World Psychiatry

OFFICIAL JOURNAL OF THE WORLD PSYCHIATRIC ASSOCIATION (WPA)

Volume 20, Number 3 *October 2021*

WILEY

NEW IMPACT FACTOR: 49.548

ISSN 1723-8617

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World Psychiatry

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2. McRae TW. The impact of computers on accounting. London: Wiley, 1964.
3. Fraeijs de Veubeke B. Displacement and equilibrium models in the finite element method. In: Zienkiewicz OC, Hollister GS (eds). Stress analysis. London: Wiley, 1965:145-97.

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All back issues of *World Psychiatry* can be downloaded free of charge from the PubMed system (http://www.pubmedcentral.nih.gov/tocrender.fcgi?journal=297&action=archive).

Socioeconomic and sociocultural factors affecting access to psychotherapies: the way forward

Huge progress has been made in the development of evidence-based psychotherapies for a wide array of mental disorders[1]. However, significant socioeconomic and sociocultural divides exist in the access to these interventions. The unavailability of psychotherapies for a large proportion of the world's population presents a major challenge to the future of mental health care.

There are currently both structural and attitudinal barriers to accessing psychotherapies. In relation to structural barriers, a major problem is that, in many countries worldwide, evidence-based psychotherapies are scarcely available in public mental health services, being mostly practiced by psychologists and psychiatrists in their private offices, which creates a socioeconomic divide in accessing them. The introduction of e-mental health was expected to fill some of these gaps in access to psychotherapies. However, digitally and socioculturally disadvantaged and minority groups remain underrepresented in studies of e-mental health and effective uptake of e-health. Indeed, the digital and language skills required for e-mental health engagement are beyond the reach of many, particularly from minority ethnic groups[2].

Attitudinal barriers play an equally, if not more, significant role. The dominant model of psychotherapy is largely pro-rich and pro-highly educated, and therefore is met with suspicion and/or is felt to be out of reach by many. Moreover, psychotherapists are often poorly trained to accommodate the highest level of need, and the ethnic and cultural diversity of mental health professionals rarely reflects the diversity of the population[3]. These problems are exacerbated by the large-scale international migration of families presenting with the consequences of the enduring psychological impact of displacement, uprooting and culture change. Data from the World Mental Health Surveys show that, even in Western countries, reluctance to seek help for mental health problems due to suspicion about the treatments on offer is a far more important barrier than structural barriers to initiating and continuing treatment, and predicts 39% of treatment dropout[4].

The implicit value system behind evidence-based psychotherapies presents a poor fit in relation to some ethnic and cultural groups. For instance, is the prioritization of individual agency implicit in psychotherapy universal or is it a peculiarity of Western cultures? Socioeconomically deprived individuals are underrepresented in clinical trials for most common mental disorders. Our knowledge of the effects of psychotherapies is largely limited to data from so-called "WEIRD" (Western, Educated, Industrialized, Rich and Democratic) individuals, who comprise 90% of study participants in psychological studies, from countries constituting only 12% of the world's population[5]. In this respect, the COVID-19 pandemic has magnified underlying social inequalities, with new remote therapy platforms, for instance, often failing to reach those who may need mental health support the most.

What can be done to increase access to psychotherapies, particularly by socioeconomically disadvantaged people and sociocultural minorities? First, the applicability of psychotherapies needs to be broadened to include non-traditional service providers and self-help interventions. Programmes ongoing in low- and middle-income countries to train "barefoot" therapists by creating e-learning platforms represent an important model. These programmes ensure increased reach by trusted and familiar individuals, as well as high levels of fidelity, and direct supervision providing quality control and outcomes reporting[6].

Second, interventions need to be adapted to specific populations. Studies suggest that, when interventions for mental health problems are adapted to make them culturally appropriate, they are typically as effective in minority groups as in the populations for which they were originally created and tested. Likewise, increasing the multicultural competence of psychotherapists has been associated with improved treatment outcome[7]. This suggests that disadvantage does not rest with the disadvantaged; rather, it results from the unwarranted assumption of psychological universalism, namely that no adjustments need to be made when reaching out to the "hard-to-reach".

Third, the field of mental health needs to actively engage with racial and other issues of inequalities. For example, a history of exploitation of certain racial groups inevitably leaves its psychological mark, and the pervasiveness of racism in many Western societies generates microtrauma which, if not explicitly addressed, leaves psychotherapies to be experienced as irrelevant to the concerns of minoritized groups. Consistent with these assumptions, areas with a high density of minority groups are associated with an increased prevalence of mental health problems and poor treatment seeking, but only when combined with low levels of social support and cohesion. Similarly, social deprivation and minority ethnic status have been associated with delays in initiating treatment for mental health problems, but not with continued treatment once engagement is achieved[8].

Early adversity defines a transdiagnostic ecophenotype that has been associated with earlier onset of mental health problems and high service utilization, but poor treatment response and high levels of dropout[9]. Beyond preventing early adversity, increasing social capital – that is, the resources available to individuals through social relationships with an emphasis on reciprocity, trust, collaboration and kindness – may be an important component of countering social inequalities relevant to access to mental health care. People with a relatively high degree of power tend to focus on themselves as individual agents, while marginalized individuals with low economic power tend to focus on their communities. When that community support is absent, those with low power are, as a result, both more vulnerable to mental health problems and at the same time less inclined to seek help.

Finally, the way the effectiveness of psychotherapies for men-

tal health problems is depicted by the media may have an important impact on their use and perhaps also their effectiveness, decreasing or reinforcing stigma related to mental health problems. Without explicitly addressing issues of stigma and shame, those who feel alienated with mental health needs will remain mistrustful of those perceived as privileged, while, at the same time, those offering support will continue to place responsibility on those appearing to be unwilling to accept help.

We need to empower a massive trusted workforce to deliver effective psychotherapies, harvesting the results of over five decades of research, to the large numbers in our societies who need them. This will require not only a significant change in the training of those delivering these treatments, but also an increased willingness on the part of mental health professionals to immerse themselves in the concerns of minority groups. Allyship requires a commitment which is long-term, not just during crises.

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DOI:10.1002/wps.20911

The importance of listening to patient preferences when making mental health care decisions

Listening to patient preferences when making health care decisions is increasingly considered an essential element of evidence-based practice. Patient preferences refer to the specific activity, treatment and provider conditions that patients desire for their health care experience[1,2]. For example, patients may prefer medication or psychotherapy, have preferences for one type of medication over another based on side effects, or have preferences for one type of psychotherapy over another based on the focus of the treatment (e.g., present cognitions or past relational conflicts). As another example, patients may have preferences about their provider's experience level, personal style (e.g., humor, personal examples), or demographics (e.g., age, gender, race, ethnicity, sexual orientation).

Two main arguments can be made for including patient preferences in the decision-making process in mental health care – one based on ethics and another based on outcomes.

First, attending to patient preferences is in line with ethical principles of respect for patients' rights and dignity[3]. As the party whose life will be most affected by the treatment, patients should have a say in what that treatment will look like. Importantly though, ethical principles also require providers to ensure that patients receive adequate care. As such, ethical practice entails active participation from both providers and patients, which should include discussion and incorporation of patient preferences in treatment to the extent possible.

Second, the existing research on clinical outcomes supports accommodating patient preferences[2,4,5]. Studies suggest that patients are more willing to initiate and engage in treatments that match their preferences. Evidence of this can be found in a meta-analysis including data from 187 randomized clinical trials comparing medication management strategies to psychotherapies[4]. Even though participants in these studies all agreed to be randomized to an intervention, 8.2% dropped out after learning of their assignment, and dropout rates were 1.76 times higher for the medication conditions than psychotherapy. Presumably, the assigned intervention did not match patient preferences in many of these cases. In another meta-analysis that directly tested the preference effect in clinical medicine, data from 32 studies indicated that preference accommodation resulted in greater treatment initiation, though only small improvements in treatment outcomes[5].

More recently, we conducted a meta-analysis examining the preference effect in psychotherapy and medication management for mental and behavioral health concerns[2]. This meta-analysis included data from 53 studies and over 16,000 patients. We found that patients whose preferences were accommodated were almost two times (odds ratio, OR=1.79) more likely to complete their treatment compared to patients who did not receive a preferred option. In addition, preference accommodation was associated with more positive treatment outcomes (d=0.28). The preference effects were consistent regardless of whether the choice was between two forms of psychotherapy or between psychotherapy and medication. Further, the preference effect was consistent across preference types (e.g., treatment, activity and provider) as well as patient demographics.

Taken together, this body of research suggests that accommodating patient preferences is linked with improvements in both treatment initiation and outcomes.

There are several possible explanations for the positive effect of preference accommodation in mental health care. First, patients may often be good judges of what treatments are best for them. Specifically, they know what they have already tried, what generally works or does not work for them, and what they are willing to engage in. Even the most effective treatment will have a 0% chance of success if the patient is unwilling to engage in it.

Second, allowing patients to have a choice may enhance motivation. Research shows that, when individuals are allowed to make choices, they are more invested to make sure that the choice

they made is the "right" one[6]. Thus, patients who get to pick their treatment might be more likely to fully engage in it (i.e., more consistent in their follow through, exerting more effort to achieve recovery). Allowing patients to participate in the decision-making process also encourages an overall collaborative approach to treatment. In psychotherapy, in particular, collaboration is a key part of the therapeutic alliance, which is consistently linked with positive treatment outcomes[7].

In addition, involvement in the decision-making process can build hope for patients, who often seek treatment in a demoralized state (e.g., low self-efficacy beliefs, low well-being). When "expert" providers express beliefs that patients can make good decisions by involving them in the decision-making process, this can lead patients to also believe in themselves and their decision-making capabilities. Increased hope and self-efficacy beliefs can in turn lead to improved treatment outcomes[8].

Given ethical arguments and the existing research support, it is essential that mental health care providers work to include patient preferences. These can be accommodated in a variety of ways. First, providers can assess initial preferences by using a pretreatment questionnaire or having a simple discussion at the start of the intake appointment. This discussion can focus on provider preferences, activity preferences, and broad treatment preferences (e.g., medication vs. psychotherapy). Second, after reviewing the patient's presenting problems and background information, providers can share information about potential specific treatment options. This information should include a discussion of the nature of the treatments, their relative efficacy, side effects, and other potential pros and cons. Third, both parties (patient and provider) should discuss preferences and come to a collaborative decision[9]. This process can occur repeatedly throughout treatment, as patient preferences may change over time.

At times, providers may be unable to fulfill patients' preferences in one area or another (e.g., patient asks for a specific type of provider that is unavailable, patient prefers a treatment approach that the provider is not competent in). When this happens, providers can seek to understand the reasons behind the specific preference and see if those reasons can be addressed through another option. Providers should also seek to provide those patients with several other choices in different areas (e.g., frequency of appointments, format of meetings), so the patients can still feel like they are participating in the decision-making process.

Listening to patient preferences and taking steps to accommodate them when making mental health care decisions can enhance treatment experiences and improve treatment outcomes. It should, therefore, become part of ordinary clinical practice.

