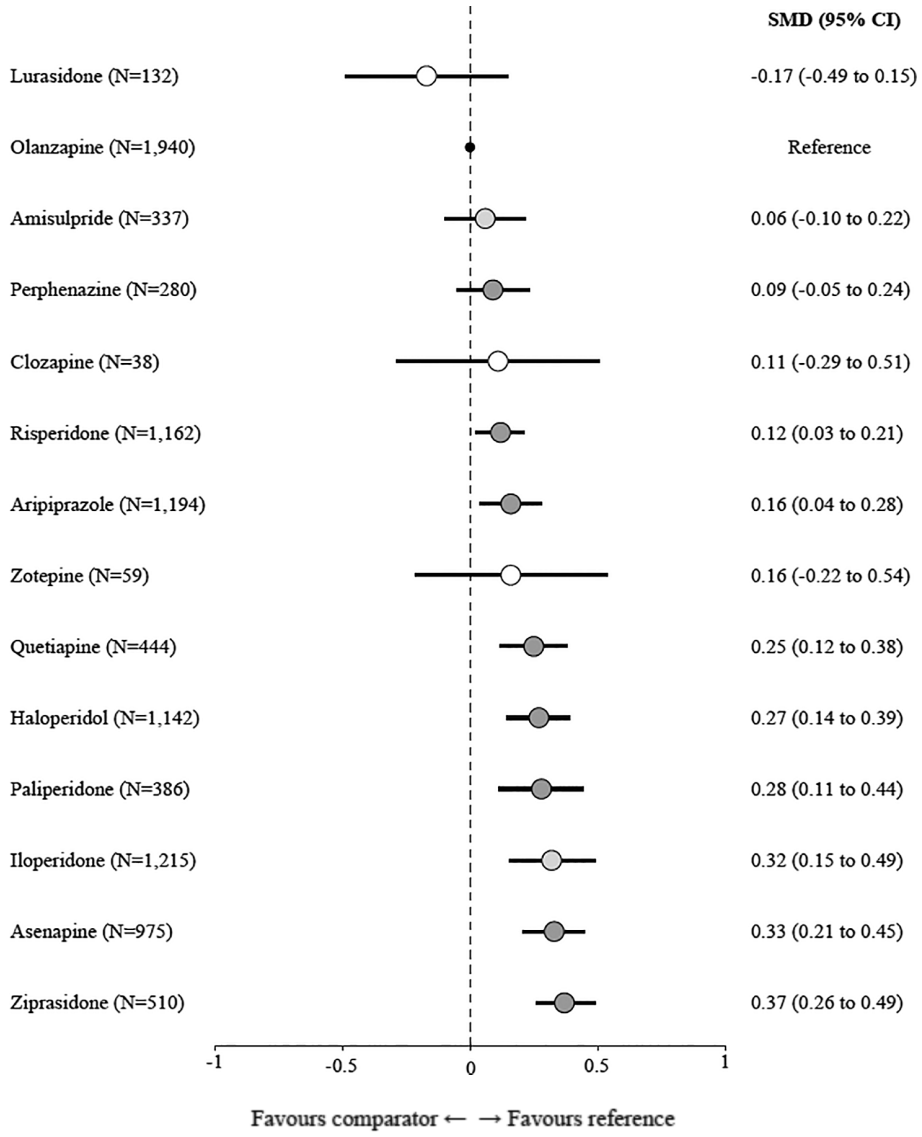

Figure 2 Forest plot for change in overall symptoms (primary outcome). Olanzapine was used as a reference. The numbers in parentheses are those of participants in the trials. The colors represent the confidence in the evidence according to CINeMA (dark grey – moderate confidence, light grey – low confidence, white – very low confidence). SMD – standardized mean difference, CI – confidence interval.

lurasidone, amisulpride, perphenazine, clozapine and zotepine were either small or uncertain.

Table 1 shows further results of the network meta-analysis (left lower part) as well as the results of pairwise meta-analyses (right upper part). Lurasidone, amisulpride, perphenazine, risperidone and aripiprazole were on average more efficacious than several other drugs, with 95% CIs making opposite effects unlikely. Confidence in the evidence of these comparisons was between moderate and very low (see Table 1 and supplementary information).

Fluphenazine, fluspirilene, pimozide, loxapine and chlorpromazine were disconnected from the network (see supplementary information for pairwise meta-analyses involving these drugs).

In the sensitivity analyses, the results did not materially change. When studies conducted by the manufacturer of olanzapine were excluded, the differences of olanzapine compared to risperidone, aripiprazole, haloperidol and iloperidone were no longer clear, in that the 95% CIs included a possibility of opposite effects, but the direction of the differences remained the same as in the main analysis. In the analysis of oral versus LAI formulations, the few RCTs on LAI formulations were disconnected from the network. Comparison-adjusted funnel plots did not suggest small-trial effects (see supplementary information).

All-cause discontinuation

Concerning all-cause discontinuation, based on 26 RCTs and 8,882 participants, olanzapine was superior to fluphenazine (RR= 2.00, 95% CI: 1.44-2.28), pimozide (RR=1.93, 95% CI: 1.04-2.32), quetiapine (RR=1.55, 95% CI: 1.35-1.72), fluspirilene (RR=1.53,

Table 1 League table for the change in overall symptoms (primary outcome)

Lurasidone	NA	NA	NA	NA	NA	NA	NA	**-0.42 (-0.71 to -0.13)**	NA	NA	NA	NA	NA
-0.17 (-0.49 to 0.15)	**Olanzapine**	-0.02 (-0.22 to 0.18)	-0.09 (-0.24 to 0.07)	NA	**-0.14 (-0.25 to -0.04)**	-0.17 (-0.33 to 0.00)	NA	**-0.24 (-0.39 to -0.10)**	**-0.29 (-0.47 to -0.11)**	NA	NA	**-0.29 (-0.42 to -0.16)**	**-0.39 (-0.51 to -0.27)**
-0.23 (-0.58 to 0.12)	-0.06 (-0.22 to 0.10)	**Amisulpride**	NA	NA	-0.01 (-0.23 to 0.21)	NA	NA	NA	NA	NA	NA	NA	NA
-0.26 (-0.59 to 0.07)	-0.09 (-0.24 to 0.05)	-0.03 (-0.24 to 0.17)	**Perphenazine**	NA	0.00 (-0.16 to 0.16)	NA	NA	-0.16 (-0.32 to 0.00)	NA	NA	NA	NA	**-0.30 (-0.49 to -0.11)**
-0.28 (-0.78 to 0.23)	-0.11 (-0.51 to 0.29)	-0.05 (-0.47 to 0.38)	-0.02 (-0.43 to 0.40)	**Clozapine**	NA	NA	NA	NA	NA	NA	NA	-0.37 (-0.82 to 0.07)	-0.11 (-0.56 to 0.33)
-0.29 (-0.61 to 0.03)	**-0.12 (-0.21 to -0.03)**	-0.06 (-0.22 to 0.10)	-0.03 (-0.17 to 0.12)	-0.01 (-0.42 to 0.39)	**Risperidone**	NA	NA	**-0.16 (-0.31 to -0.01)**	-0.12 (-0.38 to 0.14)	**-0.16 (-0.32 to -0.01)**	NA	NA	**-0.30 (-0.48 to -0.12)**
-0.33 (-0.67 to 0.01)	**-0.16 (-0.28 to -0.04)**	-0.10 (-0.29 to 0.10)	-0.07 (-0.25 to 0.12)	-0.05 (-0.46 to 0.36)	-0.04 (-0.18 to 0.11)	**Aripiprazole**	NA	NA	-0.12 (-0.23 to 0.00)	-0.09 (-0.48 to 0.31)	NA	NA	NA
-0.33 (-0.82 to 0.16)	-0.16 (-0.54 to 0.22)	-0.10 (-0.51 to 0.30)	-0.07 (-0.47 to 0.33)	-0.05 (-0.60 to 0.49)	-0.04 (-0.42 to 0.34)	-0.00 (-0.37 to 0.37)	**Zotepine**	NA	-0.11 (-0.46 to 0.25)	NA	NA	NA	NA
-0.42 (-0.71 to -0.13)	**-0.25 (-0.38 to -0.12)**	-0.19 (-0.38 to 0.01)	-0.16 (-0.32 to 0.00)	-0.14 (-0.55 to 0.27)	-0.13 (-0.27 to 0.01)	-0.09 (-0.27 to 0.08)	-0.09 (-0.49 to 0.31)	**Quetiapine**	NA	NA	NA	NA	-0.14 (-0.32 to 0.04)
-0.44 (-0.78 to -0.10)	**-0.27 (-0.39 to -0.14)**	**-0.21 (-0.40 to -0.01)**	-0.18 (-0.36 to 0.01)	-0.16 (-0.57 to 0.25)	-0.15 (-0.29 to 0.00)	**-0.11 (-0.21 to -0.01)**	-0.11 (-0.46 to 0.25)	-0.02 (-0.19 to 0.16)	**Haloperidol**	NA	-0.05 (-0.17 to 0.06)	-0.20 (-0.64 to 0.23)	NA
-0.45 (-0.80 to -0.10)	**-0.28 (-0.44 to -0.11)**	**-0.22 (-0.43 to -0.01)**	-0.19 (-0.39 to 0.02)	-0.17 (-0.60 to 0.26)	**-0.16 (-0.30 to -0.02)**	-0.12 (-0.31 to 0.07)	-0.12 (-0.52 to 0.29)	-0.03 (-0.22 to 0.17)	-0.01 (-0.20 to 0.18)	**Paliperidone**	NA	NA	NA
-0.49 (-0.85 to -0.13)	**-0.32 (-0.49 to -0.15)**	**-0.26 (-0.49 to -0.04)**	**-0.23 (-0.45 to -0.01)**	-0.21 (-0.64 to 0.22)	**-0.20 (-0.39 to -0.02)**	**-0.16 (-0.32 to -0.01)**	-0.16 (-0.53 to 0.21)	-0.07 (-0.28 to 0.14)	-0.05 (-0.17 to 0.06)	-0.04 (-0.27 to 0.18)	**Iloperidone**	NA	NA
-0.50 (-0.84 to -0.16)	**-0.33 (-0.45 to -0.21)**	**-0.27 (-0.47 to -0.07)**	**-0.24 (-0.42 to -0.05)**	-0.22 (-0.62 to 0.18)	**-0.20 (-0.39 to -0.02)**	-0.17 (-0.34 to 0.00)	-0.17 (-0.56 to 0.22)	-0.08 (-0.26 to 0.10)	-0.06 (-0.23 to 0.11)	-0.05 (-0.25 to 0.15)	-0.01 (-0.21 to 0.19)	**Asenapine**	0.26 (-0.18 to 0.70)
-0.54 (-0.87 to -0.22)	**-0.37 (-0.49 to -0.26)**	**-0.31 (-0.50 to -0.12)**	**-0.28 (-0.44 to -0.12)**	-0.27 (-0.66 to 0.13)	**-0.25 (-0.39 to -0.12)**	**-0.22 (-0.38 to -0.05)**	-0.21 (-0.61 to 0.18)	-0.12 (-0.28 to 0.03)	-0.11 (-0.27 to 0.06)	-0.10 (-0.29 to 0.10)	-0.05 (-0.25 to 0.15)	-0.05 (-0.21 to 0.12)	**Ziprasidone**

The left lower field presents the results of the network meta-analysis; the right upper field presents the results of pairwise meta-analyses. Treatments are in order of their point estimate compared to olanzapine. Each cell provides the standardized mean difference and the corresponding 95% confidence interval (CI) of a comparison (treatment in column vs. treatment in row for the network meta-analysis; treatment in row vs. treatment in column for the pairwise meta-analysis). Bold prints indicate 95% CIs excluding opposite effects. Please note that in Figure 2 olanzapine was always the reference, which explains why in that figure and in the text the sign of all comparisons with olanzapine was always + except for lurasidone. For the results of the network meta-analysis, the background colors of the cells reflect confidence in the estimates, with dark grey representing moderate confidence, light grey low confidence, and white very low confidence. NA – not available.

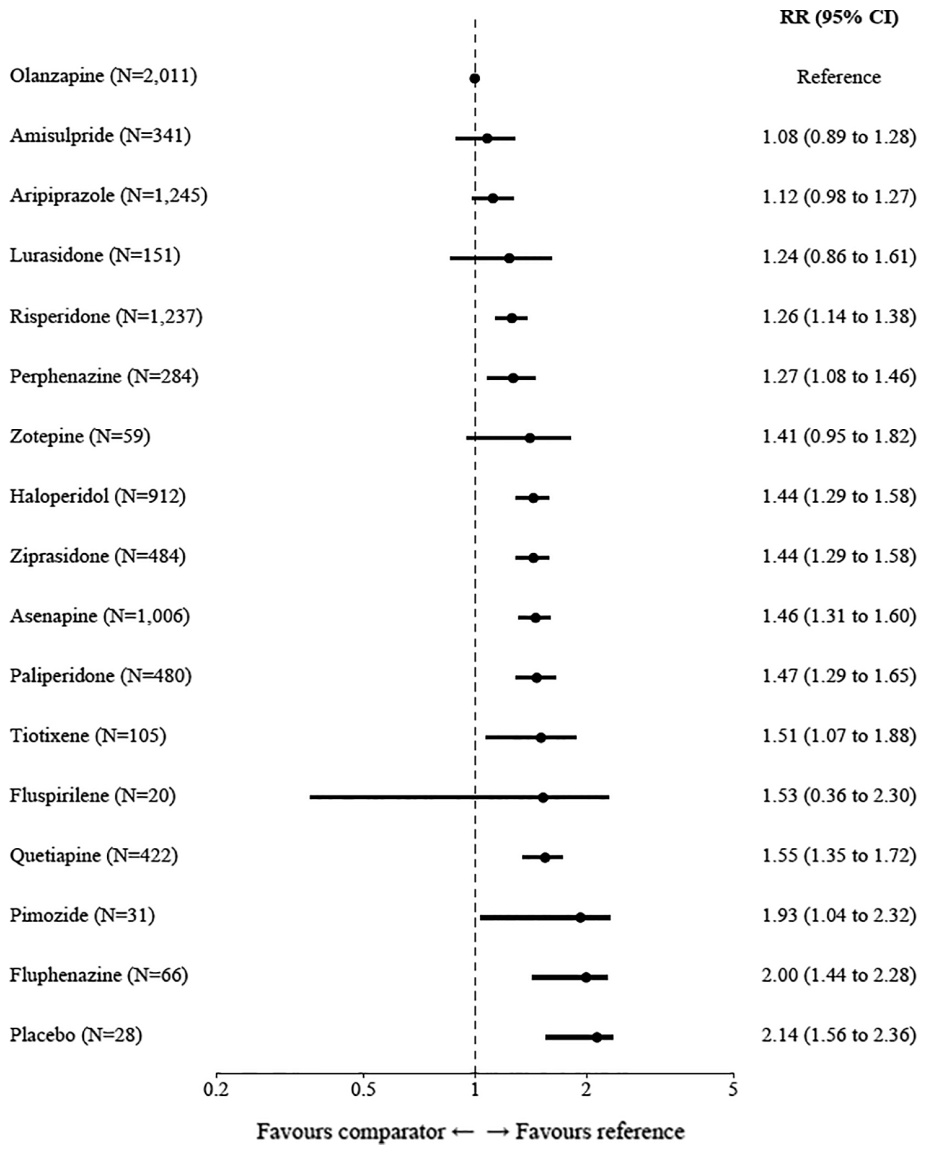

Figure 3 Forest plot for all-cause study discontinuation. Olanzapine was used as a reference. The numbers in parentheses are those of participants in the trials. RR – relative risk, CI – confidence interval.