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DOI:10.1002/wps.20912

The growing field of digital psychiatry: current evidence and the future of apps, social media, chatbots, and virtual reality

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As the COVID-19 pandemic has largely increased the utilization of telehealth, mobile mental health technologies – such as smartphone apps, virtual reality, chatbots, and social media – have also gained attention. These digital health technologies offer the potential of accessible and scalable interventions that can augment traditional care. In this paper, we provide a comprehensive update on the overall field of digital psychiatry, covering three areas. First, we outline the relevance of recent technological advances to mental health research and care, by detailing how smartphones, social media, artificial intelligence and virtual reality present new opportunities for "digital phenotyping" and remote intervention. Second, we review the current evidence for the use of these new technological approaches across different mental health contexts, covering their emerging efficacy in self-management of psychological well-being and early intervention, along with more nascent research supporting their use in clinical management of long-term psychiatric conditions – including major depression; anxiety, bipolar and psychotic disorders; and eating and substance use disorders – as well as in child and adolescent mental health care. Third, we discuss the most pressing challenges and opportunities towards real-world implementation, using the Integrated Promoting Action on Research Implementation in Health Services (i-PARIHS) framework to explain how the innovations themselves, the recipients of these innovations, and the context surrounding innovations all must be considered to facilitate their adoption and use in mental health care systems. We conclude that the new technological capabilities of smartphones, artificial intelligence, social media and virtual reality are already changing mental health care in unforeseen and exciting ways, each accompanied by an early but promising evidence base. We point out that further efforts towards strengthening implementation are needed, and detail the key issues at the patient, provider and policy levels which must now be addressed for digital health technologies to truly improve mental health research and treatment in the future.

Key words: mHealth, digital health, psychiatry, mental health, smartphone apps, virtual reality, social media, chatbots, digital phenotyping, implementation

(World Psychiatry 2021;20:318–335)

Mental health problems impact over one billion people worldwide annually[1], with depression representing the leading cause of disability across the globe[2]. The World Health Organization's Mental Health Gap Action Program (mhGAP) outlines evidence-based interventions to address this global crisis, yet acknowledges that barriers include lack of available services and funding[3].

The extent of these barriers, even for high-income countries, is highlighted in a December 2020 report from the US government, which indicates that offering evidence-based mental health care in the US alone would require an additional 4 million trained professionals[4]. On a global scale, it is simply not feasible to propose that practices based entirely on in-person care will ever be able to meet this demand. Thus, even before the emergence of the COVID-19 pandemic, there was growing interest in the possible role of new technologies to extend care.

The rapid international growth in access to and capabilities of digital health technologies (DHTs) presents a feasible route towards augmenting traditional mental health care and bridging the gap between the need for treatment and the capacity to deliver it. In this paper, we consider DHTs to be innovations beyond electronic medical records or classical telepsychiatry, to instead focus on the recent developments in smartphone apps, virtual reality, social media, and chatbots.

While the integration of these DHTs into mental health care began somewhat slowly, restrictions driven by the COVID-19 pandemic have sparked a paradigm shift as assumptions, interest and utilization of digital health have undergone a fundamental transformation. Although there has been variability in the response of health care services to the unmet needs raised by the pandemic, a recent study encompassing 17 different countries reported an overall increased use of digital health in mental health care settings, as well as a renewed support for facilitating uptake during the pandemic[5]. This increased uptake in response to the pandemic is related not only to DHTs' ability to connect people to care while social distancing regulations are in place, but also to recent innovations in these technologies that enable them to deliver scalable, affordable and accessible mental health care solutions[6,7].

In this state-of-the-art review, we explore the technologies, the available research evidence and the implementation issues most relevant to integrating digital psychiatry within mental health care. In the first section, we discuss technology mediums of smartphones, social media, virtual reality and chatbots as innovations in the digital psychiatry revolution. The second

section critically discusses recent research informing the clinical evidence-based uses of DHTs, with a focus on smartphone studies, covering their use across multiple contexts, from the promotion of public mental health and well-being, to the management of long-term psychiatric conditions. The third section identifies the forefront challenges towards implementation, and discusses potential solutions for improving the use and facilitating evidence-based adoption of DHTs into mental health care across the world.

TOOLS AND TECHNOLOGIES

The aptly titled 2012 *New York Times* article *The Therapist May See You Anytime, Anywhere*[8] highlights that the use of smartphone devices in mental health care has been discussed and anticipated for nearly a decade. Smartphones have quickly become a driving force of digital health, due to special properties defining both the hardware and software of these devices.

From a hardware perspective, they are compact and wireless, with low purchasing and running costs, making them the first devices to provide ubiquitous connectivity/Internet access for a sizeable proportion of the global population. The sensors on these devices allow for new data capture and graphical/computing power for delivery of individualized interventions.

According to 2018 survey data, 76% of people in advanced economies and 45% in emerging economies owned a smartphone[9], with recent data from the US showing that ownership rates may be as high as 70% even among people with severe mental illness[10-12]. While a digital divide still does exist, it is feasible to envisage that, in the near future, the majority of the world will have access to some form of a smartphone device.

From a software perspective, the relative ease of building new smartphone programs (termed applications or "apps"), combined with the centralized online platforms for finding, sharing and downloading these (i.e., the "app store"), creates an almost infinite potential for any new idea to quickly become an "app", which can in turn be readily proliferated across any number of users, potentially reaching billions of people across the world. Further, smartphones can serve as a digital "hub" for integration of novel devices such as wearables and other sensors.

In the context of mental health, the clearest result of this focus on smartphones has been the massive influx of apps aiming to provide therapeutic interventions for virtually all known mental health problems[13]. Alongside app-based therapeutic interventions, smartphone devices also hold the potential for bolstering mental health care in a number of other ways, including: a) capturing longitudinal, dense and multimodal mental health data for use in diagnosis and monitoring; b) analyzing data, increasingly via machine learning paradigms, to generate clinically individual-level actionable insights and predictions; and c) offering a wide range of interventions often outside of the app itself, through facilitating connections to clinical care, peer support, personalized resources, emergency care, and even novel therapies. Below, we explain in more detail the evidence behind the multifaceted and large-scale applications of smartphones.

Smartphone sensor data and digital phenotyping

Until recently, a large portion of the understanding around the determinants of the onset, relapse or temporal variation in mental disorders was primarily based on data from large prospective studies. Although useful, the broad insights gained from such data may fail to capture individual differences or the more fine-grained temporal relationships between causes and consequences of mental ill-health. Across the entire field of health care, smartphones are providing a plethora of data enabling new insights into various conditions, through combining their increasingly detailed streams of longitudinal, multimodal and temporally dense data collection. To better clarify the nature and clinical utility of these data, the concepts of "active" and "passive" data are useful.

Active data typically refers to smartphone-based surveys – i.e., active symptom monitoring or ecological momentary assessment – which can be completed by the user either spontaneously or in response to a prompt, and then stored while crucially time-stamped (a digital record of the date and time when an item was completed) onto the collecting app. Active data capture offers a new means to characterize a patient's clinical course.

While most clinical assessment scales have not been validated for deployment on mobile devices, strong correlations between traditional in-clinic metrics and their often-simplified mobile versions suggest adequate face validity[14]. The evolution of these assessments to focus on non-traditional metrics such as perception of self, functioning and social life (which research has shown to be particularly important to patients[15]) provides new opportunities for furthering the potential of active data collection. The use of smartphones for cognitive assessment[16] and for remotely monitoring symptoms[17] also appears feasible, with promising results even for severe mental illness such as schizophrenia[18,19].

While concern is often raised around using mental health apps for monitoring suicidal thoughts and urges, or even eliciting an increase in symptoms through reactivity to monitoring, research shows that actively collecting data on suicidal thoughts and urges does not elicit adverse effects[20].

Passive data are obtained automatically through sensors, either on the smartphone or via a wearable device, ranging from simple device use metrics to accelerometry, global positioning system (GPS), and even now voice tone (via microphone) or facial expression (via camera) data. These automatically collected data offer a means to reduce patient burden typically related to active data collection, while also capturing novel digital markers of behavior.

Often referred to as "digital phenotyping"[21] within the emerging framework of precision psychiatry, the multimodal nature of passive data obtained from consumer grade devices offers a means to understand the lived experiences of mental health in context[22]. For example, GPS data have recently offered insights into the relationship between reduced mobility and poorer mental health

during the COVID-19 pandemic[23]. Passive data from smartphones have also been shown to correlate with outcomes such as social functioning and loneliness[24,25]. An important trend emerging from passive data studies in various conditions is that variance, or measures of entropy or deviation from a personal mean, appear of more value than absolute measurements from any sensors[23-25].

Recent reviews suggest that "most studies still only scratch the surface of advanced smartphone capabilities"[26], and less than 2% of apps on the commercial marketplaces appear to leverage digital phenotyping potential[27]. Still, recent studies are employing digital phenotyping methods across diverse mental disorders[28-30], and research interest in this field is expanding at a rapid pace.

The density and complexity of passive data[31] is far greater than current clinical assessments, which continue to rely on static scales that ask a patient to recall symptoms over a defined period of time – e.g., a two week period in the case of the ubiquitous depression assessment by the Patient Health Questionnaire-9 (PHQ-9)[32]. However, the depth and diversity of passive data (which already typically combine measures such as step counts from wearables, text analytics from social media, metadata from electronic medical records, or green-space exposure from geolocation) require new techniques in data science, such as artificial intelligence and machine learning, to meaningfully combine and utilize such "big data" to inform mental health care[33].

Advances in artificial intelligence and machine learning will likely represent a prominent bridge for translating new data into clinically relevant digital biomarkers[34-36]. Like all biomarkers, though, impact will be determined not only by statistical significance but also by clinical utility. A case in point refers to digital markers of self-harm and suicide, which, according to a recent review, possess high classification accuracy yet near zero accuracy for predicting future events[37].

However, other approaches to digital phenotyping for different conditions/outcomes are beginning to show some promise. For instance, relapse risk in schizophrenia may be foreseen by "anomaly detection", which involves the use of smartphone sensor data to monitor divergences of an individual's behavioral patterns compared to his/her personal baseline. Preliminary studies in small samples have found reasonable sensitivity and specificity from applying this approach to date[30].

Overall, while active and passive data have the potential to make smartphones crucial elements for the development and implementation of precision psychiatry[38], the validity of the measures, how the data can be meaningfully represented, and the potential for ethical and effective uses in treatment delivery have all yet to be established.

Smartphone technologies for closed loop interventions

A rich legacy of Internet-delivered and computerized therapy research and experience[39] is now in the process of being translated into new smartphone-based interventions, with promising results as well as challenges. These app-based interventions often utilize established aspects of cognitive and behavioral therapies to offer patients "on demand" access to evidence-based care tools. Examples abound of studies targeting mental health problems such as depression and anxiety[40-43], and early psychosis and schizophrenia[44,45], that have been the subject of previous reviews[46-51]. The existing clinical evidence for digital health interventions across specific disorders is reviewed in more detail in the second section of this paper.

The potential for more personalized digital health interventions is bright. Known as a just-in-time-adaptive-intervention (JITAI), active and passive symptom data capture may aid in the development of personalized and real-time intervention strategies[52,53]. For example, the smartphone may be able to infer low mood in the context of social isolation and offer a relevant intervention, whilst, in another circumstance, it may infer low mood in the context of poor sleep and recommend an alternative intervention. Although in its infancy, using JITAIs to offer "closed loop" mental health interventions is a promising area for future research.

Nevertheless, app marketplaces rarely reflect evidence from recent studies, or otherwise take advantage of the unique potential of app interventions[54]. For instance, just one percent of marketplace apps support use of sensors[55], suggesting that concepts of digital phenotyping to support JITAI or behavioral interventions via apps are largely not incorporated into existing commercial technologies. Rather, even when considering more static interventions that do not take advantage of advanced smartphone features, the evidence base for widely proliferated apps remains poor[54]. For example, one review suggests that only ~2% of commercially available mental health apps are supported by original research evidence[27]. As we explore more details of app interventions in later sections, it is useful to consider that integration with sensors and digital phenotyping will likely soon transform this space.

Social media

The relationship between social media and mental health has received much attention from not only the academic literature, but also the traditional media and general public[56]. Frequently accessed via smartphone apps and connecting people from their own devices to global networks of friends, information, and health resources, social media can represent both a means to quantify mental health as well as a source of both positive and negative interactions.

Increasingly, research suggests that absolute screen time or exposure itself is not strongly associated with adverse mental health outcomes[57]. This is in marked contrast to the more popular conception that screen time and social media use is detrimental to mental health. In part, this view gained ascendence from the older literature, which was largely based on self-reported usage and cross-sectional analysis, thus offering limited evidence in this regard. Recent studies, however, based on objective screen use and social media engagement measurements,

prospective cohorts, and new scales to assess problematic Internet use, are painting a more nuanced picture of social media and mental health[58,59]. For example, during the COVID-19 pandemic, social media have been a source of social support for many who have been socially isolated and lonely.

While excessive use of social media and screen time is likely not beneficial for mental health (in the same manner that excessive use of any activity or behavior is often associated with deleterious outcomes), the quality of screen time and social media interactions appears to be more important than the quantity[60]. It is interesting that in recent years social media companies such as Facebook and Pinterest have undertaken new efforts to flag content that may be related to self-harm or suicide[56]. Nevertheless, it is currently difficult to determine the results of such interventions. The impact of social media on the developing brain also remains an unresolved[61] yet frequently discussed topic, especially as the pandemic has forced increasing reliance on technology to connect people.

Patterns of social media use may represent a means to detect worsening of mental health symptoms. For example, changes in the content and style of social media posts may offer an early warning sign of relapse in schizophrenia[62]. Social media, combined with natural language processing methods, also offer a practical means to understand population-level mental health trends. For example, an analysis of 60 million Twitter posts in March-May 2020, as compared to one year prior, was able to detect pandemic-related increases in coping mechanisms[63]. These methods have also been employed in studies exploring psychosocial reactions to the COVID-19 pandemic[64,65], as well as the effects of psychiatric medications[66].

While currently available work has largely focused on text-based natural language processing methods, the increasingly voice- and video-based nature of newer social media content has sparked interest in emotion recognition[67]. For example, early studies identified relationships between negative mood and posting pictures with darker colors[68], although such relationships are now known to be more nuanced, thus highlighting inherent challenges in assessing mental health without a broader context.

Social media can also be used as a therapeutic tool. Novel research using carefully curated and monitored social networks as interventions has shown promise in youth with diverse mental health needs[69-71]. For example, the PRIME app[72] is designed to help people with schizophrenia through the promotion of functional recovery and the mitigation of negative symptoms (e.g., amotivation) through a supportive and personalized network. The Moderated Online Social Therapy (MOST) platform is another example of an innovation that offers personalized therapy combined with social connections among other features[71,73].

It is noteworthy that social media are not without risk. Disinformation[74] and stigma on social media are forces that cannot be ignored. Stigma on social media is common[75], although efforts are also underway to challenge and reverse this trend[76]. Using social media for mental health work also remains a catalyst for ethical tensions, and a recent review offers a practical taxonomy of these tensions as well as guidance for navigating through these ongoing challenges[77].

Chatbots

Conversational agents, such as Apple's *Siri* or Amazon's *Alexa*, have become common in the digital marketplace. Termed "chatbots", the use of these conversational style interfaces offers an intelligent, automated system for detecting and responding to immediate mental health needs. Chatbots have the look and feeling of interacting with a human, despite being run by an automated software program. Thus, chatbots or "robot therapists" have become a galvanizing force for those seeking to automate therapy where software programs listen and respond to people's mental health needs. While the words "robot therapist" conjure images of a physical robot, most are actually text based, although animated video and even physical robot versions have been researched[78,79].

One ongoing challenge in chatbot work is seeking to offer emotional support from inherently inanimate computer code. There is some evidence that people can develop therapeutic relationships with digital technologies (referred to as "digital therapeutic alliance"[80]). As therapeutic alliance with an in-person therapist is related to more positive outcomes in mental health treatment[81], harnessing the digital therapeutic alliance through human-style interactions with a chatbot might promote change without the need of human support[82]. Research has found that some people feel more comfortable conversing anonymously with a chatbot[83], and that this may open up the possibility to improve detection of distress and in turn provide momentary interventions to those who feel less comfortable with face-to-face contact[84].

Chatbot interfaces have become a key feature of many commercially available mental health apps. However, their evidence base is not well established[85]. Across two recent systematic reviews, 24 studies investigating chatbots for health care were identified[85,86]. Of the 11 trials targeting mental health problems, most were for depression, with a smaller number targeting anxiety, schizophrenia, post-traumatic stress disorder (PTSD), and autism spectrum disorder. Only two randomized controlled trials were included, and, while some mental health benefits from chatbot interventions were indicated, the types of benefits observed were not consistent across studies, which were further limited by small sample sizes, short duration, and a lack of follow-up data.

While the development and implementation of more complex interactive systems is inevitable, current chatbots are limited in their ability to deliver appropriate contextual responses to complex language inputs, presenting important safety concerns. One study of commercial chatbots such as *Siri* found that they often failed to recognize serious mental health concerns and provide appropriate responses such as referral to a support service[87]. For example, chatbots were found to not recognize when suicidal ideation was being discussed, and these devices also seemed to

ignore domestic violence problems. Further, surveys of consumer attitudes reveal concerns about the privacy of chatbots as well as their potential to replace human care. Nevertheless, satisfaction ratings in the limited number of pilot and feasibility studies tend to be high, and rates of adverse events low[88]. Given the evidence and governance in place at this time, chatbots are best used only as a supportive tool in the context of a broader treatment plan.

Virtual reality

Virtual reality involves an immersion in an interactive, computer-simulated environment via a headset. The ability to create and control exposure to real-world environments presents important opportunities for mental health assessment and treatment[89-91]. Standard psychological assessments are limited by a lack of real-world validity and overreliance on subjective ratings[92]. Virtual reality allows precise, real-time data capture of responses to stimuli within controlled virtual environments, and hence provides critical insight into the way in which clinically relevant phenomena develop in real world[89,93].

Controlled exposure to anxiety-inducing stimuli within a virtual environment offers a safe, convenient and accessible medium to deliver exposure-based behavioral treatments. The benefit of virtual reality treatment lies in the repeated exposure to feared stimuli, enabling the individual to adapt to triggers and develop healthy responses in a safe and controlled therapeutic platform[94]. For example, randomized controlled trials have shown that learning to engage in virtual social interactions can reduce paranoia in people experiencing psychosis[95,96].

A recent meta-review of 11 meta-analyses, covering predominantly anxiety disorders and PTSD, found that effect sizes for virtual reality exposure treatments were overall moderate to large, and were typically maintained at follow-up[97]. A smaller number of trials have been conducted for other psychiatric disorders, with emerging evidence that virtual reality treatment may be effective for depression, schizophrenia[97] and eating disorders[98]. However, in the studies that have compared virtual reality to traditional treatment, there was little evidence for superior efficacy. Further, the quality of evidence is overall low to moderate, due to the predominance of studies with small sample sizes, the relatively limited number of randomized controlled trials, and issues around publication bias.

Fewer studies have explored virtual reality treatments beyond exposure therapy, with the exception of skills training, which has also demonstrated positive results[99]. Pilot studies have also shown that virtual reality applications can guide people to learn therapeutic skills such as mindfulness[100-102], relaxation[103] and self-compassion[104,105]. Using virtual reality as a vehicle to deliver experiences that help people develop skills to manage mental health difficulties may increase treatment engagement and efficacy.

Virtual worlds offer a compelling solution to increased demand for technology platforms that can deliver personal clinical care remotely[106]. Virtual worlds enable users to meet within virtual environments, represented as personalized avatars, and interact with other users in real time. Whilst few studies have been conducted in mental health, there have been promising early results especially in psychosis[107]. Delivering therapy via virtual worlds has the clear potential of offering highly accessible care within personally tailored, engaging therapeutic environments that provide a safe and comfortable medium for social interactions.

Whilst commercial growth in virtual reality is occurring rapidly, with an estimated growth of $54 billion over the next 7 years[108], the technology remains unfamiliar and inaccessible to many users, presenting a barrier to implementation[89]. As costs decrease and virtual reality becomes more mainstream (partly due to the increased capacity to deliver it via smartphones), there is a need for further research and subsequent provision of evidence-based treatments and protocols, with adequate training for relevant workforces to enable their implementation.

EVIDENCE FOR DIGITAL PSYCHIATRY WITHIN SPECIFIC CONTEXTS

The research base on the efficacy and acceptability of the various types of DHTs is rapidly expanding. In this section, we explore recent and notable findings from empirical studies of the DHTs described above, with a focus on smartphones, across four specific contexts of mental health care: self-management of depression and anxiety; clinical management of major mood disorders; remote monitoring and interventions for psychosis, eating disorders and substance use disorders; and child and adolescent mental health.

Self-management of depression and anxiety

Depression and anxiety disorders are among the most common types of mental health conditions in the world[109], and many more individuals experience subthreshold albeit disabling symptoms. Due to the high demand for self-management strategies for depression and anxiety, smartphone apps claiming to help with these problems are widely available on app marketplaces[110,111].

A recent large-scale meta-analysis of 66 randomized controlled trials explored the efficacy of smartphone apps for mental health problems including depression and anxiety across clinical and non-clinical populations[112]. For depressive symptoms, this meta-analysis found that smartphone apps outperformed control conditions, with larger effect sizes found when waitlist or educational resources (health tips, information) were used compared to attention/placebo controls (e.g., gaming apps)[112]. Smartphone apps also outperformed control conditions for generalized anxiety and social anxiety symptoms[112]. App interventions for anxiety did not differ significantly from face-to-face or other computer-based interventions in terms of outcomes, although only a small number of studies were used in these comparisons. For both depression and anxiety, studies which

provided professional support alongside the smartphone app (e.g., through supportive phone calls or personalized therapist feedback) produced larger effect sizes compared to studies which did not.

A common criticism of smartphone apps for depression and anxiety is that they lack an underlying evidence-based framework[111,113]. A review of 293 commercially-available apps for anxiety and/or depression found that just over half (55.3%) included a reference to an evidence-based framework in their app store descriptions[111]. When a reference was included, a range of therapeutic frameworks were mentioned, including cognitive behavioral therapy techniques (30.0%), mindfulness (15.7%), positive psychology (9.2%), dialectical behavior therapy (3.4%), acceptance and commitment therapy (1.7%), and other techniques (6.8%). However, of the 162 apps that claimed to use a theoretical framework, only 6.2% had published evidence supporting their efficacy[111].