95% CI: 0.36-2.30), tiotixene (RR=1.51, 95% CI: 1.07-1.88), paliperidone (RR=1.47, 95% CI: 1.29-1.65), asenapine (RR=1.46, 95% CI: 1.31-1.60), ziprasidone (RR=1.44, 95% CI: 1.29-1.58), haloperidol (RR=1.44, 95% CI: 1.29-1.58), zotepine (RR=1.41, 95% CI: 0.95-1.82), and perphenazine (RR=1.27, 95% CI: 1.08-1.46). Amisulpride, aripiprazole and risperidone were also superior to several other antipsychotics, with 95% CIs making opposite effects unlikely (see Figure 3 and supplementary information).

Positive and negative symptoms

The results concerning positive and negative symptoms, based on 14 RCTs with 6,155 participants, were similar to those for overall symptoms.

On positive symptoms, olanzapine was more efficacious than chlorpromazine (SMD=0.51, 95% CI: 0.09-0.93), ziprasidone (SMD =0.37, 95% CI: 0.21-0.54), paliperidone (SMD=0.32, 95% CI: 0.12-0.52), asenapine (SMD=0.27, 95% CI: 0.14-0.41), zotepine (SMD= 0.19, 95% CI: –0.19 to 0.56) and aripiprazole (SMD=0.18, 95% CI: 0.05-0.31). No data on perphenazine, clozapine and iloperidone were available. Based on a single study[24], disconnected from the network, lurasidone improved positive symptoms more than quetiapine (see supplementary information).

On negative symptoms, olanzapine was more efficacious than chlorpromazine (SMD=2.35, 95% CI: 1.84-2.87), ziprasidone (SMD=0.33, 95% CI: 0.17-0.50), haloperidol (SMD=0.27, 95% CI: 0.14-0.40), asenapine (SMD=0.22, 95% CI: 0.08-0.35), and risperidone (SMD=0.21, 95% CI: 0.07-0.34). Again, no data on perphenazine, clozapine and iloperidone were available (see supplemen-

tary information).

Chlorpromazine had the lowest symptom reduction, but the results were based on a single small study[25] with only 50 participants.

Depressive symptoms

Concerning depressive symptoms, 11 RCTs and 6,686 participants were available for network meta-analysis. Most results were uncertain according to 95% CIs. Lurasidone appeared to be more efficacious than a number of other drugs, but these findings stemmed from the above-mentioned single RCT comparing it with quetiapine[24], with the remaining evidence being indirect (see supplementary information).

Quality of life and social functioning

Eight RCTs with 2,949 participants yielded no clear differences in quality of life (see supplementary information). There were no inconsistent comparisons according to the SIDE-test[20], but the design-by-treatment interaction test suggested some inconsistency of the overall network (p=0.092)[26]. Similarly, in five RCTs with 1,390 participants, there were no clear differences in social functioning (see supplementary information).

Weight gain

Concerning weight gain, there was low-to-moderate heterogeneity (common tau = 1.05), and the network based on 16 RCTs with 7,542 participants was inconsistent (12.5% inconsistent comparisons, design-by-treatment interaction test: p=0.0002). We, therefore, present only the results of the pairwise meta-analyses comparing olanzapine with the other antipsychotics.

Olanzapine produced more weight gain than all other antipsychotics. MDs ranged from –4.58 kg (95% CI: –5.33 to –3.83) versus ziprasidone, to –3.90 kg (95% CI: –6.73 to –1.08) versus perphenazine, –3.76 (95% CI: –4.89 to –2.63) versus quetiapine, –3.37 (95% CI: –7.21 to 0.47) versus haloperidol, –3.30 (95% CI: –4.20 to –2.40) versus asenapine, –3.16 (95% CI: –4.06 to –2.26) versus aripiprazole, –2.37 (95% CI: –3.70 to –1.03) versus risperidone, and –2.30 (95% CI: –3.35 to –1.25) versus amisulpride (see Figure 4 and supplementary information).

Antiparkinson medication

Concerning use of antiparkinson medication, 14 RCTs with 7,794 participants provided data. Aripiprazole (RR=0.71, 95% CI: 0.54-0.96) and quetiapine (RR=0.56, 95% CI: 0.29-1.04) outperformed olanzapine. Zotepine (RR=0.92, 95% CI: 0.43-1.85, N=59) was about as prone as olanzapine to be associated with the use of that medication, while amisulpride (RR=1.32, 95% CI: 0.90-1.89), risperidone (RR=1.57, 95% CI: 1.27-1.94), paliperidone (RR=1.59, 95% CI: 1.13-2.18), ziprasidone (RR=1.59, 95% CI: 1.11-2.23), perphenazine (RR=1.63, 95% CI: 1.07-2.40), haloperidol (RR=2.35, 95% CI: 1.87-2.92), and asenapine (RR=3.05, 95% CI: 1.51-5.10) were associated with a greater use (see also supplementary information).

Akathisia

In 16 RCTs with 7,916 participants, paliperidone (RR=0.82, 95% CI: 0.50-1.48), amisulpride (RR=0.95, 95% CI: 0.54-1.69), quetiapine (RR=1.03, 95% CI: 0.58-1.79) and aripiprazole (RR=1.09, 95% CI: 0.78-1.52) were associated with approximately the same risk of akathisia as olanzapine. Risperidone (RR=1.32, 95% CI: 0.96-1.81), perphenazine (RR=1.34, 95% CI: 0.76-2.30), ziprasidone (RR=1.43, 95% CI: 0.97-2.06), haloperidol (RR=2.39, 95% CI: 1.72-3.27), asenapine (RR=2.57, 95% CI: 1.54-4.12) and lurasidone (RR=4.69, 95% CI: 1.21-11.01) were associated with higher risk. The results of risperidone, perphenazine and ziprasidone were uncertain, because 95% CIs left some possibility of opposite effect. The 95% CI for lurasidone versus olanzapine was very wide. Results on fluphenazine, trifluoperazine, tiotixene and thioridazine were disconnected from the network (see also supplementary information).

Serum prolactin level

The network of 10 RCTs and 5,152 participants was inconsistent (20% inconsistent loops, common tau = 6.15, design-by-treatment interaction test: p=0.001). Based on pairwise meta-analyses, several drugs were associated with lower average prolactin levels than olanzapine: aripiprazole (MD=–8.89 ng/ml, 95% CI: –14.87 to –2.91), asenapine (MD=–4.00 ng/ml, 95% CI: –7.68 to –0.32) and quetiapine (MD=–3.20, 95% CI: –6.81 to 0.41). Ziprasidone (MD=2.36, 95% CI: –0.75 to 5.48), perphenazine (MD=6.50, 95% CI: 2.42-10.58), haloperidol (MD=7.36, 95% CI: 0.52-14.20) and risperidone (MD=30.50, 95% CI: 19.36-41.65) were associated with higher average prolactin levels than olanzapine (see also supplementary information).

QTc prolongation

In the network meta-analysis of 7 RCTs with 4,060 participants, paliperidone (MD=–2.22 msec, 95% CI: –7.13 to 2.68), risperidone (MD=–0.12 msec, 95% CI: –3.94 to 3.69), asenapine (MD=0.40 msec, 95% CI: –1.83 to 2.63), perphenazine (MD=0.68 msec, 95% CI: –4.10 to 5.46) and ziprasidone (MD=0.71 msec, 95% CI: –1.98 to 3.39) were associated with a similar average QTc prolongation as olanzapine. The values for amisulpride (MD=5.00 msec, 95% CI: –1.81 to 11.81), quetiapine (MD=5.18 msec, 95% CI: 0.55-9.81) and lurasidone (MD=8.38 msec, 95% CI: –0.03 to 16.79) were a bit

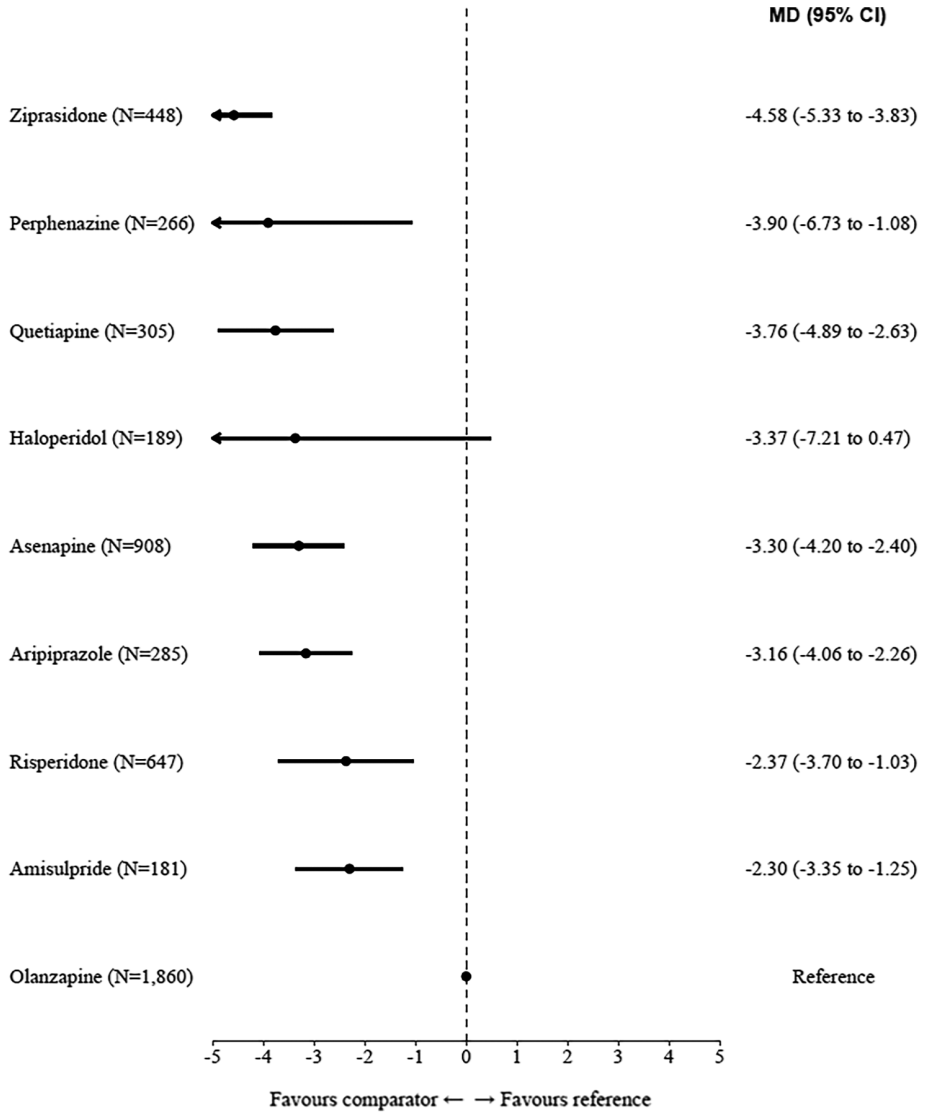

Figure 4 Forest plot for weight gain (pairwise meta-analyses). The numbers in parentheses are those of participants in the trials. MD – mean difference, CI – confidence interval.

larger, but the 95% CIs were wide and included opposite effects for lurasidone and amisulpride. The data on aripiprazole and haloperidol were disconnected from the network (see also supplementary information).

Sedation

The network meta-analysis of 16 RCTs with 8,096 participants did not indicate clear differences between antipsychotics, because almost all results had wide 95% CIs. The only exception was aripiprazole, which had less risk of sedation than olanzapine (RR=0.58, 95% CI: 0.38-0.86) and several other drugs. Data on fluphenazine, fluspirilene, chlorpromazine, thioridazine and tiotixene were disconnected from the network (see also supplementary information).

DISCUSSION

It is an important criticism that most antipsychotic drug trials in acutely ill patients with schizophrenia last only six weeks, although these drugs usually need to be taken much longer. Relapse prevention studies in remitted or stable patients cannot fill this gap, because they are conducted in a different phase of the illness, have different outcomes and usually follow drug-withdrawal designs[5,6]. In this network meta-analysis, we examined studies in initially symptomatic patients with schizophrenia who were subsequently followed up for at least six months.

The main result was that olanzapine is more efficacious than several other FGAs and SGAs, with SMD point estimates between very small (0.12 vs. risperidone) and small to medium (0.37 vs. ziprasidone), and is associated with the lowest all-cause discontinuation rate. The results were robust to sensitivity analyses (in

the analysis excluding studies from the manufacturer of olanzapine, some differences were no longer clear, but their direction remained the same as in the main analysis). On the other hand, on pairwise meta-analyses, the impact of olanzapine in terms of weight gain was higher than all other antipsychotics, with an MD ranging from –4.58 kg compared to ziprasidone to –2.30 kg compared to amisulpride.

Olanzapine was among the most efficacious drugs in recent network meta-analyses in short-term acute phase studies, and long-term relapse prevention studies[2,6]. It was also superior to other antipsychotics in several trials which lasted between 14 and 22 weeks[27,28] and, therefore, were not included either in the current network meta-analysis of long acute-phase trials or in the previous analysis of short acute-phase RCTs[2]. The superiority of this drug to other antipsychotics in three large trials of 6-month duration, which were excluded because conducted in patients with predominant depressive[29] or negative symptoms[30,31], should also be mentioned. Olanzapine, therefore, appears to be a particularly efficacious antipsychotic drug across the different phases of treatment of schizophrenia.

However, the difference between olanzapine and risperidone concerning change in overall symptoms was statistically significant but very small (SMD=0.12), and the differences of olanzapine vs. amisulpride and perphenazine were not significant (SMDs of 0.06 and 0.09, respectively). Perphenazine is an important FGA, because it induces fewer extrapyramidal symptoms than haloperidol and little weight gain, but the data concerning this drug stem almost entirely from the CATIE study[22]. This was a very large, industry-independent trial, but, if only one study is available, a replication is necessary. The results on clozapine (38 participants), zotepine (59 participants) and all FGAs except haloperidol and perphenazine are uninterpretable, because too few data were available.

Lurasidone ranked (non-significantly) higher than olanzapine in overall efficacy (Figure 2). However, it was only examined in a single RCT in which it was superior to quetiapine[24]. Thus, its difference compared to drugs other than quetiapine was entirely derived from indirect evidence, and the confidence in these results was often very low.

Taking together the current and previous evidence, risperidone and amisulpride can be currently considered the best alternatives to olanzapine with respect to efficacy in patients with schizophrenia.

The results from the side effect analysis matched with previous findings[2,5,6]. Risperidone and paliperidone produce most prolactin increase, and partial dopamine agonists are most benign in this regard[2,5,6]. High-potency FGAs such as haloperidol cause most extrapyramidal side effects. The main problem with olanzapine is weight gain, which it produces more than all antipsychotics it has been compared to. This side effect is particularly relevant because it is associated with cardiovascular events and may increase mortality in the long term[32]. Therefore, olanzapine is not a drug that can be recommended without reservations for all patients. If more benign antipsychotics are an option, they should be preferred and, in case olanzapine is used, monitoring of cardiovascular risk factors as well as countermeasures to weight gain should be considered. Adjunctive metformin had the best evidence in a Cochrane review[33], and lifestyle interventions such as diet and physical activity were found effective as well[34].