The selective adoption of self-management apps for depression and anxiety has also been explored. A consumer data-driven review highlighted that the proliferation of depression and anxiety apps on the marketplace is in contrast with the relatively small number of apps which are regularly downloaded and used. The review reported that just three apps (*Headspace*, *Youper* and *Wysa*) accounted for about 90% of app downloads for depression. Similarly, three apps (*Headspace*, *Calm* and *Youper*) accounted for approximately 90% of downloads and daily active users of anxiety apps[114]. Moreover, most apps for depression (63%) and anxiety (56%) had no active users for the one-month period under review[114]. While commercial app companies do not publish engagement data, it is clear that downloads do not automatically translate into active use. For example, the popular (and free) *COVID Coach* app designed to address stress during the pandemic reported over 140,000 downloads, but only 1.56% of individuals who have downloaded the app recorded at least two weeks of use[115].

There are several areas in which improvements can be made for apps dedicated to depression and anxiety. They include: ensuring substantive involvement of relevant health care professionals in the development of the apps[110]; embedding apps within local health care settings[116]; more robust testing of apps, specifically more well-designed randomized controlled trials to assess their efficacy[114]; understanding engagement techniques to ensure optimal use[114]; and using validated treatment techniques/interventions within the apps[116]. Further evaluation of anxiety and depression apps is clearly warranted[114], including the need for additional research into the efficacy of app-delivered interventions compared with face-to-face "care as usual"[116]. Further research is also needed to understand the long-term engagement, as well as to examine any possible deleterious effects related to app usage[111].

The evidence to date suggests that smartphone apps could provide an accessible, scalable and low-cost mechanism to deliver effective self-management interventions for symptoms of depression and anxiety, particularly to non-clinical populations and those who cannot access face-to-face services[110,116]. However, the promise of apps to increase low-cost access to evidence-based treatment for depression and anxiety has not yet been fully realized. Efficacy trial data are needed to support many anxiety and depression apps available on the marketplace. Most of such apps have no clear evidence of efficacy[47,51,117].

Clinical management of major mood disorders

Despite the growing evidence base described above on the use of DHTs for self-management of depression and anxiety, much of the existing research has been conducted in general population samples or people with mild-to-moderate symptoms. Thus, the current applicability of such research in the actual clinical management of severe mood disorders, such as bipolar disorder and major depressive disorder, remains unclear.

A recent systematic review and meta-analysis concerning the efficacy of digital interventions in bipolar disorder found positive effects on both depressive and manic symptoms[118], but only four of the ten included studies were randomized controlled trials[45,119-121]. As to unipolar depressive disorder, while an increasing number of randomized controlled trials of apps with psychotherapy-related content have been published[26], several of them have shown no evidence that delivering psychological interventions via smartphone confers a significant advantage beyond control conditions[122-124]. However, randomized controlled trials which have used app-based interventions alongside human coaching to bolster their usage in community patients with depression have produced more robust evidence[42], suggesting that human engagement in supporting app-based interventions is critical. New roles such as digital navigators to support app use in mental health care may provide one solution to offer human support without overburdening the clinician[125-128] (see below).

The fact that bipolar disorder and major depressive disorder are characterized by episodic fluctuations in mood and behavior may suggest that smartphone-based interventions which provide fine-grained monitoring and real-time treatment (including JITAIs) may improve outcomes, either by fostering early identification of deterioration and/or by providing means for flexible and timely treatment interventions. Preliminary evidence in patients with major depression indicates that smartphones do indeed represent an available platform for real-time monitoring of patient-reported symptoms, such as changes in mood and activity, through ecological momentary assessments[129-131], and that this can feasibly be supported through collection of sensor-based data such as the number of incoming and outgoing calls and text messages, or location information which may reflect changes in behavior and psychomotor activity. Similarly, in bipolar disorder, several recent studies have shown that smartphone-based active and passive data reflect digital markers of symptoms[132-134], and classifications of affective states[135,136] and affective traits[28,137] have been published. Collectively, these studies suggest that such digital data could provide important real-time information reflecting the psychopathological status of patients with major mood disorders.

An important consideration is that patient-reported symptoms collected in clinical encounters have an inherent risk of recall bias[45]. On the other hand, establishing the extent to which patient-reported mood ratings collected via smartphones are consistent with clinical symptom ratings in patients with severe mood disorders is imperative for determining the role of such technologies in the clinical landscape. Studies examining this issue have largely indicated that smartphone-based mood assessments represent promising alternatives or adjuvants to traditional clinical measures, while acknowledging the methodological limitations in the existing evidence base, including that the overwhelming majority of trials and observational studies to date have enrolled small samples[138-140].

To determine how worthwhile these new approaches could be in routine practice, it is also crucial to examine whether the use of monitoring technologies as an adjuvant ongoing evidence-based tool for major mood disorders would result in an improvement of outcomes. In keeping with this view, two recent pragmatic randomized controlled trials have examined the effect of smartphone-based monitoring and treatment in patients with bipolar disorder[139] and unipolar depressive disorder[140] in real-world settings. These trials found no effect on primary or secondary outcome measures, including rates of rehospitalization or severity of depressive or manic symptoms, whilst showing higher levels of patient-reported recovery, compared to the control condition.

Overall, there are several promising trends in the use of smartphones for treatment and monitoring[141-144] in clinical samples with bipolar disorder and major depressive disorder. Continuous data analysis (potentially paired with machine learning models) could support prediction of relapse and use of smartphone-based interventions in real-time within the context of precision psychiatry. However, validating the measures used, establishing clinically useful interventions, and ensuring that patients are indeed able to engage with these long-term interventions, are all key steps to be undertaken by researchers prior to the evidence-based implementation of these novel technologies in routine clinical practice.

Psychosis/schizophrenia

While those outside of the mental health field at time wonder if smartphones and digital technology could induce paranoid delusions in people with schizophrenia spectrum disorders, the reality is quite the opposite. People with psychosis/schizophrenia are interested and eager to use innovative tools to possibly augment their care and ultimate recovery. Adverse events related to paranoia are nearly non-existent. Research in this area features innovative works around both remote monitoring and app-based interventions.

Remote monitoring is of interest in psychotic disorders, especially to augment self-reported information when cognition may be overly impaired. Real-time and in-context patient-generated symptom data, obtained through remote-monitoring platform technology, have the potential to timely warn clinicians about the need for intervention, improve treatment decisions by providing a clearer picture of changing patterns of symptoms, and support scheduling of health care contacts based on need[145].

Research groups around the world have started to explore how integrating this active data collection with passive remote monitoring can both predict relapse and allow delivery of time-sensitive intervention strategies. To date, these data streams have been predominantly used in small (N<100) studies in selected populations, with promising results. A systematic review[146] of studies conducted in samples with psychotic disorders identified 17 active monitoring apps. App use duration ranged from 1 week to 14 months, with self-assessment prompts ranging from multiple times per day to weekly. People typically adapted their response strategy to less frequent active data collection over time. App assessments were well tolerated, with 69% to 88% assessments completed. All studies showed that people found this active data collection acceptable and useful, despite some negative effects reported (e.g., increased awareness of symptoms).

Sensors on the smartphone or a wearable device have emerged as tools to assess behavioral patterns in a range of populations, and have been utilized to both reduce the burden associated with active symptomatic monitoring and to obtain additional objective behavioral data. A systematic review of studies[146] identified four passive monitoring studies, with usage ranging from 5 to 365 days in sample sizes ranging from 5 to 62 participants. Two studies found that passive monitoring was largely acceptable, although 20% of participants reported privacy concerns and 20% felt upset by it.

More specifically, Barnett et al[147] followed 17 patients with psychosis using a passive monitoring app installed on their smartphone for up to three months, and identified anomalies in mobility patterns and social behavior in the two weeks prior to relapse. A further study in 83 patients with psychosis using digital markers found similar results[30]. This was also observed in a study (N=60) using a neural network approach[148].

Ben-Zeev et al[149] identified sensor data changes – including physical activity, geolocation, phone unlock duration, and speech frequency and duration – in participants with psychosis in the days leading up to a relapse. Wisniewski et al[150] also noted high variability in behavioral patterns observed through passive monitoring in individuals who were deemed to be at clinical high risk for psychosis. However, the utility of passive monitoring in predicting conversion to psychosis among these individuals remains unclear.

Although in their infancy, passive monitoring studies have shown that most patients with psychotic disorders are comfortable, able and willing to use wearable devices to monitor outcomes in their daily life[151], with emerging evidence supporting identification of an impending relapse through changes in passively collected behavioral data. However, robust safety data are needed to understand the utility of this approach more clearly[152].

Beyond monitoring, DHTs have also played a significant role in delivering intervention strategies and support for psychosis. A

recent systematic review identified 21 DHTs for psychosis published in the peer-reviewed literature, incorporating a mixture of computerized, avatar, and app-based approaches. The studies included a total of over 1,500 participants, and were mostly conducted in Europe and North America[152].

Whilst it is difficult to compare these studies, given the different technologies used and outcomes measured, there is emerging evidence that DHTs can improve symptoms, as well as cognitive and other clinical outcomes, in people with psychosis[152]. For example, the *Actissist* app targets negative symptoms (e.g., reduced socialization), general psychotic symptoms, mood, and cannabis misuse through offering tools to help with cognitive appraisals, belief conviction, emotions and associated behaviors[153]. Another app (*SlowMo*) targets paranoia through offering tools to help with jumping to conclusions and belief inflexibility as part of blended care[154]. A study of 361 patients with a diagnosis of schizophrenia, randomized to receive either *SlowMo* therapy or usual care, found no significant difference between groups on the primary outcomes related to paranoia at 24 weeks (the primary end-point), though significant effects between groups were apparent post-treatment[154].

While these approaches are promising, further well-powered efficacy trials are needed to appraise their full potential. Co-design of the technology with the actual end users is vital in ensuring that engagement to DHT is maximized[155]. Furthermore, with some exceptions[153,156], trials have not robustly measured adverse events, which is needed when determining the safety of DHTs not only in people with severe mental health problems but in health care more broadly.

There is, of course, the challenge of implementing these intervention approaches, should they prove to be effective and cost-effective. There are very few examples of successful implementation of DHTs into routine clinical services, though research groups have proposed frameworks to support implementation from the outset of digital health program development[157-159].

Eating disorders

The interest in smartphone app technologies for eating disorders is growing, either as a standalone intervention or an adjunct to traditional treatment services.

People with eating disorders are a clinical group that could be well suited to app-based interventions, as the ego-syntonic nature of these conditions usually results in treatment refusal, ambivalence to change, or low motivation to engage in the therapeutic process[160,161]. The ability for apps to allow an individual to approach treatment at his/her own pace may address these concerns and could help individuals feel more in control of their treatment. Similarly, tailored reminders and motivational messages to practice key therapeutic skills may help increase these patients' motivation and adherence to the treatment program.

Furthermore, their scalability, flexibility, and cost advantages over traditional face-to-face services indicate that smartphone app technologies could offer a potential solution to many existing help-seeking barriers and the widespread treatment gap reported in this clinical group[162]. Importantly, recent survey data show that a significant proportion of individuals with an eating disorder report a preference for, and willingness to use, smartphone apps and other DHTs[163,164], indicating that their demand is high.

The quality of information in publicly available eating disorder apps has been widely discussed. Existing eating disorder apps tend to serve one or more of four broad functions: delivery of information, self-assessment, self-monitoring, and provision of advice or treatment. Two earlier systematic appraisals of the quality of commercially available eating disorder apps concluded that very few of them incorporated components of evidence-based treatments, with some even providing potentially harmful information[165,166]. However, four commercially available eating disorder apps (*Mental Health Tests*, *Recovery Road*, *Rise Up*, and *Psychiatry Pro-Diagnosis*, *Info*, *Treatment*, *CBT & DBT*) — each of which are grounded in an evidence-based framework — account for 96% of monthly active users according to a recent review[167], indicating that those resorting to apps to help manage their eating disorder are likely exposed to credible information.