Our analysis has limitations. First, compared to our recent meta-analysis of short-term trials[2], the current database is smaller. However, the number of participants was substantial. For several drugs more than 1,000 participants were available for the primary outcome, a threshold which makes results robust[35]. In contrast, clozapine, zotepine and lurasidone had approximately 100 participants or less, and FGAs other than haloperidol and perphenazine were not connected to the network or had no data at all.

Second, quality of life and social functioning are particularly important long-term outcomes, but the evidence is too scarce to allow firm recommendations. Third, there were several comparisons which lay outside the general networks. Finally, confidence in the evidence was generally moderate to low according to our evaluation with CINeMA[23].

We conclude that olanzapine is more efficacious than a number of other antipsychotics in the longer-term treatment of acutely ill patients with schizophrenia. Its superior efficacy must be balanced with its risk for weight gain and, when it is used, monitoring of cardiovascular risk factors as well as initiation of relevant preventive measures appear advisable.

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Meeting the UN Sustainable Development Goals for mental health: why greater prioritization and adequately tracking progress are critical

The United Nations (UN) Sustainable Development Goal (SDG) 3, adopted by all the world's nations in 2015, is to "ensure healthy lives and promote well-being for all at all ages". For the first time, the global goals explicitly included mental health: in target 3.4, countries agreed to "promote mental health and well-being" through prevention and treatment to reduce premature mortality by one-third, and in target 3.5 countries committed to "strengthen the prevention and treatment of substance abuse".

Yet, halfway to the 2030 deadline for achieving the SDGs, the available evidence suggests that we are not on track to meet even these important but modest goals. Despite taking the first step of creating mental health targets, the UN has only been measuring one mental health outcome indicator, the suicide mortality rate, and official monitoring statistics show that global suicide rates decreased just by 3% from 2015 to 2019 (the most recent year for which data are available)[1] – far too slowly to meet the one-third reduction target.

Accelerating reduction in suicides requires that we support and monitor advances in access to preventive care. Currently, however, the global community is not only failing to meet the SDG suicide reduction target, but also failing to measure whether people can access the services that could make a difference. The SDG target 3.8 envisions the achievement of universal health coverage, while additional targets focus on the development of the health workforce and access to essential medicines. Yet the UN's measurement of these targets overlooks questions critical to improving mental health outcomes: do countries' health systems cover not only physical but also mental health services, including treatment for depression? How robust is the mental health workforce? How widely available are essential medicines for depression and other mental health conditions?

SDG indicator 3.b.3 measures the share of health facilities with "a core set of relevant essential medicines", but does not specifically account for mental health therapeutics. Similarly, the indicator on "health worker density and distribution" includes data on physicians, nurses, and pharmaceutical and laboratory staff, but not mental health care providers specifically.

This neglect is striking, given that the World Health Organization (WHO) ranks depression as the "single largest contributor to global disability"[1], and research has shown that mental health conditions are responsible for 13% of disability-adjusted life years[2]. The inadequate attention to mental health is even more concerning in the context of prior studies documenting disparities between mental and physical health services. Globally, median government expenditure on mental health services comprises just 2.1% of health spending overall[3]. Past WHO estimates found that just 13 mental health workers are available per 100,000 population[3], compared to approximately 620 total health workers[4], making clear that developing the mental health workforce requires greater attention. Moreover, the most recent WHO Mental Health Atlas, which reports on a subset of countries every three years, indicated that only around half of member states covered mental health in their national insurance programs[3]. Yet, the UN has bypassed the opportunity to measure global progress in these areas regularly as part of SDG monitoring, despite demonstrating the feasibility of doing so for other urgent health issues.

Indeed, the global community already tracks other areas effectively, accelerating progress. Past global efforts to improve monitoring of maternal health coverage yielded the consistent collection of national-level data about number of prenatal visits, use of modern contraceptives, and presence of a skilled birth attendant, and, while much work remains, global maternal mortality rates fell 38% from 2000 to 2017[5]. Likewise, past efforts to measure global vaccine access have collected detailed annual data from all countries on immunization financing, coverage and policies, supporting substantial increases in uptake of life-saving vaccines globally. If all countries devoted similar attention to mental health services – quality, access and affordability – we could achieve the suicide and substance abuse targets of the SDGs, while simultaneously improving prevention and treatment of a wide array of mental health conditions.

To be sure, access to mental health care and medication are not the only factors that influence suicide risk; social and environmental factors – including job loss, discriminatory norms, isolation, and access to lethal means – are important contributors to suicide attempts and deaths[6]. Nevertheless, adequate mental health services and pharmacological treatments are essential to addressing the biological, psychological and clinical factors that independently affect suicide risk.

Moreover, the SDGs provide a framework not only for improving prevention and treatment of mental health conditions, but also for improving the quality of life of people living with mental health conditions. As recognized by the UN Convention on the Rights of Persons with Disabilities, both mental and physical health conditions often are not innately disabling, but have the potential to limit full participation depending on the social environment and degree of discrimination versus inclusion.

Countries agreed through SDG 4 to "ensure inclusive and equitable quality education" and reduce disparities across disability status and other measures. Both the goals for decent work (SDG 8) and inequality (SDG 10) also recognize the full equality of people living with disabilities, and countries' responsibility to uphold equal rights and full inclusion. Target 8.5 explicitly calls for "achiev[ing] full and productive employment and decent work for… persons with disabilities". Similarly, indicator 10.3.1 measures the share of the population that has faced discrimination based on disability status in the past year.

Currently, however, with respect to both work and education,

youth and adults with mental health conditions or intellectual disabilities face among the highest rates of stigma and exclusion[7]. Yet, the SDG monitoring process has collected little data on access to quality education for children with disabilities overall, and even less on the experience of children with mental health conditions. Meanwhile, data available from other sources suggest that we have far to go: our study of policies in 193 countries found that over one-third fail to even guarantee integrated education along with individualized supports for children with disabilities, and much less specifically address the needs of children with mental health conditions[8].

Regarding employment, the SDG indicators require tracking average wages and unemployment rates for workers with disabilities, but data are currently only available for the latter; similarly, though indicator 10.2.1 calls for data on income inequality by disability, measures are currently unavailable. Moreover, there are no specific efforts to monitor improvements in inclusive employment for people with mental health conditions. Again, these gaps are concerning, given other research indicating that many countries fall short: our center's data show that, as of 2021, only 46% of countries worldwide explicitly guaranteed reasonable accommodations for workers with mental and/or intellectual disabilities[9].

It is not too late for the SDGs to provide an opportunity for accelerating progress in preventing poor mental health, treating mental health conditions, and improving the quality of life of people living with mental health conditions. To do that, however, we need to measure annually not only the suicide mortality rate, but also comprehensive coverage of mental health services in national health systems; the density of the mental health care workforce; the accessibility of essential mental health therapeutics; and the extent to which countries are ensuring the full inclusion of people with mental health conditions in education and employment. Only by specifically prioritizing and tracking progress for mental health prevention, treatment and equal rights can we create a world where meeting mental health needs is not an afterthought, where explicit and implicit discrimination is eliminated, and where all people can lead full and healthy lives.

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Cognitive enhancement interventions are effective for schizophrenia: why not provide them early?

There has been considerable optimism in the care of early course psychotic disorders in recent years, as reflected by the rapid implementation of coordinated specialty care (CSC) services around the world in the background of steadily progressing standards of care. While benefits are seen early with CSC interventions, these results may not be sustained. In a large 10-year follow-up study (N=347), it was found that the early intervention group had less overall utilization of psychiatric bed days (suggesting less psychosis). However, there were few differences from the treatment-as-usual group in regard to improving long-term functional outcomes such as those related to independent living, relationships or work[1]. There is clearly a need to examine the critical elements of care that would improve long-term outcomes in early course psychosis[2].

Cognitive impairments are a core feature of schizophrenia and related psychotic disorders. They are present in a large majority of patients, tend to persist before, during and after psychotic episodes, and robustly predict outcomes. They are also strongly related to the underlying neurobiology and the genetic underpinnings of the illness. There is robust evidence that cognitive enhancement treatments are effective in ameliorating cognitive deficits as well as improving functional ability in schizophrenia. Improvements are stronger when they are integrated in a coordinated care model including other psychosocial rehabilitation approaches, and when efforts are made to facilitate the transfer of cognitive gains to the real world[3].

An emerging but small body of literature, including our own studies[4], points to the importance of cognitive enhancement in the early course of psychotic disorders.

First, findings to date indicate that such interventions can promote important functional gains in critical recovery domains, including employment and social functioning, in early psychosis. While a recent meta-analysis found that cognitive enhancement intervention effects appear largely consistent across durations of illness[3], other studies have found benefits, including generalization to community functioning, to be greater when using an early intervention strategy[5].

Second, deficits in cognition lead to incremental costs related to unemployment, poor quality of life and loss of independence[6]. There are unique windows of opportunity for functional gains

during the early course of illness, before the entrenchment in a disability can take hold.

Third, the early phases of psychosis are associated with greater brain "reserve", which promotes response to cognitive enhancement. This is supported by evidence that higher grey matter volumes at baseline are associated with larger early improvements with cognitive training[7]. This may reflect greater brain plasticity early in the illness and provides an impetus for the application of such intervention as early as possible.

Fourth, there is evidence of progressive cognitive decline and grey and white matter loss over the course of the illness at least in a subgroup of patients with schizophrenia[8]. Cognitive enhancement approaches have been shown to be associated with less grey matter loss over time and may therefore be neuroprotective, or may at least slow the progression of cognitive and brain function.

Finally, evidence continues to point to cognitive impairment as a key rate-limiting factor for improved outcomes from a variety of CSC components, most notably supported employment. The goals of cognitive enhancement are synergistic with those of CSC, with both emphasizing reduction of disability. Cognitive enhancement interventions are generally considered recovery-phase approaches, whereas the earliest components of CSC, such as individualized medication and family psychoeducation, must necessarily focus on stabilization. Such stability is likely critical for engagement in psychosocial interventions and, once attained, cognitive enhancement interventions could support subsequent CSC recovery goals of employment, social integration, and independence.

If cognitive impairments begin early, and cognitive enhancement interventions are generally effective across phases of psychosis, why are they not widely implemented? Current CSC models applied throughout the world have done much to advance psychosocial treatments to improve early course outcomes, but few of these programs offer the opportunity for patients to participate in cognitive enhancement interventions. In our recent review, none of the 13 published CSC programs included cognitive enhancement[2]. Challenges associated with the implementation of a novel psychosocial treatment in already resource-limited community practice settings (e.g., cost, low fidelity of implementation, lack of trained personnel, and higher prioritization for addressing more acute symptoms) are likely contributing factors limiting the availability of cognitive enhancement interventions for early course patients.

How do we go about integrating cognitive enhancement interventions in CSC settings? These interventions target broad neurocognitive impairments in attention, memory and problem-solving, and challenges in social cognition, such as difficulties in taking the perspective of others and accurately appraising the social context. Schizophrenia and related conditions are highly heterogeneous, even in the early course. As such, specific targets will vary across individuals. Brief assessments of cognition that are more clinician friendly, such as the Brief Assessment of Cognition in Schizophrenia (BACS) and the National Institutes of Health Toolbox Cognition Battery (NIH Toolbox CB), can be used early in CSC settings to help identify the subjects in whom cognitive enhancement interventions are indicated and to personalize such interventions.

Evidence is also emerging about the beneficial effects of cognitive enhancing interventions on negative symptoms[9], a domain that is largely untreated in psychosis but contributes to substantial functional disability. Further, cognitive enhancement approaches show potential for reducing some common substance use problems, and meta-cognitive interventions hold promise for promoting treatment adherence and greater insight into the condition. In addition, through participation in cognitive enhancement interventions, patients in CSC could have greater ability to engage in more frequently implemented components of the CSC programs (such as family education, supportive employment/education, social skills training and individualized psychotherapy and psychopharmacology)[2].

Fundamentally, the field needs to address several gaps in the way we understand and treat core aspects of schizophrenia. Despite the growing evidence outlined above, cognitive deficits are still not part of the diagnostic criteria for schizophrenia. Including them in future revisions of our diagnostic systems will serve to promote routine cognitive testing as part of baseline assessments. There is evidence that individuals with more severe illness, and those with baseline cognitive and functional impairments, may be optimal candidates for cognitive enhancement interventions[3]. Baseline cognitive and functional assessments are therefore likely to help identify patients most in need for cognitive enhancement interventions. We need to know whether a stratified intervention approach early in the illness may be a cost-effective strategy. Finally, there is preliminary evidence that cognitive enhancement approaches are effective in individuals at high clinical risk for psychosis, though more work is needed to confirm these observations and identify potential characteristics of who might best respond.

Introducing cognitive enhancement interventions early in the course of psychoses following symptom stabilization, in the context of the synergistic effects of an integrated, multi-element model of care, represents the next generation of early interventions for psychosis and holds promise for favorably modifying the long-term course of the illness.

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The post-traumatic growth approach to psychological trauma

Over the years, it appears that the profession of psychiatry has become increasingly wedded to diagnostic systems such as the ICD and DSM, and to biological interventions. The major professional mental health organizations have recognized manualized "evidence-based" forms of intervention as the standard for treatment of traumatic syndromes such as post-traumatic stress disorder (PTSD). But there have been challenges to these approaches[1], and here we offer an alternative.

In the mid-1980s, L. Calhoun and I were interviewing people who had experienced serious physical disabilities in adulthood or traumatic grief. Listening to their stories and performing content analyses led us to examine places in the literature of psychological trauma where there were reports of surprising personally transformative outcomes. We ultimately coined the term "post-traumatic growth" as a descriptor of these experiences. In subsequent qualitative and quantitative research, we were able to identify five domains of post-traumatic growth: improved relationships with others, new possibilities for the life path, a greater appreciation for life, a greater sense of personal strength, and new perspectives on spiritual and existential issues[2,3].

The burgeoning research on post-traumatic growth has yielded a model of the process by which people respond to trauma and develop these transformations over time[3]. It has become evident that an important aspect of this process is the challenge to the system of core beliefs or assumptive world that people maintain without questioning until events occur that appear to make that system untenable. In fact, the challenge to the core belief system or assumptive world can be a new way to define trauma, rather than making reference to certain types of events.

The assumptions people have made about their identity, life path, morality, vulnerability, and the predictability and benevolence of their world are shattered by events, and this creates anxiety and cognitive disorientation. The intrusive rumination that is then set in motion may be harnessed into a more deliberate reflection on core beliefs, and a reconstruction that can lead to post-traumatic growth. This deliberate rumination is what mental health professionals need to attend to in order to facilitate the best outcomes in the aftermath of trauma.

If we organize our post-trauma interventions around this post-traumatic growth model, we no longer focus on symptom reduction or even the traumatic events themselves. Though we do not ignore these sources of distress, we recognize that, in the long run, the distress will diminish or be better tolerated when people develop ways to live based on the perspective that their suffering is not in vain but a teacher of sorts about life's meaning and purpose. The traumatic events that they have experienced do not provide this meaning, but represent an opportunity to reconstruct a system of core beliefs that yields a life of purpose, where the trauma survivors see their value and are more devoted to a mission they find meaningful, as it benefits others as well as themselves[4].

We have developed programs based on post-traumatic growth theory and research to serve military service members and veterans as well as first responders who have been faced with trauma in personal and professional life. These programs are operated by peers and use various educational and experiential elements to promote post-traumatic growth and define a way of living a healthy life of service to others. We call this approach, which in some ways challenges the usual model of trauma treatment, and in some ways integrates elements of the usual model, "expert companionship". The philosophy that underpins this approach is rooted in an understanding that trust and connection with helpers is of crucial importance, and the peer-based program is very compatible with this.

There are five elements to this approach: education about trauma response, especially the role of core belief disruption; teaching emotional regulation strategies, especially meditation and calming; disclosure of trauma memories; development of a narrative that encompasses positive aspects of the self as well as a life course perspective that integrates trauma experience; and a plan for turning traumatic life experience toward a way to be of service to others. Our research on this approach is showing remarkable indications of post-traumatic growth, while symptoms of PTSD are greatly reduced as well[5].

There are some important lessons that we have learnt as we have been designing, revising and evaluating our programs over the past several years[6]. First, we continue to listen closely to the people served by the programs as we develop them. This is an extension of the original approach to our research on post-traumatic growth, in which we started with interviewing trauma survivors and understanding their stories in depth. Furthermore, we are convinced that these programs have a greater impact when we use peers to deliver them, and that a group approach is very helpful in showing people that they are not alone in their struggles. Trust is more quickly developed as our participants find that they are intuitively understood by those trying to help, and that others have similar experiences.

Second, we use concepts and language that immediately convey respect and recognition of strength. Instead of calling the program "treatment", we call it "training". Instead of "patients" or "clients", the participants are "students". About the symptoms they experience, we explain, "it is not what is wrong with you, it is what happened to you". We educate about post-traumatic growth, and we train the students in emotional regulation strategies such as meditation and breath control. We encourage disclosure of their stories in ways that emphasize that they are writing their own life narrative going forward. We help them see how they support each other in the group, and that they have valuable experience, capabilities, and emerging understanding of themselves and trauma's effects that they can use in service to others.

We have also seen that providing continued support to the students in the months following those spent in the program is necessary to build on what has been started. We do this with a careful and creative use of technology to teach more and keep our students connected with their peer trainers and their cohort.

These lessons and this innovative approach to trauma intervention, we believe, is a pathway to a more humane and effective way to help a variety of trauma populations. The post-traumatic growth process is very similar no matter the originating traumas[7,8]. What is necessary is for expert companions to be an essential part of the response to trauma survivors and to appreciate the opportunities for much more than a recovery. Trauma changes people, but the changes do not need to be diminishment. They are more likely to be growth.

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Chronotype and mental health: timing seems to matter, but how, why, and for whom?

Despite explosive progress over recent decades in understanding the molecular basis of circadian rhythms and their pervasive role throughout the brain and body, our understanding of a related construct – chronotype – remains incomplete.

Historical wisdom going back to Aristotle espouses the benefits of an early sleep-wake schedule for health, financial success, and intellectual prowess. Accumulating research aligns with such relationships, particularly in the realm of mental health: individuals reporting tendencies towards earlier sleep-wake timing also tend to report relatively better mental health and well-being. Nonetheless, questions remain about the nature of chronotype and its relationship to mental health. Here I briefly review the construct of chronotype, note measurement issues that require consideration, discuss evidence for chronotype's relevance to mental health and possible underlying mechanisms, and list potential future directions for research.

Clearly defining chronotype is important. Inconsistency in definition has contributed to challenges in comparing and consolidating the ever-expanding literature. Scientific literature has not converged on a definition, but generally conceptualizes chronotype as the tendency for relatively earlier or later sleep and alertness/activity within the 24-hour day, with phenotypes ranging from extreme early to extreme late. Furthermore, chronotype is often conceptualized to index overall circadian timing, and indeed tends to correlate with physiological measures of the central circadian clock, although it appears to be influenced by other non-circadian factors as well, such as homeostatic sleep propensity[1].

Two approaches to measuring chronotype predominate; one based on preference and one based on actual behavior. The more long-standing approach – morningness vs. eveningness – assesses self-reported preference for the relative timing of sleep and activity (one's own "feeling best" rhythm), producing a score that can be used continuously or to categorize individuals into putatively discrete categories. This approach has long ties to personality literature, and more often treats chronotype as a trait-like psychological construct. The more recent approach, based on the Munich Chronotype Questionnaire (MCTQ), assesses chronotype based on self-reported sleep-wake behavior on "free" days, producing a time that can be ostensibly interpreted as the phase (or timing) of entrainment of the circadian clock relative to the 24-hour light-dark cycle. Although measures from each approach tend to correlate with one another, their conceptual and methodological differences are worth consideration, and have important implications for interpreting their observed relationships to mental health[2].

Treatment studies demonstrating systematic changes in circadian preference suggest a state-like aspect[3], but longitudinal studies that address this question remain scant. Next, factor analyses of preference-type measures suggest the presence of 2+ factors, typically including both a "morning affect" factor that captures how one feels or functions upon rising after sleep (irrespective of when sleep occurred) alongside a factor capturing the relative timing of sleep and/or activity[4]. This raises concerns that observed associations between chronotype and mental health may be partly driven by how individuals feel upon rising from sleep, rather than by timing *per se*. The MCTQ's focus on "actual" sleep behavior may obviate this issue. Finally, historical social mores may bias respondents to representing themselves as more morning-type, consistent with my anecdotal clinical experience with Delayed Sleep-Wake Phase Disorder patients who nonetheless steadfastly endorse preferring an early schedule because of perceived advantages for relationships, work and health.

Measurement issues aside, the extant literature supports an association between chronotype and mental health. Greater eveningness is consistently associated with a range of mental health outcomes, including anxiety, mood disorders, obsessive-compulsive symptoms, attention-deficit/hyperactivity disorder, schizophrenia and substance use, suggesting a transdiagnostic relationship. Eveningness is also linked to worse physical health, such as obesity and cardiometabolic risk.

The most consistent findings are with respect to depression, buttressed by two meta-analyses, and substance use. The meta-analyses[5] document substantial heterogeneity across studies as well as generally small effect sizes, although the reliability of the findings

despite widely-varying measures of circadian preference is notable. A major limitation of the extant chronotype-mental health literature is its reliance on observational and cross-sectional designs, precluding a determination of directionality.

A few studies have documented changes in circadian preference in response to treatment and/or as a predictor of treatment outcomes, suggesting a potential causal role in mental health improvement[6]. These studies have generally found that shifts towards morningness during treatment parallel improvement in other domains. However, such findings deserve cautious interpretation, as they tend to be small changes on preference-type measures, potentially reflecting people feeling better upon awakening rather than a true change in timing tendencies.

The diversity of problems associated with later chronotype raises the possibility of multiple mechanistic pathways, consistent with our growing understanding of the pervasiveness of circadian influence on processes throughout the brain and periphery. A sizeable literature has focused on the most intuitive mechanism – that later chronotype leads to sleep/circadian disruption due to a mismatch with imposed school/work schedules (i.e., circadian misalignment or social jet lag), leading in turn to mental health problems. However, findings remain mixed, and multiple studies have found that chronotype correlates with mental health outcomes beyond any apparent effect of sleep/circadian disruption[7].

Other mechanistic pathways are plausible and not mutually exclusive from sleep/circadian disruption. Our recent work found substantial associations between eveningness and state-level impulsivity across multiple subdimensions, but the relationships between diary-based sleep timing and impulsivity were weak or absent[4]. This again raises questions about what aspects of chronotype are most relevant to psychological function. In that study, factor analyses confirmed that the chronotype-impulsivity associations were not driven by the so-called "morning affect" factor vs. the "timing" factor. However, that does not preclude the possibility that there is some trait-like aspect of chronotype that "travels together" with other processes such as impulsivity or sensation-seeking. Indeed, emerging research suggests shared genetic variance between chronotype and risk for mental problems or cannabis use[8]. Importantly, the nature of chronotype-mental health associations may vary substantively based on age, sex, gender identity, and race/ethnicity, as illustrated by a small but growing literature[9].

Despite evidence for an association between chronotype and mental health, the nature of this association remains unclear, and leveraging chronotype as a means to inform prevention and/or intervention remains elusive. So, what are the important next steps? These include disentangling "morning affect" vs. sleep/wake timing effects when using preference-type measures; conducting longitudinal studies to elucidate state vs. trait aspects of chronotype and test hypotheses around directionality; and examining the moderating effects of demographics. Improving clarity and consistency in terminology and methodology would help, as the myriad of preference-type measures and scoring approaches challenges comparison across studies.

Although MCTQ-based chronotype may be a purer measure of timing than the preference-type measures, it remains subject to biases, including how individuals conceptualize supposed "free" days, and there may be advantages to incorporating objective determination of chronotype via ambulatory measures such as wrist actigraphy and/or physiological measures of circadian phase. Besides reducing self-report bias, including complementary objective measures may help identify which aspects of chronotype are most relevant to mental health: morningness-eveningness preference, patterns of sleep-wake behavior, and/or the underlying circadian clock. Most importantly, attempts to experimentally manipulate chronotype and influence mental health outcomes will be critical to elucidating any causal role of chronotype in mental health.

Rigorous attention to these conceptual and methodological issues should greatly facilitate progress on understanding the mechanisms linking chronotype and mental health, thereby enhancing attempts to translate such knowledge into effective approaches to prevention and/or intervention.

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Mental health at work: WHO guidelines

Globally, 60% of people work[1], and an estimated 15% of working-age adults have a mental disorder at any point in time[2], with a likely higher rate in people with an increased exposure to risk factors for mental health at work, such as those facing inadequate pay or job insecurity. People living with severe mental health conditions face exclusion from work, largely due to stigma and discrimination, although participation in work activities is important for recovery[3]. Poor mental health can diminish a person's identity at work, reduce productivity and increase absenteeism, with depression and anxiety alone estimated to determine 12 billion lost workdays per year, impacting the global economy annually by nearly 1 trillion USD[2].

The right to good health, including mental health, and the right to decent work are fundamental human rights. Policies which support workers' well-being are essential to advance progress towards the United Nations Sustainable Development Goals 3 and 8. Despite international conventions calling for protection of physical and mental health[4], focus within occupational health has largely been on physical health, and few countries have work-related mental health prevention and promotion programmes[5]. In response to this burden and limited action, the World Health Organization (WHO) has developed guidelines[6] that provide recommendations to effectively address mental health at work.

The guidelines have been developed through methods outlined in the WHO handbook for guideline development[7]. WHO guidelines utilize PICO (Population/Problem - Intervention - Comparison - Outcome) questions, identified in collaboration with topic experts who form the Guideline Development Group. Systematic reviews of best available evidence are conducted, prioritizing randomized controlled studies where feasible, addressing critical outcomes. GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) methodology evaluates the certainty of available evidence. Recommendations balance benefits against harms, and consider beneficiaries' values, implementation feasibility, resources required, cost-effectiveness, health equity, equality and discrimination, human rights and socio-cultural aspects.

The WHO Guidelines on Mental Health at Work address organizational interventions, manager and worker training, individual interventions, return to work, recovery-oriented strategies, and screening programmes. Recommendations are provided for universal interventions; interventions for health, humanitarian and emergency workers; and interventions for workers with mental health conditions. Based on this, thirteen evidence profiles have been developed[6].

To prevent risks to mental health at work, the WHO guidelines recommend organizational interventions – approaches targeting the mitigation, reduction or removal of psychosocial risk factors (e.g., bullying, low job control). Organizational interventions help reduce emotional distress and improve work-related outcomes, including absenteeism, job satisfaction and work performance. These interventions are best delivered through meaningful participation of workers. However, most of the reviewed research evidence in this area has been found to be of very low quality, likely due to challenges of evaluating these highly complex interventions. Methodological rigor must be prioritized to bolster this evidence base, which exemplifies an opportunity to target determinants of mental health.

To protect and promote mental health at work, the WHO recommends the provision of mental health training to managers, aimed to strengthen their mental health-related knowledge, attitudes and skills, and improve workers' help-seeking. Such training equips managers to identify and support workers who experience distress, and address stressors related to working conditions. These trainings are not intended for managers to become mental health care providers. No recommendations have been made regarding leadership-oriented training, as evidence did not document clear effects on health outcomes. Training for workers largely targets mental health literacy and awareness. This was found to reduce stigmatizing attitudes and improve mental health-related knowledge, but, though such training is popular, there was no substantiated effect on mental health symptoms or help-seeking.

The guidelines also recommend individual interventions, such as psychosocial interventions or physical activity, which promote positive mental health, reduce levels of emotional distress, and improve work-related outcomes such as work-effectiveness. Workers' values demonstrated that they perceive individual interventions as an indication that they are singularly responsible for their mental health. Consequently, these interventions should be made available as one component of a comprehensive programme which includes organizational and managerial approaches.

To support people with mental health conditions to participate in work, reasonable accommodations which adapt working environments to match capacities and preferences of workers are recommended, in line with promotion of human rights[8]. The Guideline Development Group considered return-to-work programmes following an absence associated with mental health conditions. Evidence-based mental health clinical care, in combination with work-directed care (e.g., graded return to work) or alone, leads to reductions in mental health symptoms and absence. Recovery-oriented strategies focusing on vocational and economic inclusion, such as (augmented) supported employment, are effective for persons with severe mental health conditions in obtaining and maintaining employment.

No recommendation was made for screening programmes during employment (screening plus follow-up support), owing to the uncertainty on whether the benefits outweigh the harms. The statement of no recommendation does not apply to screening as required by some occupational regulations.

The WHO Guidelines on Mental Health at Work are based on the best available recent evidence, yet a substantial research-gaps agenda is proposed to address the limited high-quality and undiverse research. Work-related outcomes are often absent from research on mental health at work. Science must go beyond defining psychosocial risks at work, to develop high-quality evidence on what organizational approaches work for whom. The world's largest working populations remain unusually under-researched, includ-

ing informal workers, and those who work in small- and medium-sized enterprises and in low- and middle-income countries.

A WHO and International Labour Organization joint policy brief was released alongside the guidelines to support stakeholders in their application[9]. This brief provides a roadmap to improve mental health at work through creating an enabling environment for prevention of exposure to risks, protection and promotion of mental health at work, and support for people with mental health conditions to participate and thrive at work.

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Implementation of self-binding directives: recommendations based on expert consensus and input by stakeholders in three European countries

Self-binding directives (SBDs) are psychiatric advance directives including a clause in which mental health service users give advance consent to involuntary hospital admission and treatment, and grant mental health professionals permission to overrule anticipated treatment refusals during future mental health crises[1,2]. They are also known as "Ulysses contracts" or "Ulysses arrangements".

SBDs can enable people with mental disorders which involve fluctuating mental capacity and regular treatment refusals during crises (e.g., psychotic and bipolar disorders) to stay in control of their life and treatment[1]. During episodes, these people may make decisions that are incompatible with their deeply-held values, convictions and preferences. Such decisions regularly involve refusal of hospital admission or treatment and can have far-reaching consequences. By enabling service users to authorize professionals to overrule such refusals, SBDs are essential to advance care planning in people with psychotic or bipolar disorders.

While potential ethical benefits and risks of SBDs have been discussed extensively in the ethics and legal literature, little was known about stakeholders' views on the opportunities and challenges of SBDs until recently. Recent studies conducted in Germany, The Netherlands and the UK reveal that stakeholders perceive promotion of autonomy, avoidance of harm, possibility of early intervention, improvement of the therapeutic relationship, and involvement of trusted persons as opportunities of SBDs[3-9]. Perceived challenges include lack of awareness and knowledge of SBDs, lack of formal support for SBD completion, undue influence during the drafting process, inaccessibility of SBDs during crisis, lack of cross-agency coordination, problems of interpretation of SBD content, difficulties in mental capacity assessment, restricted therapeutic flexibility due to narrow SBD instructions, infeasibility of SBDs due to scarce resources, disappointment due to non-compliance with SBD instructions, and outdated SBD content[3-9].