Limited research has been conducted on the efficacy of smartphone apps as a standalone intervention approach for eating disorders. The most up-to-date meta-analysis of self- or minimally-guided DHTs for the treatment and prevention of these disorders did not locate any published randomized controlled trials of standalone app-based interventions up until June 2020[168]. One randomized controlled trial has since been published, finding preliminary support for the short-term efficacy of a transdiagnostic cognitive-behavioral app (*Break Binge Eating*) on numerous symptom measures among individuals with a threshold or subthreshold binge eating-type disorder[169]. Although these results are promising, additional evidence from randomized controlled trials with longer follow-ups is needed to determine whether smartphone app technologies are an appropriate standalone intervention modality or first step in the treatment and management of eating disorders.

More attention has been devoted towards understanding the role of smartphone apps as an adjunct to traditional face-to-face services. In light of evidence demonstrating a robust relationship between low skills utilization and poor treatment outcomes among individuals with eating disorders[170,171], app technologies have been proposed to augment face-to-face treatments by allowing patients to more regularly practice essential homework tasks between sessions[172].

Indeed, evidence from existing randomized controlled trials indicates that the addition of smartphone app technology to traditional face-to-face services may lead to greater treatment adherence and skills utilization, and quicker symptom improvements in adults with binge eating[173,174]. However, whether these benefits persist in the longer term, and for whom specifically app technology offers an added benefit, remains unclear.

Overall, although significant interest has been generated towards understanding what role apps might play for the treatment and management of eating disorders, further rigorous trial de-

signs with longer follow-up assessments across different diagnostic categories (e.g., anorexia nervosa) are needed.

Substance use disorders

Interest in the clinical utility of smartphone app technologies for substance use disorders is also growing. Inbuilt app features such as machine learning algorithms, that automatically adjust in response to active and passive data, can facilitate the delivery of highly specific, tailored intervention strategies in moments of need[52]. This functionality is especially applicable for substance use disorders, as affected individuals often find it difficult to anticipate upcoming internal or external events that trigger a relapse[175].

Although an increasing number of apps for substance use disorders are commercially available, their focus is largely restricted to targeting smoking or alcohol consumption, with few apps specifically designed to address other costly and debilitating disorders, such as cocaine or methamphetamine use[176].

Apps to address opioid use disorder have recently become available and received Food and Drug Administration (FDA)'s approval in the US. However, a 2020 report examining the economic benefit of these apps for opioid use disorders noted: "At current… pricing, and given available evidence, these potential cost offsets and clinical gains were not enough to generate incremental cost-effectiveness estimates beneath commonly cited cost-effectiveness thresholds"[177].

Empirical research investigating the efficacy of app-based interventions for substance use disorders remains limited, but is rapidly expanding. In the context of smoking, one recent meta-analysis[51] of three randomized controlled trials comparing standalone apps to control conditions observed a significant although small effect size for reduced smoking frequency in favor of the app conditions (g=0.39, 95% CI: 0.21-0.57). In contrast, a recent Cochrane review[178] of five randomized controlled trials found no significant differences in rates of smoking cessation between apps and non-app smoking cessation support conditions (risk ratio, RR=1.00, 95% CI: 0.66-1.52). For alcohol use, the above meta-analysis[51] identified three randomized controlled trials comparing a standalone app to a control condition, reporting a small and non-significant pooled effect size (g=–0.03, 95% CI: –0.22 to 0.17). Other recent qualitative reviews have not been able to identify any randomized controlled trials of app-based interventions for other substance use disorders[179,180].

Additional research is needed to better understand what role smartphone app technologies could play towards the treatment, prevention or management of substance use disorders. Although the quality of commercially available apps for these disorders is suboptimal, it is promising to see research teams from around the globe beginning to develop smartphone apps in this area that have a clear underlying evidence-based framework, capitalize on latest advancements in technology (e.g., gamification, conversational agents), are routinely tested for their usability, involve feedback from end users, and are registered for evaluation in prospective clinical trials[181-185].

Child and adolescent mental health

Child and adolescent mental health is a public health priority, with a prevalence of up to 20% of mental disorders across child and adolescent populations worldwide[186]. The increasing ubiquity of smartphone use among these populations suggests that smartphones could be an ideal mode of delivery for mental health interventions[187]. A systematic and meta-review of DHTs for children and young people identified anxiety and depression as the most common mental health problems targeted, with many other areas (e.g., psychosis) being relatively underresearched[188].

The strongest evidence of effectiveness of DHTs for children and young people is reported for approaches using computerized or Internet cognitive behavioral therapy (iCBT)[49,188]. A meta-analysis of 34 randomized controlled trials for depression or anxiety in child and adolescent populations supported the effectiveness of iCBT-based interventions in comparison to waitlist controls[189]. More favorable outcomes were achieved when the treatment was therapist- or parent-supported[189].

Alongside the growing evidence for digital therapies in young people, passive sensing technology is likely to be used in future research. While currently in its infancy, there is an increasing body of research suggesting that passive data collected through DHTs may aid in the understanding of how behavior relates to mood and anxiety in children and young people[190].

Overall, most reviews in the area of digital mental health for children and young people recognize the need for further research into the effectiveness of DHTs, but highlight the promise of smartphone apps[49,188]. A core challenge in this research is the additional privacy issues inherent to working with young people, as well as continued screen time concerns (as noted in above sections). Still, the future is promising, and particular progress has been made on iCBT-based interventions for anxiety in children[190]. It is to be acknowledged that many of the technologies tested in young people have been first developed for adult populations, rather than being designed and co-produced by young people themselves.

IMPLEMENTATION: CHALLENGES AND OPPORTUNITIES

The potential and evidence around digital mental health must be considered in the context of real-world use, given that much of the interest and excitement around DHTs stems from perceived feasibility and scalability of real-world implementation. In actuality, however, implementing DHTs has proven challenging. Even the relatively simple task of translating effective face-to-face interventions directly into digital versions is often more complex than once thought[191,192].

There are numerous implementation science frameworks. In this section, we utilize the Integrated Promoting Action on Research Implementation in Health Services (i-PARIHS)[193] framework, which focuses on three elements: the innovation itself, the

recipients of that innovation, and the context surrounding the innovation. While the prior two sections of this paper have focused on innovations across DHTs and clinical use cases, here we focus on recipients (patient/clinician implementation) and context (health care factors, including regulatory, market, ethical, and global mental health forces). Only when the three elements – innovative DHTs, recipients primed to utilize DHTs, and contextual forces that support and sustain DHT use – are all aligned, can the full potential be realized. Despite rapidly advancing work around DHT innovation, the latter two elements have not received equal attention.

Recipients of innovation: patient factors

While smartphone ownership is above 80% in the general population in the US, US-based Medicare data from 2018 suggests only 61% of beneficiaries have access to a smartphone with a wireless plan, and that access is more likely to be lacking in those who are older, less educated, and Black or Hispanic[194].

While disparities in ownership must be acknowledged and addressed today, they are projected to diminish as technology becomes more affordable. Thus, a larger threat to access may be a new digital divide around technology literacy. If DHTs become a part of routine practice within mental health services, will the most vulnerable patients be able to navigate these technologies and access care? Formal data on digital literacy in mental health is scarce, but there are mounting calls for new resources and tools to help ensure that patients have the skills, training and confidence to utilize DHTs[195-197]. Training programs designed to teach patients how to utilize DHTs are becoming available. An example is the Digital Outreach for Obtaining Resources and Skills (DOORS) program[198], that offers a suite of in-person and online training resources.

Many DHTs rely on end-user engagement in offering monitoring or interventions, yet engagement remains a core challenge[199,200], both in and outside the context of research trials. Without standard measurements for evaluating or comparing engagement across DHTs[201,202], progress towards improved engagement has been fragmented. Extracting engagement data from apps and other technologies, especially outside of academic research efforts, is often impossible, except through market research companies that can only offer general population-based samples.

Using this type of data, a 2020 study examined engagement rates of popular (over 100,000 downloads) mental health apps on the app stores/marketplace, and found that 90% of users abandon apps within 10 days[200]. Actual data on app engagement from over 100,000 participants in different studies across various health conditions showed that the median participant retention was just 5.5 days[203]. As mentioned before, this drop-off in use was also found in a 2021 report of the stress app *COVID Coach*, which reported that only 1.56% of users remained engaged for at least 14 days[115]. Research data also do not confirm commonly held assumptions that older adults will engage less than younger people[203], although other reviews suggest the opposite[197].

Studies suggest that human support alongside app use offers the strongest contribution towards improving engagement[112]. However, human facilitation of app-based tools limits the scalability and underlying potential of many apps to expand access to care. An increasing attention is now devoted to co-designing and co-producing digital mental health tools with end users and all stakeholders at the outset, in the hope that digital solutions will reflect the actual needs and preferences of those they are designed to serve[204,205].

DHTs hold an unique potential to extend access to care in middle- and lower-income countries, where there is less investment or infrastructure around mental health[206]. Yet, a recent review on this topic found only 37 relevant studies published in those countries between 2016 and 2020, with the majority reporting feasibility and accessibility outcomes instead of efficacy, cost-effectiveness or implementation[207]. Yet, smartphone use is common and rapidly expanding in those countries, and thus represents a promising tool to reduce the mental health gap.

Research in low-resource countries has focused to date on medication and appointment adherence as well as relapse and rehospitalization prevention[208], which offer important targets with transdiagnostic potential. Leaders in the field have called for a focus on data science, task sharing by empowering community health workers, and early interventions as promising leads[209]. The untapped potential for global mental health is to adapt current digital health tools with strong efficacy data, and devote resources towards establishing local effectiveness and routes towards implementation. While this has not frequently occurred to date, recent research in implementation science holds lessons for this translation, suggesting that context, culture, and personal connections cannot be ignored when deploying an app in a novel setting[158,210,211].

Recipients of innovation: clinical and clinician factors

While clinicians are aware of the potential benefits of DHTs, they are also concerned about several factors, ranging from safety of apps to therapeutic alliance rupture[212,213]. Furthermore, the rapidity of developments of digital mental health technologies represents a challenge to clinicians. Medical education programs often do not cover digital mental health, and many clinicians are left without the resources to utilize the newest innovations. Educational efforts focusing on the clinical workforce are now emerging[126].

On the other hand, it may be necessary to consider in this area a new team member analogous to the radiology or pathology technologist, a "digital navigator" who is able to support both the clinician and the patient in implementing digital technology into clinical care[127]. The role of this digital navigator will include helping to match patients to the useful apps, helping set up and trouble shoot technology, assisting the patient with customizing the technology based on clinical needs, offering support for continued use, and summarizing data for presentation to both the clinician and the patient. Another version of this concept is the "coach", who is more patient-facing and often employed to drive engagement[214].

Alongside workforce considerations, the positioning of DHTs within the clinical workflow must also be determined. While downloading an app onto a smartphone is relatively simple, recent reviews highlight many challenges in implementing an app into the clinical workflow in this way[191,215]. Solving these issues is a high priority and significant challenge[216]. New workflow considerations were critical to designing a digital psychiatry clinic in Boston in order to ensure that apps were a core part of treatment[217].