Stakeholders who participated in these studies tended to see the implementation of SBDs as ethically desirable, provided that the above-mentioned challenges are addressed through the implementation of appropriate safeguards. Based on suggestions made by stakeholders and a structured expert consensus process among authors, we have derived the following recommendations for the legal and clinical implementation of SBDs.

Legal regulation. The implementation of SBDs requires legal provisions stating clear criteria for the validity, content, activation and revocation of SBDs. There should be an expedited procedure for arranging involuntary hospital admission and treatment based on an SBD to enable early intervention.

Authorization by an independent party. Involuntary hospital admission and treatment based on an SBD must be authorized by an independent party. The authorization can take the form of a prospective approval or a retrospective review by a judge, a second opinion by an independent medical specialist, or another

kind of non-legal monitoring mechanism (e.g., approval or review by an interdisciplinary panel). The procedure for obtaining legal authorization of involuntary hospital admission and treatment should pose no obstacle to early intervention.

Awareness raising. Awareness about SBDs should be raised among service users, professionals, informal caregivers, third sector organizations, and the public. Useful tools can be flyers, information sheets, online information sites, and campaigns in traditional and social media.

Target population. Professionals should check eligibility for SBD creation. Service users who are most likely to benefit from SBDs have fluctuating mental capacity, a tendency to refuse hospital admission and treatment during mental health crises, good recovery between episodes, previous experience with involuntary hospital admission and treatment, and a reasonable understanding of their illness and its effects on their lives. SBDs are less likely to be of help to people with neurodegenerative disorders such as Alzheimer's disease. SBDs in people with personality, substance use and eating disorders must be tailored to their specific needs.

Support for SBD completion. Professionals should support service users in the SBD drafting process. User-friendly and accessible SBD templates including guidance should be developed and offered to service users and informal caregivers. Training materials and guidance should be developed and offered to professionals. Enabling reimbursement of time invested in support for SBD completion provides professionals with an incentive to give support.

Provision of medical information and expectation management. Professionals should inform service users about the nature, benefits and risks of requested treatments. They should also provide feedback and point out impossibilities if complying with the proposed SBD content would be unfeasible or incompatible with legal or professional standards. Finally, professionals should make service users aware of the consequences of granting clinicians permission to overrule treatment refusals, and of the practical challenges associated with SBDs (e.g., that they might be inaccessible during a crisis).

Specific SBD content. SBDs must specify in detail the circumstances in which involuntary hospital admission and treatment must be arranged, the kind of treatment that must be provided, and the circumstances in which involuntary hospital admission and treatment must be terminated. It must be ensured that treatment preferences described in the SBD are unequivocal, and that the described activation and termination criteria of involuntary hospital admission and treatment can be assessed reliably. SBDs should also include the name and contact information of a person of trust.

Involvement of persons of trust. Persons of trust (e.g., family members or friends) should be involved in the SBD drafting process and play an important role in the assessment of early warning signs and SBD activation. Service users should have the opportunity to appoint a legal representative in their SBD.

Involvement of a neutral party. The involvement of a professional and a person of trust in the SBD drafting process provides mutual checks and balances, and reduces the risk of undue influence exerted by either of these parties. The involvement of a neutral party as a facilitator in the drafting process can minimize the risk of undue influence. Peer support workers seem especially suitable for this role, in virtue of their lived experience and their ability to function as a bridge between service users and professionals.

Accessibility and privacy. An institutional framework and technical infrastructure to ensure SBD accessibility across agencies is required. A digital infrastructure enabling both the creation and registration of SBDs can be particularly helpful. Data security and privacy should be ensured. Providing access to SBDs by the police is discouraged.

Self-defined indicators of impaired mental capacity. Service users can describe self-defined indicators of impaired mental capacity in their SBD, to facilitate mental capacity assessment at the time when the SBD should be activated.

Compliance with SBDs. Professionals should commit to complying with SBD instructions within legal and professional limits to prevent legitimate disappointment among service users and possible deterioration of the therapeutic relationship.

Updating and evaluation. SBDs should be updated regularly to ensure that they continue to reflect service users' considered preferences. Regular updates can be facilitated by automatic notifications at set times, depending on the preferences of the individual service user. Compliance of the involuntary hospital admission and treatment with SBD instructions should be evaluated retrospectively by all parties involved. If necessary, the SBD should be updated based on the results of this evaluation.

We believe that these implementation principles and safeguards can address the challenges of SBDs, and make it possible for SBDs to fulfil their promise of enabling people with episodic disorders that involve fluctuating mental capacity and anticipated treatment refusals to stay in control of their life and treatment.

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Childhood gender non-conformity, sexual orientation and mental health problems among 18 to 89 year-old Danes

Children who do not comply with social norms and expectations concerning their biological sex are generally referred to as gender non-conforming[1]. Childhood gender non-conformity has been associated with various psychosocial stressors and mental health problems[1,2], but these associations remain to be investigated at a nationwide level.

Prior research on this topic has focused primarily on non-probability-based samples of young people and sexual or gender identity minority groups, documenting strong links between childhood gender non-conformity and both non-heterosexuality and non-cisgender identity[3-5]. Same-sex oriented individuals considerably more often report childhood gender non-conformity than heterosexual peers, and it has been suggested that childhood gender non-conformity might, at least in part, explain the excess mental morbidity observed among sexual minorities[6,7].

The aim of the present study was to investigate potential links between recalled childhood gender non-conformity and mental health problems in the general Danish population as well as in strata of heterosexual, homosexual and bisexual Danes. We used baseline questionnaire data from 27,548 individuals aged 18-89 years who participated in Project SEXUS, a prospective cohort study launched in 2017 with the aim of exploring the interplay between sexual and general health[8,9]. The cohort was established using a probability-based sampling frame, and an individual weighting procedure ensured national representativeness with respect to key demographic factors (see supplementary information).

Childhood gender non-conformity was defined using the following question: "*How well, or how poorly, does the following statement fit you: As a child or young person, I had difficulties living up to other peoples' perception of 'a real girl'* (for respondents assigned female sex at birth) / *'a real boy'* (for respondents assigned male sex at birth)". Respondents who answered that the statement fitted them "well" or "very well" were considered as childhood gender non-conforming.

We included measures of mental health problems ranging in severity from loneliness to suicidal thoughts/attempts. Respondents were asked how often they felt lonely, and we considered the responses "sometimes", "often" and "always" as indicators of loneliness. To capture symptoms of depression or anxiety within the last 14 days, respondents were presented with the two-item Patient Health Questionnaire (PHQ-2) and the seven-item Generalized Anxiety Disorder (GAD-7) scale. Respondents with a PHQ-2 score ≥3 were considered to have depressive symptoms, while respondents with a GAD-7 score ≥5 were considered to have anxiety symptoms. Additionally, respondents were asked if they had ever received treatment by a doctor, a psychologist or a similar professional for a mental health problem, and they were asked if they had ever self-harmed without suicidal intent or if they had ever had suicidal thoughts with or without actual suicide attempts.

We calculated prevalence estimates and performed chi-square tests to determine whether covariate distributions (age, educational attainment, difficulties paying bills within the last year, partner status, gender identity, sexual identity, same-sex sexual experience and attraction, and history of sexual assault before age 18 years) differed significantly between childhood gender conforming and non-conforming participants.

Using binary logistic regression analyses, we calculated prevalence odds ratios (ORs) with 95% confidence intervals (CIs) for associations between recalled childhood gender non-conformity and the studied mental health outcomes using childhood gender conforming individuals as reference. Additionally, we performed analyses stratified on sexual identity categories (heterosexual, homosexual and bisexual) using gender conforming heterosexuals as reference. ORs were adjusted for age in 10-year categories, and fully adjusted ORs (aORs) were further adjusted for educational attainment, difficulties paying bills within the last year, partner status, gender identity, sexual identity, and history of sexual assault before age 18 years.

We used demographically weighted data in all statistical analyses, which were carried out using the stats package in R (version 4.0.2).

Of 27,548 study participants, 5,355 (demographically weighted proportion, 19.0%) reported having experienced difficulties living up to other people's perception of 'a real girl' or 'a real boy' during childhood or adolescence, with a larger proportion among women (21.2%) than men (16.9%) (p<0.001). More childhood gender non-conforming than conforming individuals reported ≤10 years of education, difficulties paying bills, and not having a spouse or a partner. Childhood gender non-conformity was reported markedly more often by non-cisgender respondents, individuals with a non-heterosexual identity, and those reporting any same-sex sexual behavior or attraction. Further, larger proportions of childhood gender non-conforming than conforming individuals reported having been the victim of a sexual assault before age 18 years (all p values <0.001) (see also supplementary information).

Childhood gender non-conformity was associated with consistently greater odds of mental health problems in both age-adjusted and fully adjusted analyses, including loneliness (women: aOR=1.47, 95% CI: 1.34-1.62; men: aOR=1.45, 95% CI: 1.29-1.63); depressive symptoms (women: aOR=1.48, 95% CI: 1.32-1.65; men: aOR=1.51, 95% CI: 1.32-1.73); symptoms of anxiety (women: aOR=1.72, 95% CI: 1.56-1.90; men: aOR=1.63, 95% CI: 1.45-1.83); having ever received treatment for a mental health problem (women: aOR=1.54, 95% CI: 1.41-1.70; men: aOR=1.45, 95% CI: 1.29-1.62); self-harm (women: aOR=1.93, 95% CI: 1.66-2.25; men: aOR=1.83, 95% CI: 1.50-2.24); and suicidal thoughts/attempts (women: aOR=1.98, 95% CI: 1.78-2.19; men: aOR=1.54, 95% CI: 1.36-1.73).

Several associations between childhood gender non-conformity and mental health problems remained statistically significant in analyses stratified by categories of sexual identity. Among heterosexual participants, mental health challenges were reported consistently more often by childhood gender non-conforming than conforming individuals, most notably so for self-harm (women: aOR=2.11, 95% CI: 1.79-2.48; men: aOR=1.81, 95% CI: 1.46-2.25).

Using childhood gender conforming heterosexual peers as reference, childhood gender conforming homosexual participants generally did not exhibit statistically significantly increased odds of mental health problems. In contrast, childhood gender non-conforming homosexual participants had elevated odds of most mental health problems, with particularly high odds for suicidal thoughts/attempts (women: aOR=3.32, 95% CI: 1.89-5.82; men: aOR=2.62, 95% CI: 1.75-3.91) (see also supplementary information).

For bisexual participants, odds of several mental health problems were increased among both childhood gender conforming and non-conforming individuals when compared to the reference group of childhood gender conforming heterosexuals. Particularly elevated odds were observed for self-harm (women: aOR=3.12, 95% CI: 2.06-4.71; men: aOR=5.27, 95% CI: 2.71-10.25) and suicidal thoughts/attempts (women: aOR=3.14, 95% CI: 2.12-4.65; men: aOR=2.33, 95% CI: 1.28-4.25) among gender non-conforming bisexuals (see also supplementary information).

With approximately one-in-five study participants recalling difficulties living up to other people's gender-specific norms and expectations as a child or young person, our nationally representative findings demonstrate that childhood gender non-conformity is by no means a rare phenomenon restricted to specific subsets of the general population. While proportions of non-cisgender and non-heterosexual individuals reporting childhood gender non-conformity are clearly higher than corresponding proportions among cisgender and heterosexual peers, the vast majority of childhood gender non-conforming people in the general population are cisgender, heterosexual individuals.

Importantly, we document that childhood gender non-conformity is linked to a considerably increased burden of mental health problems among both women and men, and among heterosexual, homosexual and bisexual individuals alike. These findings should raise awareness about the elevated burden of mental health problems among individuals with recalled childhood gender non-conformity, and stimulate initiatives to increase societal acceptance of gender diversity and eliminate bullying and violence against gender atypical children and adolescents.

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Supplementary information on this study is available at https://www.projektsexus.dk/publikationer/2023/cgn_supplementary_information.

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First evidence of a general disease ("d") factor, a common factor underlying physical and mental illness

The links between mental and physical illness are an emerging topic, with the potential to transform research and practice in medicine and psychology[1].

Symptoms of mental illness have been found to be underpinned by one single factor explaining the propensity to develop any mental health condition, which has been termed the "p" (for psychopathology) factor[2]. The "p" factor has been demonstrated not only at the symptom[2], but also at the genetic level[3], and in overlapping neural correlates across a wide range of psychiatric disorders[4].

However, there is evidence of comorbidity not only among mental conditions, but also between mental and physical conditions, as shown by studies pointing to transdiagnostic associations across a wide range of physical and mental disorders[1,5]. These findings suggest that there may be another factor that accounts for the individuals' propensity to develop mental as well as physical conditions, that we termed the "d" (for disease) factor[6]. The existence of this factor would have highly relevant research and clinical implications regarding our understanding and management of mental and physical conditions, as well as for service organizations.

We empirically tested the hypothesis of a "d" factor in the 1970 British Cohort Study (BCS), which recruited 19,196 individuals born in a single week of 1970 in England, Scotland and Wales[7]. We used the biomedical sweep of the BCS[7], collected in 2016 from 8,581 participants aged 46-48.

Mental conditions included anxiety, phobia, depression, schizophrenia, obsessive-compulsive disorder, insomnia, and stutter. Physical conditions included chronic fatigue syndrome, migraine, stroke, seizures, asthma, eczema, hay fever, arthritis, back problems (prolapsed disc/pain), ulcer, ulcerative colitis/Crohn's disease, irritable bowel syndrome, gallstones, kidney/bladder stones,

hearing impairments, visual impairments, tinnitus, obesity, diabetes, heart problems, high blood pressure, and cancer. Physical problems were assessed via self-report and/or by asking participants whether the condition had been diagnosed by a physician. Mental health conditions were assessed by one-item self-report questions or questionnaires (see supplementary information).

We ran three hierarchical models, that are typically used to investigate hierarchically structured constructs[2] using confirmatory factor analysis, as follows: a) a correlated factors model, assuming that all conditions (mental and physical) would be correlated, b) a unifactor model, assuming that all conditions would be best explained by one underlying factor, and c) a bifactor model, assuming that mental and physical conditions would load on individual factors, but that an underlying disease dimension ("d") would explain the data best.

Model fit was assessed by weighted least square mean (WLSM) and variance estimator, and compared using chi-square values, the comparative fit index (CFI), the Tucker-Lewis index (TLI), and the root-mean-square error of approximation (RMSEA). Lower RMSEA values indicate better model fit (<0.06 = good model fit); higher CFI and TLI values indicate better model fit (>0.95 = good model fit)[8]. Data analyses were conducted in Mplus v8[9].

We found that the bifactor model fitted the data best (CFI=0.98, TLI=0.98, RMSEA=0.016). All physical and mental conditions loaded positively onto a common disease factor, with the highest factor loadings for chronic fatigue syndrome (0.71±0.04), heart problems (0.66±0.04), irritable bowel syndrome (0.57±0.03), ulcer (0.56±0.06), and obsessive-compulsive disorder (0.53±0.03). The majority (15/22) of physical conditions loaded significantly on a "physical factor", apart from cancer, chronic fatigue syndrome, ulcers, gallstones or kidney stones, vision impairments, and seizures. Cardio-metabolic variables (obesity, diabetes, hypertension, heart problems) loaded negatively onto the physical conditions factor. Mental conditions loaded highly positively onto a psychopathology ("p") factor (see supplementary information).

Therefore, we found that the data were best explained by a bifactor model with a mental conditions factor, a physical conditions factor, and an additional underlying disease dimension, reflecting a general vulnerability to develop any of the included conditions. Therefore, our results support the assumption of the existence of a general "d" factor in adults.

Although our study does not test underlying mechanisms, several suggestions can be made based on existing literature. First, it is likely that a range of physical and mental conditions share common genetic polymorphisms that generate a vulnerability towards developing a wide range of diseases[3]. Other possible mechanisms include common lifestyle and socioeconomic factors. For instance, smoking, high alcohol consumptions, disrupted sleep, and lack of exercise are associated with increased cardio-metabolic risk. Unhealthy lifestyle is also associated with immune system dysfunction, which in turn is related to a variety of physical and mental conditions.

Our findings have relevant implications for the conceptualization and classification of mental and physical conditions. Current classification systems have been criticized[2] because of the high comorbidity between mental disorders. Our results contribute to this debate by showing the existence of a common dimension, beyond mental health conditions, that includes also physical health conditions. Transdiagnostic research assessing risk and pathways of transmission of diseases might benefit from taking both mental and physical conditions into account. A pertinent question is whether it is still meaningful to differentiate between mental and physical disorders or whether it might be more useful to view them both as health conditions.

The results of this study have also important implications for clinical practice and policy. Our findings stress the need to reduce the gap between physical and mental health care regarding assessment and treatment. Furthermore, our results strongly call for health care policies to promote more integrated health care systems, bridging the current gap between mental and physical health care services that exists across countries and health systems.

Strengths of this study include the large sample size and the broad range of physical conditions that were included. Limitations include the limited number of mental health variables related to thought disorders and externalizing disorders, which is why a three-factor solution (internalizing, externalizing, thought disorder)[2] could not be modelled. Additionally, data were limited to a predominantly White, middle-aged British sample, and replications are needed in younger and older samples and in samples from various areas of the world, including low-income countries. Furthermore, the physical conditions were ascertained largely by single self-report items, with no direct assessment of the conditions.

Future studies should use data from health registries around the world with comprehensive mental health assessments, assess the temporal links between mental and physical disorders, evaluate the possibility of a "d" factor across development, and explore possible common genetic and pathophysiological pathways.

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The price of peace in our time

The Russian invasion of Ukraine – starting on February 24, 2022 – is a global catastrophe. It is a moral and a public health crisis posing challenges for individuals, families and nations. Leaders of international and national psychiatric associations gathered in Warsaw, Poland on February 24, 2023, aiming to work together to address the horrific consequences of an immoral war, and the traumatic damage both within and beyond the war zones.

For this purpose, there must be a careful consideration of what is necessary to provide peace and safety in Ukraine and in the hearts of all those who have been deeply affected by this war and the consequential political and economic crisis. It is essential to bear witness to this horrific war, as well as to consider the vital work ahead. Success will require a new political and social order, new health care systems, and a new confidence that political leaders can maintain peace in a rapidly changing global world that faces other looming crises.

The leaders of the psychiatric associations posed the following questions: a) what is the impact of the Russian war on Ukraine and the world?; b) how has the global crisis due to the Russian war affected mental health and mental health systems in other countries?; c) what lessons can be learned from this global medical, economic, political and moral crisis?; d) what are the roles of public entities, including the WPA, the European Psychiatric Association (EPA) and other international and national professional societies, as we face these moral and medical challenges?

Some of these questions are specific to Ukraine and its people; others are relevant to crises facing all countries. Death, destruction, forced migration, as well as economic disparity and disruption are all too common in the contemporary world, creating an uncomfortable and unsettling context within which the Ukrainian situation must be considered. This context creates catastrophic effects that are overwhelming already inadequate systems of care, in Ukraine and beyond.

Children and young families are at highest risk, because their social support systems are being destroyed, their schools and career opportunities are disappearing, and their homes and families are being obliterated by rockets. The Ukrainian infrastructure – especially energy systems, public institutions, schools and hospitals – have been deliberately targeted and destroyed, with many deaths of innocent non-combatants considered merely "collateral damage".

As the terror continues, a large proportion of the population is experiencing symptoms that are often the prodromes of traumatic disorders, while symptoms of anxiety, depressive and other mental disorders are being exacerbated. The situation is worsened by the loss or absence of clinical caregivers, psychosocial support, medications and other essentials for patient care.

The levels of trauma from the Russian invasion of Ukraine are unprecedented. The start of the Russian war in Ukraine has followed the death and disability from the COVID-19 pandemic and the ravages of climate change. Disaster is building on disaster, leaving people and resources depleted. The magnitude of destruction in Ukraine and its impact on the world are astounding. The real impact on people is captured by the numbers[1,2]: from a 2019 Ukraine pre-war population of 43.7 million people, there are now 13.5 million people displaced (5.4 million internally and 8.1 million externally).

The best of Ukraine's next generation is in jeopardy, with many already dead or maimed. For those who have survived, schooling and careers have been put on hold or destroyed. Many buildings and businesses have been destroyed and supply chains disrupted. Homes and schools are gone, livelihoods irreparably damaged, hospitals unable to provide care, and civil infrastructure (power, water, food, Internet, government services) limited.

Eight million Ukrainian refugees have flooded other countries[2]. Another estimated 1.6 million have been forcibly "evacuated" to Russia[3]. Ukraine's agricultural production has been disrupted by Russia's blockade of exports and placement of landmines in wheat fields, leaving millions at risk of starvation, since 40% of World Food Program grain comes from Ukraine. Additionally, there is grave environmental danger, especially with Russian attacks on nuclear power stations and threats to use nuclear weapons.

Solutions to crises are never evident nor easy. The pursuit of peace with justice will always be our foremost goal, with a full Russian withdrawal from the Ukraine's territory, massive rebuilding within Ukraine, restoration of public infrastructure (including the mental health and general health care systems), and restoration of grain shipments to the developing world.

World leaders in the mental health and general health fields can promote peace and prosperity, while making every effort to manage the mental health crisis facing Ukrainians at home and abroad, by: a) bearing witness to the atrocities and violence committed in this war, and wherever they occur; b) identifying the expanding mental health crises associated with war and forced migration; c) supporting sanctions against Russia with the goal of increasing the burden of the war on Russia; d) supporting Ukraine, its people, and the Ukrainian Psychiatric Association.

The WPA and other psychiatric associations around the world should: a) speak out about the moral and clinical crisis and its worldwide implications; b) support services for the growing mental health crises, by: i) providing training for mental health professionals serving Ukrainian refugees, along with broad-based mental

health collaborations; ii) developing mental health services tailored to address the trauma and other consequences of the Russian war; iii) providing medications and other resources to treat patients with mental health needs; iv) developing remote tele-mental health services, making treatment available for all; v) preparing to re-build Ukrainian facilities, services, and education systems, so that Ukrainians can benefit from the skills and resources of modern psychiatric practice; vi) establishing research programs, so that Ukrainians and people of other countries can learn from these circumstances and be better prepared, if such events occur in the future.

World leaders in the mental health and general health fields should: a) support the process of bringing war crimes prosecutions before the War Crimes Tribunal in The Hague, and human rights violations before the European Court of Human Rights, as part of the recovery process for Ukraine's collective trauma; b) recognize and address the special needs of children and young families (i.e., i) provide safety and security for all children, including shielding them from the atrocities of war, trafficking, and emotional and physical damage; ii) provide parent guidance and support for families who are displaced or facing the trauma of injury, war crimes, and death; iii) help children maintain contact with family members from whom they have been separated; iv) build online facilities to re-establish supportive social networks for developing youth; v) sustain virtual Ukrainian schools, so that children who had to leave homeland can continue their intellectual and social development, while also giving them the tools and hopes for a future in Ukraine; vi) provide evidence-based general interventions that give comfort and promote resilience, such as mindfulness training and evidence-based single-session interventions); c) never forget: the Russian war; the Ukrainian people; the threats to all of us; the need to promote healthy development, mental health, and peace.

There is great power in unity. Now is the time to stand together. A strong way to support resilience and recovery is for medical and mental health professionals to speak in one voice supporting the end of this and other wars.

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Mental health literacy for supporting children: the need for a new field of research and intervention

The concept of "mental health literacy" (MHL) was first defined in 1997 as the "knowledge and beliefs about mental disorders which aid their recognition, management or prevention"[1]. MHL originally encompassed: a) the ability to recognize specific disorders; b) knowing how to seek mental health information; c) knowledge of risk factors and causes; d) knowledge of self-help and of professional help available; and e) attitudes that promote recognition and appropriate help seeking. Later revisions added: f) knowledge of how to prevent mental disorders; g) recognition of when a disorder is developing (i.e., early identification); and h) first aid skills to support others affected by mental health problems[2]. Some scholars also include: i) knowledge for mental health promotion[3]. Since its articulation, MHL has been instrumental in the creation of interventions, policy and funding for mental health in many countries.

Much of the research influenced by the concept of MHL has focussed on adolescents, as this is the period of life where mental disorders often first develop, and schools provide a suitable setting for promoting adolescents' MHL[4]. However, we believe that there is an urgent need to define a new field of research focussed on the knowledge and beliefs of adults about mental ill-health in school-aged children (those around 5 to 12 years), to aid better recognition, management and prevention. The rationale for a separate field is clear: the MHL required to recognize, manage and prevent mental ill-health in childhood is unique to this life stage. The diagnoses and symptom profiles, the help-seeking pathways, the modifiable risk and protective factors, as well as stigmatizing attitudes, are particular to pre-adolescent children and thus require tailored research methods and interventions.

Population-based surveys indicate important differences in the psychiatric epidemiology of children aged 5 to 12 years, as compared to adolescents aged 13-18. For example, attention-deficit/

hyperactivity disorder (ADHD), as well as separation and phobia-related anxiety disorders, are much more prevalent among younger children, particularly boys, whereas depression and social phobias take centre stage in adolescence, particularly among girls[5].

The clinical interventions required across the childhood and adolescent years are also different. Parents play a much larger role in treatment for children than for adolescents; many frontline treatments for pre-adolescents involve parent training (e.g., psychoeducation or parent management training), or combined parent and child psychological therapy. Frontline treatments for adolescents, instead, are more likely to involve individual therapy or pharmacotherapy[6].

Relatedly, the help-seeking pathways and access to treatment for children versus adolescents (or adults) are also distinct. For diagnosing child conditions, multi-informant assessments are preferred, whereas for adolescents this is not as common[6]. It is possible for adolescents to access mental health care through their school, community-based primary care, or sometimes even private providers, without the knowledge or input of their guardians. This is not possible for children, who are totally dependent on their caregiving adults to recognize mental ill-health and engage in appropriate help seeking for it.

We therefore propose a new concept – mental health literacy for supporting children (MHLSC) – to refer to adults' knowledge and beliefs that support action to prevent or manage mental health problems in children. We suggest that MHLSC involves adults': a) ability to recognize when a child is developing a mental health problem (e.g., not coping, experiencing increasing distress, or difficulty functioning as expected); b) knowledge and attitudes about how to seek and engage critically with information about child mental health, risk factors and causes of mental health problems in children, and sources of formal and informal help for both the child and caregivers; and c) ability to communicate about child mental health and supportive strategies with the child in a developmentally-appropriate manner, and with other adults who care for or are responsible for the child.

Because children may not have the capacity to understand their mental health problem, manage it, or seek help for it, the MHL that adults need to support children with mental ill-health is more complex than adolescent or adult MHL. We also believe that it is important to distinguish between the knowledge and beliefs which adults hold about child mental health problems (MHLSC), and the knowledge and beliefs that children hold about their own mental health (i.e., "child mental health literacy"). As gatekeepers to recognition, treatment and management strategies, adults' knowledge and beliefs are arguably more important than the child's own knowledge and beliefs. In addition, we consider MHLSC to be different to mental health promotion, as the knowledge, attitudes and skills required to promote good mental health in childhood are fundamentally different (though closely related) to those required for the recognition, prevention or management of mental ill-health.

Since its conceptualization in the 1990s, MHL research has grown in size and impact. In the late 2000s, there was a shift in focus from the knowledge and beliefs that adults held about their own mental health towards literacy for adolescent mental health. Population surveys around the world soon examined how youth understood and sought help for their mental health, and how interventions could improve their MHL. MHL is now considered "the foundation" for prevention, early identification, intervention, and ongoing care for mental ill-health[3]. Indeed, it is now inconceivable that any national strategy on mental health would omit MHL, given its necessity in fostering appropriate help seeking, management and prevention of mental health problems.

Mental ill-health, however, is not only common among adolescents and adults. Around 13% of children experience a diagnosable illness in any 12-month period[5,7]. Recent global estimates suggest that 35% of all mental illnesses begin before age 14[8]. Yet, a persistent issue encountered in the "paediatric", "child and adolescent" or "youth" mental health literature is that sample age tends to be ill-defined; some studies sample infants through to those aged 18 years, while others include pre-school or school age through to young adulthood (25 years)[7]. An entrenched proclivity in this approach is to prioritize adolescents while younger children are ignored[9]. What the history of MHL research shows us, however, is that with precise conceptualization we can identify knowledge gaps, understand attitudes, and highlight help-seeking barriers, which can then be effectively targeted by interventions. But until MHL research can illustrate the necessary focus on children aged 5 to 12 years, advancements in policy and funding to improve outcomes in child mental health will remain out of reach.

We are confident that articulating the scope and need for a new field of MHLSC research will lead to new high-quality measures, representative population-level surveys, effective interventions, and evidence-based policy targets, just as it has for adult and adolescent mental health globally. If history repeats itself, this new research endeavour will help us improve the mental health outcomes for the children of the future.

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Antidepressants in primary care: limited value at the first visit

When patients with a depressive condition first visit a general practitioner, they often get the prescription of an antidepressant[1]. We think that it is better to prescribe medication at a later stage, if at all. Here we explain why.

It is well known that most patients in primary care have mild to moderate depression, while severe depression is an exception. For example, we found that, among primary care patients in waiting rooms, 13% had a score on the Patient Health Questionnaire-9 (PHQ-9) between 9 and 11, which is above the threshold for major depression, but only 5% had a severe depression (PHQ-9 score higher than 14)[2].

There is also considerable evidence that the effects of antidepressants in mild and moderate depression are small, and may not be clinically relevant. In one individual patient data meta-analysis, the risk difference (percent response to medication minus percent response to placebo) was only 6% in mild depression, which corresponds to a number needed to treat (NNT) of 16[3]. In very severe depression, the risk difference was 25% (NNT=4); in severe depression, it was 9% (NNT=11). These results were recently confirmed in a large individual patient data meta-analysis of 232 trials with more than 73,000 patients[4]. Furthermore, a recent pragmatic placebo-controlled trial confirmed that antidepressants are not very effective in patients with mild depression seen in primary care: with an average PHQ-9 score of 12, the NNT was only 12.5[5].

It is also well known that many patients in primary care who use antidepressants are not willing to stop their medication, even when it is clearly not working, because they are afraid that they will get worse.