In the US, the Kaiser Permanente Health system reported that, through offering training to clinicians on using apps in the context of care relationships, the number of referrals to using a mental health app doubled from 20,000 in January 2020 to over 44,000 in May 2020[218]. The US Veterans Administration has outlined best practices for use of apps and offered training and resources to help integrate its suite of apps into care settings[219].

As so few DHTs discussed in this paper have been implemented into real-world care, workflow considerations remain among the least explored but most needed factors towards facilitating implementation. DHTs offering immediate feedback for patients, medical record integration for clinicians, and data portals for administrators hold potential for better fitting population health needs.

Contextual factors

The COVID-19 pandemic has already transformed the context for telehealth and DHTs. While the various governments across the world have opted for different approaches, common aspects have been temporary increases of reimbursement for telepsychiatry, reduction in some licensing requirements, and waiving of certain liability concerns. It remains to be seen whether these regulatory changes will become permanent, and the extent to which this recently increased use of telepsychiatry can extend to DHTs such as smartphone apps, chatbots, virtual reality, and social media. Taking examples and adopting models from other areas of health care may speed up the process of building appropriate regulatory frameworks. For example, remote monitoring in cardiology is well established and regulated already, with appropriate reimbursement models in place[220].

One area where the context for DHTs has made less recent progress is that of trust. Trust from both patients and clinicians around DHTs remains low, especially with respect to sharing data with companies[221]. Lax privacy regulations as well as their limited enforcement[222,223] further limit trust. A 2021 report by the magazine *Consumer Reports* highlighted numerous privacy policy flaws in popular mental health apps[224], underscoring that progress around privacy enforcement/legislation remains lacking.

Compounding this, the amount of misinformation about apps continues to present challenges to both clinicians and patients in evaluating their risks as well as benefits[225]. Transforming the image of DHTs from the current "lawless wild west" will require advancing evidence but also censuring false claims that obscure actual evidence-based tools which patients and clinicians should feel comfortable using today. While evolving regulatory approaches will help bring order and trust, an important step will be general education about risks and benefits for both clinicians and patients. Such education programs are emerging[127,198,226] and will continue to evolve.

Not all regulatory hurdles have been reduced by the COVID-19 pandemic. Many DHTs continue to live outside of any effective regulation by declaring themselves a wellness device (rather than a medical device). With so many thousands of apps and emerging virtual reality, artificial intelligence, and chatbot programs, it is clear that new regulatory approaches are necessary. In the US, there is an ongoing pilot testing of a novel regulatory framework called "pre-certification", which would move much of the regulatory burden towards self-certification by the technology developers. Such a system is not without critics, and its utility in the mental health field remains unclear[227]. Already some groups have raised concerns about regulations for new apps – such as those around substance use disorders that are approved for use only in conjunction with medication assisted treatment, but not psychotherapy – which exclude non-prescribing mental health professionals[228]. Other countries are also looking for new ways to regulate DHTs, with developing policies from Australia, the UK, and the European Union[229].

The app marketplaces themselves serve as another source of informal regulation around DHTs. Today the commercial app stores, namely the *Apple iTunes* and *Android Google Play* stores, have a role in advertising claims, privacy protections, and payment models around app-based DHTs. Entrepreneurial investing and startups have also become a proving ground for new DHTs. The aptly entitled paper published in this journal in 2016, *Tech Giants Enter Mental Health*[230], was a harbinger for increasing investment from venture capital, entrepreneurs, and a wave of startups in digital mental health. However, understanding the value of DHTs, and their related companies, remains elusive, as the necessary data around engagement, effect sizes, necessary dose, and duration of effect remain unknown for almost all DHTs[231].

Still, funding has continued to grow, with the marketplace of investors now focused on DHTs that can offer a sustainable business model. This has fueled trends in DHTs that focus on the needs of employees (for employer payers) or offer traditional telehealth services, such as Internet-delivered therapies, which have been found to be viable and cost-effective for improving several mental health outcomes[232]. Understanding the cost-effectiveness of DHTs will likely become the new point of competition for companies, as the markets begin to saturate with new product offerings.

The technical integration of DHT data presents a final challenge related to contextual factors. The digital information that is eponymous to DHTs is only as useful as it can integrate across devices, networks, and health care settings. Yet, most apps today do not draw on data from existing medical records, and predictive models based on social media or app data (active or passive) are not routinely integrated into the clinical visit or history, largely because of technical integration challenges in sharing data

between devices and systems. The Substitutable Medical Applications and Reusable Technologies (SMART) on Fast Healthcare Interoperability Resources (FHIR), often called SMART on FHIR, has emerged as the likely standard that can ensure privacy as well as interoperability.

A related challenge is that, even with such standards in place, utilization cannot be assumed. Barriers must be overcome at the level of patients, clinicians and systems, with one recent study showing that only 1% of patients at a large hospital chose to link their app data with their medical record[233]. In April 2021, new rules to limit information blocking have taken effect in the US, and even mental health notes must now be electronically shared with patients.

As more mental health data become easily available, interoperability will be even more critical in the DHT ecosystem. Creating new DHTs that are able to comply with and interface with different data systems is an important first step towards building the next generation of useful technologies.

Recommendations around implementation

Considering all the issues discussed in this section, it becomes clear that the main limiting factors of digital psychiatry are not the technologies or innovation themselves, but rather the challenges related to priming the recipients (i.e., patients/clinicians) and the context of health care delivery (e.g., regulation). Therefore, the most immediate benefits in the field could be realized through making effective and ethical use of existing technologies in real-world settings. While it is unlikely that there will be a single solution to these implementation challenges, various options can be considered depending upon local conditions and clinical needs.

Using a recent app evaluation model[7,234] as a scaffold, we put forward the following recommendations around high-priority opportunities for advancing the field:

- *Privacy and security*. Without a renewed focus on privacy and protecting users' data, DHTs will lack the trust necessary for uptake. Across all conditions and technologies, ensuring privacy remains critical. Co-producing digital solutions with end users, starting with the fundamentals around data use, is critical.
- *Efficacy*. Increasing evidence shows that DHTs are feasible and acceptable to those with mental health problems. Likewise, efficacy studies suggest that, under ideal research conditions, DHTs can offer benefit and have clinical utility. As DHTs seek reimbursement or addition into national formularies, the need for high-quality effectiveness data can no longer be ignored. High-quality studies that compare DHTs to active control or placebo groups are required to support this.
- *Engagement*. Downloads are a poor proxy for app engagement. Available data suggest that engagement remains limited across all apps. Augmenting app use with human support appears to offer one solution to sustain engagement, though this detracts from apps' potential to offer scalable and affordable solutions to health care access. Research on why people use DHTs, and how best to encourage sufficient engagement, is necessary.
- *Clinical integration*. Integration of DHTs into clinical practice is feasible, but remains cumbersome. Creating new "digital" clinical services and rethinking care models is necessary to realize the full benefit of DHTs. Advances in digital health standards, policies and regulation are more feasible in the post-COVID-19 era, and the field must be prepared to offer viable solutions.

These recommendations apply across all DHTs, but there are special considerations for each technology that are summarized in Table 1. Understanding the future potential, key issues, and priority actions is most productive in the light of the above discussion of challenges concerning recipients and context.

Table 1 Summary points related to common digital health technologies in mental health

Technology	Main uses	Future potential	Key issues	Priority actions
Digitally-delivered psychological therapies	Self-management of symptoms of depression and anxiety	Precision interventions; preventive treatments	Lack of engagement; saturated consumer marketplace; claims outpacing clinical evidence	Establishing evidence base for use in people with diagnosed mental disorders
Smartphone data (active + passive)	Tracking mood and lifestyle in people with major depression, bipolar disorder and psychosis	Machine learning towards individualized risk prediction and delivery of targeted "just in time" interventions	Lack of validation across studies; establishing trust around data usage	Data standards for interoperability and validation; industry-academic partnerships around access
Social media	Population level monitoring of mood and anxiety	Real time monitoring of mental health state; accessible peer support	Sampling bias; access to data from social media companies; privacy	Industry-academic partnerships and privacy standards
Virtual reality	Exposure therapies	Higher engagement and potentially higher efficacy than apps	Increased accessibility	Low-cost headsets; expanded clinical targets
Chatbots		Increased access to care	Limited range of appropriate responses	Establishing evidence base for use in people with diagnosed mental disorders

CONCLUSIONS

The role of the Internet and digital technologies in providing wider access to psychological interventions and mental health care has long been discussed. However, only in recent years have the abilities, affordability and accessibility of ubiquitous Internet devices (particularly smartphones) advanced to such a point as to allow digital psychiatry to move from a theoretical concept to a realistic option for augmenting traditional mental health care globally.

The development of related technologies, including artificial intelligence and machine learning algorithms, chatbots, and virtual reality, alongside empirical research on the utility of each within mental health contexts, has presented a number of promising avenues. The uptake of this has further been accelerated by the COVID-19 pandemic, which has highlighted how digital approaches can offer some level of adaptive care under circumstances where access to in-person services is precluded.

In terms of DHTs for the clinical management of long-term mental health problems, there are several lines of research emerging, in multiple different conditions, to support the use of DHTs for individuals to self-manage their symptoms, as an adjunctive to usual care. Alongside digitally delivered therapies, there has also been progress towards the use of smartphone-collected data for predicting clinical outcomes or risk of relapse. Future research should aim to combine these two areas, in order to harness the available data to provide timely and targeted remote interventions, termed JITAIs, to prevent relapse and other adverse outcomes[235]. Finally, the considerable interest and investment in the application of DHTs within child and adolescent mental health should aim to take advantage of young people's apparent proclivity towards new technologies.

All of the aforementioned advances in both the technologies themselves and research supporting them, however, are not enough to ensure that their potential is realized in real-world settings. Instead, a number of pitfalls and possibilities surrounding implementation must now be addressed. At the patient level, a better understanding of user engagement with these technologies, and how this relates to benefits observed, is required. At the provider level, improved training for "prescribing" DHTs by the mental health care workforce, clearer expectations of where DHTs should sit within the clinical workflow, and improvements of interoperability for new DHTs within existing systems are all necessary if integration is to be at all possible. At the policy level, further action is required to ensure that clinical regulations are suitably flexible to allow for innovation to be effectively adopted within health care services, while stricter regulations for commercial settings may be needed to protect the public and increase their confidence in these new approaches.

Each of these implementation issues must also be considered and actioned with an understanding of the complex ethical issues surrounding DHTs, and their related data. Overall, it now seems inevitable that digital technologies will change the face of mental health research and treatment. The extent to which these changes are genuinely beneficial for those with mental disorders will depend on equitable access, robust research, and ethical, evidence-based implementation of these new technologies within global mental health care.

ACKNOWLEDGEMENTS

J. Firth is supported by a University of Manchester Presidential Fellowship (P123958) and a UK Research and Innovation Future Leaders Fellowship (MR/T021780/1). J. Torous and M. Keshavan receive support from the Natalie Mental Health Foundation. J. Torous receives support from the US National Institute of Mental Health (K23MH116130) and the American Psychiatric Association Foundation. S. Bucci is supported by a National Institute for Health Research (NIHR) Research Professorship.