Much of the confusion about the effects of medications in depressed patients seen in primary care is due to an earlier Cochrane review[6], reporting that the NNT was 8.5 for tricyclic antidepressants and 6.5 for selective serotonin reuptake inhibitors, which would be considered a reasonable clinical effect by most clinicians. However, the problem with that review was that the included trials focused on patients with severe to very severe depression, thus being not representative of the majority of patients with depression seen in primary care. The above-mentioned meta-analyses and pragmatic trial provide a much better evidence of the effects of antidepressants in this population.

Even for patients with more severe depression seen in primary care, antidepressants may not be the best treatment at the first visit. Many of the few patients who initially present in primary care with a severe depression get better over time with or without medication[7]. Indeed, the above-mentioned Cochrane review found a median response rate of 42% with pill placebo.

So, what to do at the first visit in primary care with a patient who presents with a depressive condition? Most treatment guidelines, such as those of the National Institute for Health and Care Excellence (NICE), recommend watchful waiting or a psychological intervention before medication for mild to moderate depression, unless it is the person's preference to receive an antidepressant. Behavioural activation may be the best intervention[8], but also other brief therapies specifically developed for this context, such as problem-solving therapies, may be good treatment options.

It is less clear what should be done for severe depression at the first visit in primary care. The best strategy may be to reframe some of the negative cognitions of the patient and advice physical activity. In those who do not improve over the subsequent weeks, a psychotherapy or antidepressant medication should be considered. A recent meta-analysis showed that, at one-year follow-up, psychotherapies had better results than antidepressants[9]. This meta-analysis also found that a combination of psychotherapy and medication was better than either therapy alone.

We conclude that most patients in primary care have mild to moderate depression, and that severe depression is an exception. Antidepressants should not be prescribed at the first visit if the patient has mild to moderate depression, because they have a limited efficacy and may have significant side effects. Antidepressant medication should be considered in severe depression, but not at the first visit and as an alternative to or in combination with a psychological intervention.

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The WPA Action Plan 2020-2023: an updated report

The WPA has been severely affected in the past three years by the impact of the COVID-19 pandemic and its after-effects, the war in Ukraine, and several other adversities in many regions of the world. However, all of its components have adapted their activities, learnt to work in new ways and sought innovative ways to support mental health professionals worldwide.

We have focused in particular on selected areas – public mental health; early intervention in psychosis; managing comorbidity of mental and physical health problems; promotion of psychiatry among medical students[1-10] – according to the priorities set out in our Action Plan 2020-2023, through the work of dedicated Working Groups.

In 2020, the WPA has launched its Education Portal, which now houses many educational resources and online courses. Following the pandemic, online learning has emerged to be an everyday part of life. As such, the WPA has been committed in developing, implementing, supporting, collaborating on and co-sponsoring as many online courses and webinars as possible[11]. In the period 2021-2022, the WPA has uploaded on the Portal a series of learning modules and webinars covering a variety of topics. The system has also played a key role in the WPA's response to world emergencies – for example, through its extensive COVID-19 Mental Health Resources online library.

The WPA has contributed significantly to the dissemination of the new ICD-11 Clinical Descriptions and Diagnostic Requirements, by sponsoring online courses which have provided psychiatrists and other mental health professionals with a well-structured and comprehensive learning experience. Following the overwhelmingly positive feedback of the November 2021 course, we ran another course in March 2022, with similar great success, and are now planning a Spanish version of the course in 2023.

The WPA Scientific Sections have been holding video conferences and latterly in-person meetings on a quarterly basis. These meetings have become the marketplace for exchanging ideas about inter-sectional activities, such as joint research projects, papers, workshops and conferences[12].

The WPA has strengthened the activity of its Collaborating Centres, which have been involved in various scientific initiatives, including joint educational seminars and support to young psychiatrists in research and other related activities[13].

The WPA's Advisory Council on Response to Emergencies (ACRE) has addressed efficiently the COVID-19 pandemic and other emergencies, bringing together the leaders of the larger Member Societies to facilitate practical and concrete support to Member Societies in need. Concerning the war in Ukraine, the WPA has established an education resource center for mental health professionals – in Ukrainian, Russian and other languages – to help with the mental health challenges that people from Ukraine are currently facing. The ACRE has also raised funds for the Sri Lankan Member Society, providing support for buying psychotropic medicines, and for Afghan mental health professionals, offering ongoing support through the provision of medicines, patient assessments and training.

We continued to work on our website (www.wpanet.org), in order to improve not only the user experience but also how we share relevant information. We also continue to work hard on our social channels and are regularly posting topical information on WPA events, news, articles, webinars, and lots more. As part of the WPA "Meet the Leaders" series, we have released interviews with the current Executive Committee and Council members. In this insightful series of interviews, leaders have not only shared a summary of their valuable contributions to the Association and the field of mental health in general over the years, but also their personal views on the contributions made by the WPA and its Member Societies.

In 2021, we have launched the new WPA eNewsletter[14]. The need for information that is freely distributed and easily accessible remains an essential requirement in our lives today. We have been delighted to see how the eNewsletter has been positively received and we are motivated to continue this project. The eNewsletter is a quarterly review and provides an opportunity for all WPA components to share insights and experiences as we continue our essential work to address the mental health issues around the world.

In October 2022, we launched a new educational project – the "WPA e-Journal Club". This project consists of commentaries about the most relevant articles selected from the main scientific journals in psychiatry.

World Psychiatry is the WPA official journal. It is published regularly in three languages (English, Spanish and Russian), with individual issues or articles also available on the WPA website in other languages (Chinese, French, Russian, Arabic, Turkish, Japanese, Romanian and Polish). More than 60,000 mental health professionals regularly receive the electronic or the print version of the journal. All the back issues can be freely downloaded from the PubMed system and the WPA website. With an impact factor of 79.683, it was recently reaffirmed that *World Psychiatry* is ranked as no. 1 among all psychiatric journals and in the Social Sciences Citation Index, and no. 5 among all the journals in the Clinical Medicine category.

In August 2022, we were delighted to hold our first in-person World Congress in two years. In collaboration with the Psychiatric Association of Thailand (supported by the Royal College of Psychiatrists in Thailand and the Department of Mental Health, Thailand), we welcomed mental health care professionals to the beautiful city of Bangkok. Under the theme "Psychiatry 2022: The Need for Empathy and Action", we examined and discussed all the critical issues in psychiatry and mental health today and in the future. More than 2,400 registered participants from 100 countries joined the Congress. For the first time, we were also happy to be able to present travel awards to one trainee psychiatrist and two medical students, allowing them to join us in Bangkok and benefit from the in-person learning and networking opportunities. In addition, we were pleased to award 25 fellowships to young psychiatrists from 17 countries to help support them in their careers and research work. Along with World Congresses, the WPA has maintained its tradition of organizing regional and thematic

congresses in Europe, Asia, Africa and the Americas during the current triennium[15].

When approaching the conclusion of the triennium, we continue to face challenges following the global crises and their consequential impact on mental health. The WPA, however, stands motivated and inspired by the commitment and hard work of our fellow professionals when dealing with such difficult situations.

The WPA looks forward to the future with enthusiasm and confidence, convinced that it will be able to transform new challenges into opportunities. Let's shape the future of psychiatry and mental health together.

Afzal Javed
WPA President

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COVID-19 and psychiatrists' responsibilities: an update of the WPA position paper

The increased awareness by mental health professionals of the effects of the COVID-19 pandemic and of post-COVID-19 conditions, and of the consequent need for augmenting and increasing access to mental health services, requires an update of the WPA Position Paper on this topic published in this journal in 2020[1].

Most international evidence suggests that the COVID-19 pandemic has generated an increased incidence of mental health problems, especially anxiety and depression[2]. Elevated symptoms of depression are particularly prevalent among people with low household income, unmarried, and experiencing multiple stressors. Females, adolescents and younger adults are most affected. Poor coping skills, previous trauma exposure, deteriorating physical health, problems in family relationships, and lack of physical exercise are other risk factors.

The impact of the pandemic has been greatest for people with serious mental illness, including schizophrenia and other psychotic disorders, bipolar disorder and major depression, with significantly higher rates of COVID-19 infection, hospitalization and death[3]. The disproportionate impact of the pandemic on people with serious mental illness is likely due to worse pre-existing health and poorer access to medical services. Even in the absence of infection, people with serious mental illness have experienced marked decreases in measures of well-being and mental health during the pandemic[4].

Overall, suicide rates have not increased or have even declined during the first year of the pandemic[5]. Nevertheless, increased suicide rates have been reported in certain groups. For example, suicide rates have increased among females and adolescents in Japan, males in India, females in Poland, adolescents in Spain and France, and ethnic minorities in the US[5]. Detecting at-risk groups requires continuing alertness and improved monitoring strategies, which will permit the development of targeted preventive measures.

Health care workers have experienced very high levels of stress, as they were asked to respond rapidly to an unexpected crisis in situations of extreme work pressure. Meta-analyses estimated a 30-40% prevalence of anxiety and depressive symptoms among health care workers during the pandemic[6]. An even higher prevalence of post-traumatic stress symptoms and sleep disorders has been reported. The pandemic highlighted an already existing need for mental health resources for health care workers, that is now amplified. Effective approaches should address challenges such as the reluctance of health care workers to access psychological support, and the effects of racism and gender inequalities in these professions[7].

The COVID-19 pandemic has had many effects on family life, including job or income loss, working from home, quarantine, increased workloads, social isolation, food insecurity, school closures, and diminution of social supports, all of which have disproportionately affected marginalized populations[8]. Children have been among those hardest hit by the psychological impact of the pandemic. Being quarantined at home, facing school closures, virtual learning, masking, witnessing family distress, lack of outdoor activity, isolation from friends, overcrowding, changes in diet, and altered sleep arrangements have taken their toll[9].

A United Nations Women survey reports that one in four women feels less safe at home, and new and existing conflicts have increased within households since the pandemic started. Physical, psychological and sexual abuse have also increased. Psychiatrists should be alert for and prepared to inquire about family violence and intervene appropriately when needed[10].

Lingering symptoms following COVID-19 infection have been given various names. The World Health Organization has proposed the following definition: "Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis"[11]. Common symptoms include fatigue, shortness of breath, loss of smell, cognitive dysfunction, anxiety and depression[12,13]. They can impact everyday functioning and may fluctuate or relapse over time. As the etiology of psychiatric/psychological symptoms of long COVID-19 remains un-

known, psychiatrists should be familiar with strategies known to improve coping, such as self-management, mindfulness meditation, cognitive behavioural therapy, and supportive therapies.

The burgeoning number of people needing psychiatric treatment because of the COVID-19 pandemic has strained already inadequate mental health services. Access to mental health care has become more difficult, due to restrictive measures and the shortage of staff and other resources. Digital technologies have offered an immediate solution to continue delivering mental health treatment. Nevertheless, the lack of legal and ethical regulation, standardization and preparation has posed several challenges to the large-scale application of telepsychiatry. Recognition of the opportunity to increase access to mental health care has led the WPA to develop global guidelines for telepsychiatry[14]. Public health agencies' commitment to increasing mental health awareness and self-help during the pandemic has also enhanced interest in other digital mental health interventions, such as those based on mobile apps, sensor data, social media, and virtual reality. The integration of these interventions into real-world clinical practice requires ongoing progress[15].

Even as the pandemic fades, the psychological burdens of long COVID will create new needs for care. Furthermore, the easing of restrictions and the "return to the new normality" will require coping with new sources of stress. Governments, insurers and other funders should support increased resources for mental health services, commensurate with the growth in demand for treatment. Longer-term solutions, including a commitment to augmenting the mental health workforce, are also needed.

Our recommendations for action are the following:

- Psychiatrists must not abandon their patients but should continue to take care of them by all possible means (e.g., virtual visits, online psychotherapy, rehabilitation programs) during this pandemic.
- Psychiatrists should be aware of and address COVID-19 impact on children and youth.
- As physicians, during the pandemic, psychiatrists may volunteer or agree to be redeployed if the need arises to assume other duties in their institutions or communities.
- Psychiatrists must preserve their own health by following recommendations for avoiding infection and promoting well-being.
- Psychiatrists and other mental health professionals should assist in developing self-help, peer support groups or individual supports or treatments for distressed colleagues and their families, and should avail themselves of such services when indicated.
- Psychiatrists, as leaders in their hospitals or communities, should be prepared to assist with educational activities and support groups for persons with mental disorders, health care workers, and the public about the pandemic, its restrictions and their medical and mental health implications.
- Psychiatrists should advocate for equitable interventions by governments and others to maintain the continuity of mental health services, provide COVID vaccines and treatments and reduce the toll of pandemic-related mental distress, including suicide.
- Psychiatrists should be aware of the effects of long COVID on their patients and remain current with the research on its diagnosis and treatment.
- Appropriate precautions to protect patients' health should be taken in inpatient psychiatric units and in outpatient treatment settings.
- Telepsychiatry and other virtual means of conducting psychiatric evaluations and treatment have an important role to play in protecting the health of both patients and mental health professionals. Psychiatrists should work with their governments to advocate for necessary regulatory changes if needed to facilitate access to telepsychiatry services.
- When resources are limited and triage becomes necessary, mental disorders should never be factors in establishing eligibility for admission to hospitals, medical or intensive care units or access to ventilators or other treatment.

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Mental health for all: fostering healthy lifestyles

The burden of mental health is high, affecting people from all walks of life[1]. Good mental health is an essential aspect of overall well-being and significantly impacts an individual's daily and lifelong quality of life. Despite this, there is often a lack of actions taken to address the growing mental health problems[2]. The issue of the global mental health situation is especially critical due to

the harsh consequences of the COVID-19 pandemic, wars, natural catastrophes, and climate change, causing human suffering, economic challenges, and downturns[3].

Psychological and pharmacological treatments for mental health conditions are not delivered at a pace that meets the growing demand for mental health services. Policy and decision-makers should facilitate provision of resources both to the health care system and to the communities, which need to work hand in hand to achieve best results in treatment, rehabilitation, and early prevention.

But pharmacotherapy and psychotherapy are not the only means to treat and rehabilitate. In addition, there is an important but often forgotten component aiming to involve individuals with mental health problems to take an active role in the recovery of their own health. The idea that "one's everyday life is in one's hands" can positively affect mental health by promoting a sense of agency and empowerment. This belief can help individuals feel more in control of their life, reducing feelings of helplessness, anxiety and stress. The awareness of factors such as positive social relationships, active engagement in healthy lifestyle behaviours, and exposure to nature as facilitators of positive mental health and well-being needs to be revived and boosted[4].

During my forthcoming mandate as WPA President, I will focus on increasing awareness of the role of healthy lifestyles in preservation and promotion of good mental and somatic health[5,6]. In this context, it is important to keep in mind that professionals also need to take care of their own mental and somatic health.

Pedagogically tailored examples of lifestyle activities added to the existing biological and psychological therapies, when used daily in psychiatric care, can increase feelings of governing one's life and give an additional dimension to the meaning of life[7].

The literature supports that physical activity can improve mental health in individuals who have a sedentary lifestyle. Video materials for patients and health care staff about physical activity and examples on how to easily perform physical exercises in the everyday life on psychiatric or somatic wards are being developed with the collaboration of the WPA Planning Committee and colleagues from Karolinska Institute, Stockholm, Sweden. Physical activity conducted together with psychiatric staff can increase connectivity between patients and professionals through shared experience, improved communication, increased empathy, decreased levels of hierarchy, and personalized attention as well as improved physical condition and health of the participating personnel.