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DOI:10.1002/wps.20883

The clinical characterization of the adult patient with an anxiety or related disorder aimed at personalization of management

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The clinical construct of "anxiety neurosis" was broad and poorly defined, so that the delineation of specific anxiety disorders in the DSM-III was an important advance. However, anxiety and related disorders are not only frequently comorbid, but each is also quite heterogeneous; thus diagnostic manuals provide only a first step towards formulating a management plan, and the development of additional decision support tools for the treatment of anxiety conditions is needed. This paper aims to describe systematically important domains that are relevant to the personalization of management of anxiety and related disorders in adults. For each domain, we summarize the available research evidence and review the relevant assessment instruments, paying special attention to their suitability for use in routine clinical practice. We emphasize areas where the available evidence allows the clinician to personalize the management of anxiety conditions, and we point out key unmet needs. Overall, the evidence suggests that we are becoming able to move from simply recommending that anxiety and related disorders be treated with selective serotonin reuptake inhibitors, cognitive-behavioral therapy, or their combination, to a more complex approach which emphasizes that the clinician has a broadening array of management modalities available, and that the treatment of anxiety and related disorders can already be personalized in a number of important respects.

Key words: Anxiety, anxiety and related disorders, obsessive-compulsive disorder, post-traumatic stress disorder, personalization of treatment, symptom profile, clinical subtypes, severity, neurocognition, functioning, quality of life, personality traits, psychiatric antecedents, psychiatric comorbidities, physical comorbidities, family history, early environmental exposures, recent environmental exposures, protective factors, dysfunctional cognitive schemas

(World Psychiatry 2021;20:336–356)

Anxiety disorders are the most prevalent mental disorders, with a global current prevalence estimate of 7.3%[1]. An early construct was "anxiety neurosis", but this was poorly operationalized. The differentiation of specific anxiety disorders in the DSM-III was therefore an important step forward for the field, giving impetus to the development of a more personalized approach to the treatment of the individual patient with anxiety[2]. An early hypothesis, for example, was that patients with social anxiety disorder would respond preferentially to monoamine oxidase inhibitors[3].

At the same time, anxiety disorders are characterized by significant comorbidity, and each disorder is heterogeneous in terms of phenomenology and psychobiology. Thus, for example, social anxiety disorder is often accompanied by generalized anxiety disorder (GAD), and ranges from discrete social anxiety disorder to generalized social anxiety disorder[4]. Although there is a large body of evidence on the value of selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral therapy (CBT) for anxiety disorders, this heterogeneity may explain why a significant proportion of individuals do not respond to first line therapy[5].

While current diagnostic systems are certainly useful in formulating an initial treatment plan, it behooves the field to develop additional decision support tools. These may allow us to move away from guidelines that focus solely on disorders and that emphasize SSRIs and CBT as first line steps towards more detailed assessments that provide the clinician with more specific guidance and facilitate a more personalized approach. More detailed and rigorous matching of presentation with management may ultimately improve treatment outcomes[6].

This paper aims to describe systematically important domains relevant to the personalization of management of anxiety disorders and related conditions such as obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) (Table 1). For each domain, we summarize the available research evidence and review the relevant assessment instruments, paying special attention to their suitability for use in routine clinical practice. We emphasize areas where the available evidence allows the clinician to personalize the management of anxiety and related conditions, and we point out key unmet needs. The research literatures on anxiety and depression have many important overlaps, so it is not surprising that this list of domains draws closely on previous work on depression[6].

In keeping with the aims of precision medicine, considerable effort has been paid to developing biomarkers for anxiety and related disorders. It is notable that fear conditioning and extinction provide an important paradigm for explaining the symptoms of these disorders, as well as conceptualizing treatment approaches[7]. Additional specific constructs, such as cognitive flexibility and inhibitory control, may be more relevant to particular disorders, such as OCD[8]. These concepts are emphasized in the translational neuroscience framework of the US National Institute of Mental Health's Research Domain Criteria (RDoC)[9] and contrib-

Table 1 Salient domains to be considered in the clinical characterization of a patient with an anxiety or related condition

1. Symptom profile
2. Clinical subtypes
3. Severity
4. Neurocognition
5. Functioning and quality of life
6. Personality traits
7. Antecedent and concomitant psychiatric conditions
8. Physical comorbidities
9. Family history
10. Early environmental exposures
11. Recent environmental exposures
12. Protective factors / Resilience
13. Dysfunctional cognitive schemas

uted in part to the separation of anxiety disorders in the DSM-5 and ICD-11 into anxiety or fear-related disorders, obsessive-compulsive and related disorders, and disorders specifically associated with stress (these are the terms used in the ICD-11)[10].

Despite the extent and rigor of research on the neurobiology of anxiety and related disorders, no biomarker of these conditions has to date proven sufficiently sensitive and specific for widespread adoption in clinical practice[11,12]. We therefore do not address biomarkers in detail in the current paper. However, we hypothesize that more personalized assessment of the sort proposed herein may be useful in advancing biomarker research, as well as work on the translational neuroscience of anxiety more generally, given the potential value of more fine-grained clinical assessments for delineating disorder heterogeneity in ways that may be neurobiologically informative and which may predict treatment response[6,13].

The paper focuses on anxiety and related disorders in the adult patient. These disorders often have an early onset, and pediatric anxiety is important both clinically and from a public health perspective; additional work is therefore needed to address the child and adolescent with anxiety. We also do not address in detail anxiety secondary to other mental disorders such as major depression or a psychotic disorder, or anxiety due to another medical condition, or anxiety induced by a substance or a medication, despite their clinical significance. Nor do we closely cover issues relevant to subthreshold anxiety and related disorders, despite their public health importance[14]. Gender- and culture-related issues are considered where relevant.

SYMPTOM PROFILE

Anxiety disorders share features of anxiety, fear and/or panic attacks, often accompanied by phobic avoidance or overly cautious behaviors, in reaction to perceived threats. In both the DSM-5 and ICD-11, anxiety disorders include agoraphobia, GAD, panic disorder, selective mutism, separation anxiety disorder, specific phobia, and social anxiety disorder. OCD and PTSD are included in separate but closely related groupings. In both nosologies, the diagnosis of anxiety disorders involves marked or substantial levels of fear or anxiety, that differ from stress-induced transient fear or anxiety by being persistent (i.e., lasting several months or more) and distressing or impairing.

Both the DSM-5 and ICD-11 differentiate among the anxiety disorders primarily by the focus of apprehension (i.e., perceived threat) and the types of objects or situations that induce anxiety, fear or panic attacks. The perceived threat and associated stimuli range from being tightly circumscribed (as in specific phobia), to domain-specific (as in agoraphobia, panic disorder, separation anxiety disorder, and social anxiety disorder), to pervasive (as in GAD). Thus, although highly comorbid with one another, anxiety and related disorders can be differentiated by close examination of the range and types of situations that are feared or avoided and the content of the associated thoughts or beliefs. For example, panic disorder is characterized by fears of interoceptive cues which are misappraised as being harmful, whereas social anxiety is characterized by fears of social or performance situations in which negative evaluation and rejection is anticipated to occur. Differentiation between the anxiety and related disorders is of high relevance to clinical management and treatment selection, since most evidence-based pharmacological and psychological treatments are tested for specific anxiety or related disorders.

The most significant difference between the DSM-5 and ICD-11 conceptualizations of anxiety and related disorders is in the diagnostic requirements for PTSD[15]. In the DSM-5, the criteria were expanded substantially, to include twenty symptoms across four clusters, in an attempt to capture the full scope of chronic post-traumatic expressions. In contrast, the ICD-11 simplified PTSD diagnostic requirements to three core symptoms that most clearly distinguish this disorder from other conditions, i.e. re-experiencing the traumatic event or events in the present, deliberate avoidance of reminders, and a sense of ongoing threat. Evidence suggests that the data better fit the simpler factor structure of the ICD-11 than the DSM-5 criteria[16]. The ICD-11 defines "complex PTSD" as consisting of the three core PTSD symptoms described above accompanied by problems in affect regulation, negative self-beliefs, and relationship difficulties[17]. Latent class analysis and latent profile analysis have supported the distinction between PSTD and complex PTSD as well as the association between complex PTSD and trauma in childhood in some studies[16].

Anxiety disorders are marked by fear or anxiety. Fear is conceptualized as the emotional response to perceived predictable or imminent threat when there is little or no time to consciously strategize escape, whereas anxiety is a future-oriented state of anticipation for uncertain, prolonged or distal threats when there is time to comprehend the foreboding nature of the situation. Both states are designed to activate cognitive, affective, physiological and behavioral processes that enhance safety. In the case of fear, rapid, involuntary, physiological reactions facili-

tate the selection and production of an appropriate fight or flight response; whereas anxiety activates physiological and cognitive strategic preparation for fight or flight if needed[18-20]. This view of fear and anxiety is supported by animal predatory imminence continuum models that posit distinct modes (from pre-encounter potential for threat, to post-encounter threat detection, to circa-strike predator attack) that each result in distinct well-defined behaviors and defensive circuits[21].

These canonical modes of threat are universal (although the responses are species-specific) and applicable not only to non-primates but also to humans[22,23]. Optogenetic studies in non-primates show that stimuli analogous to pre- and post-encounter threats evoke the ventromedial prefrontal cortex, hippocampus, and basolateral amygdala – regions involved in threat memory, prospection and avoidance[24,25]. In the circa-strike attack mode, activity is evoked in circuits that include the mid-cingulate cortex, central amygdala, hypothalamus, and periaqueductal gray – regions involved in fast reactions to threat (e.g., flight)[24,25]. Similar defensive circuits exist in humans: functional magnetic resonance imaging (MRI) studies show that distant threat is associated with increased activity in the ventromedial prefrontal cortex, and, as threat moves closer, more activation in midbrain periaqueductal gray is observed[26,27]. The RDoC, which take a dimensional approach to psychopathology, draw upon these models by suggesting that "responses to low imminence threats are qualitatively different than the high imminence threat behaviors that characterize fear"[9].

Whereas prototypes of fear and anxiety lie at different "places" upon a continuum of responding, clinical presentations are more fluid. For example, perceptions of threat can rapidly change from being distal to imminent through appraisals and imagery alone, without change in external circumstances. An exemplar is the person with PTSD who experiences a fearful flashback to trauma (i.e., imminent threat) in the midst of anxiety in unfamiliar surroundings (i.e., distal threat).

Anxiety and fear are expressed across multiple response modalities: behavior, physiology and subjective report[28]. States of anxiety are typically linked with behaviors of vigilance, caution and avoidance, physiological preparation for acute threat (e.g., startle response amplification, elevated muscle tension), statements of worry or concern, and appraisals of impending or uncertain threat (e.g., "What if I mispronounce a word at the dinner party next week – I will be so embarrassed" or "What if I faint in the movie theater"). States of fear are linked with behaviors of escape (or fight), autonomic arousal, statements of fear or fright, and appraisals of acute threats (e.g., "I am dying" or "I need to get out of here")[29].

Notably, these response modalities are not always concordant[30]. For example, individuals may report anxiety or fear in the absence of physiological changes or behavioral outputs, or may avoid situations in the absence of reported anxiety or fear. Even during panic attacks, people sometimes report fear without evidence of physiological changes[31]. Such discordance may be informative for treatment selection. For example, subjective distress in the absence of physiological changes may indicate the value of a cognitively oriented treatment approach rather than a biologically oriented one (such as respiratory regulation or pharmacotherapy), and behavioral avoidance in the absence of physiological changes may indicate the particular value of exposure therapy. However, evidence for such treatment matching remains only nascent, as clinical trials have focused primarily on particular anxiety diagnoses and clinical subtypes, rather than on detailed assessment of specific behaviors, physiological parameters, or cognitive appraisals.