Similar materials are in preparation on healthy nutrition[8] for psychiatric patients by the WPA Planning Committee and colleagues from the University of Campania "Luigi Vanvitelli" based on a nationwide Italian study[9]. In this study, a psychoeducational group intervention focused on healthy lifestyle significantly improved the likelihood of people with severe mental disorders to follow a healthy and balanced nutritional regimen, with positive effects on metabolic indices.

Other healthy lifestyles which I aim to focus on are sleep hygiene[10], workplace satisfaction[11], and use of active leisure time and hobbies[12]. Psychiatrists could take an active role in increasing decision makers' knowledge on how housing, habitats, public spaces and work environments influence mental health. Awareness of the influence on mental health of environment, such as green spaces with plants and art in the wards, should also be increased in everyday clinical practice and incorporated into patients' activities[13].

In the preparation of video and other educational materials for the above-mentioned purposes, the vast knowledge and resources of members of the respective WPA Scientific Sections will be utilized. Fostering lifestyles is relevant for patients with both mental and somatic illnesses treated in all types of health care facilities and public health settings.

Last but not least, promoting educational activities on how to cope with the consequences of wars and natural disasters, which have a tremendous influence on the somatic and mental health of entire populations, will be my priority.

Healthy lifestyles are critical to cognitive, emotional and behavioural changes and can have a strong impact on one's self-image. Promoting healthy lifestyles as a public mental health strategy has the potential to alleviate the mental health burden in society, thus hopefully decreasing the cost of health care services. However, they must be adopted based on the culture and context, also taking into account the acceleration of immigration and globalization. By encouraging healthy lifestyles, the WPA community can create a supportive environment that promotes positive mental health and well-being for all.

Thus, it will be possible for the WPA to contribute to the United Nations' Sustainable Development Goals, especially to Goal 3 ("Ensure healthy lives and promote well-being for all at all ages"), and reduce premature mortality due to suicide, which is the utmost consequence of poor mental health [14,15].

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WPA Scientific Sections 2020-2023: from strengthened backbone to motor of innovation

When the 145 WPA Member Societies will meet in Vienna, Austria in September/October 2023 for the 23rd World Congress of Psychiatry, they will also convene for the WPA General Assembly, taking place every three years. This Assembly, the Association's highest decision-making body, will vote on a multitude of motions brought to the floor and meant to govern the Association for the next triennium. Reflecting on what has been achieved in the prior three years, the Assembly will decide on the future overall course and plan of action.

A large part of this decision-making will be dedicated to the work of WPA Scientific Sections. I was elected WPA Secretary for Scientific Sections by the 2017 General Assembly in Berlin for two terms, the 2017-2020 and the 2020-2023 triennia. These two triennia have seen a consolidation of the activities of the Sections: they have proven to be true to their calling, that is, being the Association's scientific backbone[1-8].

In addition to this, over the past six years, the WPA has made a variety of logistic and technical efforts to improve and streamline the communication of the various Sections with each other and with the Association's other bodies. This has helped spur a high number of intersectional activities, such as symposia at WPA congresses, research projects, and publications.

The past two triennia have seen two major intersectional thematic conferences: that on "Psychological Trauma: Global Burden on Mental and Physical Health", held virtually in December 2020, and that on "New Horizons in Psychiatric Practice: Creative Ideas and Innovative Interventions", taking place in Malta in November 2022. These two conferences introduced a truly novel concept, as they were not only thematic by honing in on a specific scientific topic, but also by making the intersectional aspect a theme in and of itself. Requiring symposia to be submitted by at least two Scientific Sections helped foster an interdisciplinary spirit benefiting the work of the individual Sections and of the WPA as a whole.

Special issues on trauma[9] and stress[10], published in collaboration with the *British Journal of Psychiatry* family of journals, have been another testament to the collaborative intersectional spirit. This spirit is truly palpable among the well over 100 members of WPA's Section of Early Career Psychiatrists. Over the past two triennia, the leadership of this Section has been able to organize numerous symposia, as well as formal and informal gatherings at WPA congresses, and a large number of standalone activities all over the globe, with the recently established WPA Exchange Program being a signature project[11].

Furthermore, at our recommendation, the WPA Executive Committee bolstered its commitment to early career investigators in low- and middle-income countries by introducing the Education, Science, Publication, and Research Initiative (ESPRI), aimed at jumpstarting scientific projects in those countries[12,13].

Finally, the past triennium has seen a major uptick in WPA's direct research involvement, as the Association has been awarded principal investigator status in two large European Union Horizon research grants: the PSY-PGx Consortium, focusing on the implementation of pharmacogenetics in psychiatry (www.psy-pgx.org/PSY-PGx), and the Psych-STRATA network, aimed at the identification of biological and clinical markers predicting resistance to pharmacological treatment approaches. For the two projects combined, the WPA will be receiving more than 300,000 US$ over the next five years, which will be used to conceptualize and implement a framework for education and dissemination for the two research consortia. This research work will be jointly coordinated by the Executive Committee and several Sections in whose remit the research involved falls.

In summary, the last two triennia have seen a consolidation of the Sections as the scientific backbone of the WPA. They have served as the mediators and multiplicators of the Association's educational and scientific mission and have taken it to all corners of the world[14,15]. Having vetted the Sections for their activities and effective contribution to WPA's Action Plan and having put in place measures to increase their global diversity, the Association can now count not only on a fortified backbone but on a veritable motor of innovation in psychiatric research, education and care for years to come.

Thomas G. Schulze
WPA Secretary for Scientific Sections

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WPA scientific meetings 2020-2023

It seems now an appropriate time to reflect on all that the WPA has achieved regarding scientific meetings during the triennium 2020-2023. Although the COVID-19 pandemic has disrupted the organization of medical conferences across the entire world[1], the WPA has strived together and advanced in terms of holding high-quality meetings.

We are pride of these accomplishments, and we could have not achieved them without the strong commitment of the meeting organizers[2,3]. Also, we are profoundly grateful for the contributions made by the Executive Committee in quickly reviewing and approving the proposed meetings, and the Standing Committee for Scientific Meetings for the continuous, consistent and excellent support.

As the WPA is mindful that the COVID-19 pandemic increases risk of developing mental health problems, relapse of existing mental disorders and poor mental health, in addition to impacting the work of mental health services, it continues to promote an increasing understanding of public mental health among professionals and the public, including collaboration with patient and family organizations[4].

Sixteen working groups have been established to address the six priorities of the WPA Action Plan 2020-2023[5]. Among the current priorities, public mental health continues getting particular attention[5-8]. The WPA scientific meetings are geared up to align with the Action Plan and its six areas. The programme of these meetings has been in full swing. We are in an exciting yet challenging time, but we have continued to do our utmost to promote the mission of the Association and to contribute to its achievements and success[2,9-11].

Since 2021, the WPA has delivered a state-of-the-art platform of scientific events, consisting of both in-person and virtual meetings, to meet the needs of the global psychiatric community and provide cutting-edge information on recent advances in psychiatry. This has allowed WPA Member Societies to network, continue to build bonds with each other, and create new opportunities for collaboration.

While the world is opening up and the travel restrictions have been gradually lifted around the globe, the WPA has successfully held the following in-person meetings since the World Congress of Psychiatry held in Bangkok, Thailand, August 3-6, 2022: the 19th Congress of the WPA Epidemiology and Public Health Section "Learning from Diversity Across the World: Implications for Psychiatric Epidemiology", Marrakech, Morocco, October 12-14, 2022; the Thematic Congress "Treatment and Management of Mental Disorders in a Post-Pandemic Era", Tbilisi, Georgia, October 14-16, 2022; the Intersectional Thematic Congress "New Horizons in Psychiatric Practice: Creative Ideas and Innovative Interventions", Malta, November 10-12, 2022; the Regional Congress "African Psychiatry in the 21st Century: Achievements and Future Perspectives", Hammamet, Tunisia, December 8-10, 2022; the Thematic Congress "Mental Health in a New Era", Karachi, Pakistan, March 3-5, 2023; the Regional Congress "Building Awareness – Bridging Treatment Gap", Kolkata, India, April 14-16, 2023; the Thematic Congress "Innovations in Treatment and Psychosocial Rehabilitation", Abu Dhabi, United Arab Emirates, May 5-7, 2023; and the Regional Congress "Innovations in the Practice of Psychiatry in XXI Century", Yerevan, Armenia, June 8-10, 2023.

The 2023 World Congress of Psychiatry, "Psychiatry: Current Knowledge and Perspectives for Action", will be held in Vienna, Austria, from September 28 to October 1, 2023. The outstanding contributions by Member Societies and colleagues helped us immensely to construct the program for this congress, which is now available for review on the WPA website. Thousands of our colleagues from across the world will get together to witness the best scientific advances and cutting-edge research in the field of psychiatry. Worldwide active participation in the congress will make this a successful, gratifying and memorable event. Warmest welcome to Vienna, Austria!

The WPA is calling for Member Societies to consider organizing a World Congress of Psychiatry, Regional Congress or Thematic Congress for the next triennium 2023-2026. All relevant information and documents can be download directly from the WPA website (https://www.wpanet.org/contact-forms). Please feel free to get in touch with me or contact the WPA Secretariat at wpasecretariat@wpanet.org for additional information, including how to plan and proceed with organizing a World Congress.

As we look back on the challenges, especially related to the pandemic, we can state that the WPA has overcome these unprecedented difficulties. For sure, the WPA will adjust to and enfold whatever the future normalcy/normality we will be facing during the "post-pandemic" era. We trust that the future WPA meetings will promote the unique bonds that hold our Member Societies together, and get all these Societies re-energized and re-engaged during the coming years.

The WPA is confident that, by embracing these opportunities, taking global action, and working closely together with international collaborations, we shall move forward to maintaining our momentum into 2023 and beyond, continuing to define and shape the future of psychiatry.

Edmond H. Pi
WPA Secretary for Scientific Meetings

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WPA education initiatives in the triennium 2020-2023

As most countries have lifted their travel restrictions imposed for the prevention of the spread of the COVID-19 pandemic, the WPA has resumed organizing and co-organizing face-to-face academic conferences. While this is a welcome move to many mental health professionals who have longed for meeting up with their long-time research collaborators and friends from different areas of the world, not all professionals can afford conferences and their related expenses.

The COVID-19 pandemic has been for the WPA a catalyst to hasten the development and promotion of an online Education Portal, aiming to promote dissemina-

tion of mental health knowledge and skills worldwide[1-7]. Any WPA website visitor can register as a user of the Portal for free. As of today, WPA has hosted more than 25 webinars covering a variety of topics, from new developments in basic sciences relevant to mental health, to mental health prevention and early intervention, to psychiatric rehabilitation and services aimed to promote recovery. All webinars have been recorded and uploaded for free access and review by the Portal users. The Portal also hosts more than 20 free educational courses dealing with a variety of topics, in as many as 18 different languages, to facilitate learning by users who are not proficient in English. Updated mental health resources are also available in relation to the COVID-19 pandemic and to support professionals working for people affected by the war in Ukraine.

The number of registered users of the Portal has been steadily increasing. They are now from over 30 different countries around the globe. The origin and the number of registered users have reflected the popularity of Internet-based educational and training materials, and supported the WPA's initial conviction about the importance of Internet-based training and education as pivotal in the dissemination of psychiatric education around the globe.

While the resources available in the Education Portal address the knowledge needs of mental health professionals, they cannot efficiently meet their requirements in terms of skills transfer and acquisition. For this latter purpose, the WPA has launched a series of Volunteering Programmes, based on the involvement of expert volunteers in different fields and from different countries to address the national training needs of selected Member Societies.

As of today, the WPA Workgroup on Volunteering has successfully completed one project in Mexico[8] and another one in Pakistan[9]. Both projects had the unique characteristics of involving local trainers in the programme, emphasizing the training ingredients of experiential role-plays and live demonstrations, extensively having the participants involved in the discussions, and asking local trainers and participants to contribute to the evaluation of the effectiveness of the projects as well as rating their satisfaction with the programme.

In the coming few months, two more projects will be launched in Guatemala and Honduras, with the involvement of expert volunteers nominated by regional Member Societies. These two projects will be conducted in the native language of the host Member Societies. The third project in the pipeline will involve a North African country that is in dire need of training and educational support in rebuilding its mental health capacity.

The WPA is currently inviting Member Societies to produce a list of potential expert volunteers in different psychiatric subspecialties, so that the Association can continue to provide a fair and transparent platform to facilitate collaboration between Member Societies around the globe.

Finally, a WPA global survey on the training landscape of psychiatrists has been conducted with the aim to depict a comprehensive profile of training levels and experiences of psychiatrists around the world[10]. This is providing valuable guidance to the WPA so that it can focus its resources and efforts in supporting those countries with most pressing shortage of training for their psychiatrists.

Roger M.K. Ng
WPA Secretary for Education

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WPA scientific publications in the triennium 2020-2023

Four main axes have been addressed during this triennium concerning WPA scientific publications.

The first axis has been the project of publishing WPA co-sponsored thematic issues in regional journals. After the very successful experience of the thematic issue on disasters and trauma in the *British Journal of Psychiatry*[1], we published in 2022 a WPA co-sponsored supplement of the English-language Brazilian journal *Trends in Psychiatry and Psychotherapy*, produced by the Psychiatric Association of Rio Grande do Sul. The supplement was entitled "Current state of global impact of cannabis use". It contained two editorials and four original papers. The two editorials dealt with various facets of cannabis legalization and its outcomes. The four original papers included two research reports, dealing with the mediating role of use by friends in cannabis abuse and the clinical correlates of impulsivity in cannabis use disorder, and two reviews covering critical aspects of epidemiology, policies, legalization and outcomes of non-medical use of cannabis[2].

Since this publication, contacts have been made with *Children* (an American journal) for a thematic issue on psychotherapies for children, and with *l'Encéphale* (an indexed journal published in France both in French and in English) for a thematic issue we are still discussing. Based on the previous experiences of such co-sponsoring, we are currently searching for a local support for the follow-up of each of these projects.

The second axis is related to the organization of sessions on WPA-related books and other publications on the occasion of World Congresses[3-8]. We were able to keep on organizing such sessions remotely at our virtual World Congresses in 2020 and 2021, with the active participation of several WPA Scientific Sections and the partnership of several international associations. We have resumed the face-to-face organization of such sessions on the occasion of the 2022 World Congress in Bangkok. Two special

sessions allowed the presentation of 14 publications and benefited from the strong and persistent effort of K.E. Heok from Singapore and the support of N. Sartorius, as well as the in-kind support from Springer.

The third axis is related to the production of WPA co-sponsored books based on the activity of Workgroups linked to the WPA Action Plan 2020-2023 and of WPA Scientific Sections. With the support of our President A. Javed, we are going to publish a book on promotion of psychiatry among medical students (related to the activity of the relevant WPA Workgroup), one on sport and psychiatry (related to the activity of the relevant WPA Scientific Section), and one on the complex role of trust in oncology (in collaboration with the WPA Section on Psycho-Oncology).

The fourth axis is related to the continuing efforts to diversify the languages used by the WPA at various levels: first, through its website, where more than 20 free educational courses dealing with a variety of topics are now available in as many as 18 different languages[9]; second, through the organization of symposia in languages other than English at WPA congresses; and third by the publication of several editions of *World Psychiatry*, the official journal of the Association. In this last regard, the publication of the Russian edition of the journal, previously supervised by our late colleague P. Morozov[10], will be resumed shortly.

Michel Botbol
WPA Secretary for Scientific Publications

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