In clinical practice, the key first step in the assessment of anxiety symptoms is the establishment of an anxiety or related disorder diagnosis on the basis of the symptom profile. The diagnosis of anxiety and related disorders in adults can be ascertained using validated clinical interviews. Examples of such interviews include the Structured Clinical Interview for DSM-5 (SCID-5)[32], the Mini International Neuropsychiatric Interview (MINI)[33] and the Composite International Diagnostic Interview (CIDI)[34]. The Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5) is particularly focused on the differential diagnosis among anxiety disorders[35]. A structured diagnostic interview for obsessive-compulsive and related disorders may be useful for assessing this range of often overlooked conditions[36].

Determining whether the anxiety symptoms (for example, panic attacks) are occurring as a manifestation of another mental disorder (such as major depression or bipolar disorder) is important. Substance use or intoxication (e.g., use of caffeine, stimulants) and withdrawal (e.g., from alcohol use) can lead to prominent anxiety symptoms. Certain medical conditions also produce anxiety symptoms, such as cardiopulmonary (e.g., asthma), endocrine (e.g., thyroid disease) and neurological (e.g., complex partial seizures) disorders, among others.

Identifying anxiety related to medical conditions is achieved through a detailed medical history and physical examination and, when warranted, specific blood (e.g., thyroid-stimulating hormone levels) or other (e.g., electrocardiography or electroencephalography) tests. Although structural (for example, voxel-based morphometric) and functional MRI have been used to learn more about the pathophysiology of anxiety and related disorders, they are not currently useful for diagnostic purposes[11,12].

Data on the underdiagnosis and undertreatment of anxiety and related disorders underscore the importance of screening for anxiety symptoms[37]. The Generalized Anxiety Disorder-7 (GAD-7)[38] is a 7-item self-report questionnaire that has been developed specifically for GAD, but has been found to be useful in identifying any anxiety disorder with adequate sensitivity and specificity[39]. Other screening tools include the Hospital Anxiety and Depression Scale[40] and the Overall Anxiety Severity and Impairment Scale (OASIS)[41], which includes measurement of avoidance behavior (an important feature, since anxiety levels may be masked without such measurement). The Perinatal Anxiety Screening Scale is suitable as a nonspecific screener for perinatal women[42].

If an anxiety or related disorder is present, several measures can be used to assess the profile of anxiety symptoms. The Interview for Mood and Anxiety Symptoms assesses all symptoms of

DSM and ICD emotional disorders as well as other manifestations of internalizing psychopathology[43]. Each item is rated from clearly absent, to partially present (subclinical, subthreshold) to clearly present, and thus symptom profile scores can be evaluated. Aside from interviews, self-report questionnaires exist for each of the anxiety and related disorders, and provide more detailed symptom profiles. These include the DSM-5 scales developed for agoraphobia, GAD, OCD, PTSD, social anxiety disorder, and specific phobia, each one including items for affective states of fear and anxiety, physiological, cognitive and behavioral symptoms[44]. With the exception of specific phobia, these scales have been shown to have adequate to strong psychometric properties[45-52].

A number of other well-validated standardized symptom questionnaires exist. They include the Penn State Worry Questionnaire[53] for GAD; the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)[54] for OCD; the Albany Panic and Phobia Questionnaire-Agoraphobia[55], the Mobility Inventory for Agoraphobia[56], the Panic Disorder Severity Scale[57], and the Panic and Agoraphobia Scale[58] for panic disorder and agoraphobia; the PTSD Checklist-5 for DSM-5 (PCL-5)[59] and the Clinician Administered PTSD Scale for the DSM-5 (CAPS-5)[60] for PTSD; and the Social Phobia and Anxiety Inventory[61] and the Liebowitz Social Anxiety Scale[62] for social phobia. Scales for each type of specific phobia are not available, but a generic measure is the Fear Survey Schedule[63], a 51-item questionnaire that asks respondents to indicate their discomfort, or felt anxiety, to each of fifty-one stimuli.

Distinguishing the anxiety and related disorders can guide clinicians to disorder-based treatment. Particular versions of CBT have been developed to target the specific focus of apprehension of each anxiety or related disorder. There is a substantial evidence for the efficacy of such targeted treatments[64-66], and they are recommended as first-line psychological treatments for anxiety and related disorders in several guidelines, including those by the UK National Institute for Health and Care Excellence (NICE)[67]. For example, CBT for panic disorder includes interoceptive exposure to feared bodily sensations; CBT for social anxiety disorder includes cognitive restructuring around post-event rumination; CBT for GAD addresses meta-beliefs about worry; CBT for OCD includes exposure to specific cues that trigger distress and the urge to perform compulsive rituals as well as response prevention aimed at eliminating the compulsions; and CBT for PTSD includes imaginal exposure or cognitive reprocessing regarding trauma memories. Thus, differential diagnosis facilitates choice of the most appropriate form of CBT. Even if using transdiagnostic CBT, a promising alternative to disorder-specific approaches[68], the clinician will still need to implement the therapeutic strategies in ways that are tailored to each person's focus of apprehension.

In terms of pharmacotherapy, SSRIs have demonstrated efficacy for all major anxiety and related disorders. Nevertheless, it is important to distinguish between the various disorders, for several reasons. First, SSRI pharmacotherapy guidelines differ across the various anxiety and related conditions[69]. Thus, for example, it is particularly important to begin with lower doses of an SSRI in panic disorder (as standard doses may not be tolerated), while a higher dose and longer duration of treatment is particularly important in OCD. Second, agents other than SSRIs have different efficacy across different anxiety and related disorders[69]. Thus, for example, the tricyclic antidepressant imipramine is efficacious in some anxiety and related disorders (e.g., GAD, panic disorder, PTSD) but not others (OCD, social anxiety disorder); the benzodiazepine alprazolam is efficacious in a different range of anxiety disorders (GAD, panic disorder, social anxiety disorder) but not in anxiety related disorders (OCD and PTSD); buspirone is efficacious in GAD but not in other anxiety and related disorders, while OCD appears unique among these conditions in being more responsive to serotonergic than noradrenergic reuptake inhibitors[69].

Greater precision and ultimate efficacy may derive from matching treatment to symptom clusters, given the heterogeneity that exists within diagnostic labels. Indeed, there is evidence that clinicians already view symptom clusters as more informative than diagnostic categories for pharmacotherapy selection[70,71]. For example, in a sample of 318 patients, the diagnosis of PTSD was not associated with the prescription of any specific medication class, while symptom clusters were: anticonvulsant prescription was linked to avoidance symptoms, antidepressant prescription to numbing symptoms, anxiolytic prescription to intrusions, and mood stabilizer prescription to hyperarousal[71]. Similarly, in panic disorder, anxiolytics were more often prescribed for physical symptoms of the fear response, whereas antidepressants and anticonvulsants as well as anxiolytics were prescribed for psychological symptoms. A similar matching of medication class with symptom profile was found for agoraphobia (public vs. enclosure), OCD (cleaning, checking), social anxiety disorder (interactive vs. performance), and specific phobia (animal, situational, blood). Clearly, the symptom profile is guiding prescribers' current pharmacotherapy choices, and the field of personalized medicine would be advanced by randomized controlled trials to validate (or not) such matching of symptom profile to medication.

The same argument holds for psychotherapy, which has been confounded by utilization of CBT packages that combine multiple therapeutic strategies (e.g., breathing retraining, cognitive restructuring, exposure therapy, response prevention). There have been calls to match the core active ingredients of these therapy packages to specific symptom profiles (e.g., breathing retraining to arousal regulation, cognitive restructuring to cognitive distortions, exposure therapy to avoidance)[72,73]. This remains an important area of future research. Nonetheless, it is quite possible that the practicing clinician already tailors the core ingredients of CBT to symptom presentations, in the same way as observed for pharmacotherapies.

CLINICAL SUBTYPES

Each of the anxiety and related disorders is characterized by significant heterogeneity, and several clinical subtypes have been delineated. The content of the fear or anxiety (cognitive

component), the physiological reactions (such as a panic attack), and the behavioral response (which often includes avoidance and may include safety behaviors) can be useful in determining whether or not a distinctive clinical subtype is present. In addition, a range of other approaches to subtyping have been taken, including those based on age of onset and on comorbid symptoms. Here we consider the main clinical subtypes that have been posited for key anxiety and related disorders.

In GAD, it is useful to assess both the nature of the worries, as well as the range of psychic (psychological) versus somatic (physical) symptoms. The worries may focus on death (e.g., someone not calling when he said he would means he has died), disease (e.g., "headache means I have a brain tumor"), destruction (e.g., "the leak in the ceiling means I need a new roof and if I don't get it in time my house will be ruined"), and sometimes destitution (e.g., "If I lend my sister the money, she will never stop asking and I'll end up broke"). Tools such as the Penn State Worry Questionnaire[53] assess the range and focus of GAD worries, while the psychic and somatic subscales of the Hamilton Anxiety Rating Scale (HAM-A)[74] are useful for assessing the range of symptoms.

Knowing the precise nature of the worries is important for CBT, which may focus on cognitive restructuring of particular worries or exposure for particular kinds of fears. In terms of pharmacotherapy, an early suggestion was that tricyclic antidepressants are more useful for psychic symptoms, while benzodiazepines are more useful for somatic symptoms[75]. However, there has been relatively little subsequent evidence to support the selective response of psychic and somatic symptoms to different pharmacotherapies. A range of medications that are efficacious for GAD improve both psychic and somatic symptoms[76-79].

Concerning OCD, a substantial literature has emphasized that obsessions and compulsions tend to fall on a few symptom dimensions, including washing, checking, symmetry and hoarding[80]. Although many patients have symptoms that lie on different dimensions, or experience a range of symptoms from different dimensions over time, there is some evidence that symptom dimensions are associated with particular psychobiological characteristics and treatment outcomes. In particular, hoarding symptoms are less likely to respond to SSRIs. Further work is needed to determine whether patients with hoarding symptoms who do not respond to SSRIs may respond to augmentation with dopamine antagonists[81].

Insight in OCD can be ascertained by questioning the patient about the consequences of not engaging in the compulsions and the likelihood that the feared consequences will actually occur. It may be helpful to ask the patient if the feared consequences would be likely to occur for someone else, in order to assess their thought process without the influence of their own anxiety about not performing the compulsions. Insight in OCD can be formally assessed with measures such as the Brown Assessment of Beliefs Scale[82]. OCD patients with poor insight may be less likely to access or respond to pharmacotherapy and psychotherapy[83]. Such patients may require additional interventions such as family-based treatments[84] and adjunctive dopamine antagonists[85].

If OCD patients have current or past tics, it is important to determine if the compulsions are more tic-like (e.g., throat-clearing) or aimed to reduce anxiety (e.g., handwashing after feeling contaminated). Tic-related OCD is marked by a number of features, including early onset, male predominance, family history of tics, and more often having symptoms that involve responding to an urge (or premonitory sensory symptoms) or having to feel "just right". Tic severity may be formally assessed with a number of measures[86]. Tic-like compulsions do not respond well to exposure and response prevention, and may respond better to augmentation with dopamine antagonists[83].

A range of other subtypes of OCD has been proposed, including early onset OCD[83]. While such work has been valuable to better understand the heterogeneity of OCD, there is insufficient treatment evidence for such subtyping to have clinical utility.

Concerning panic disorder, a number of different sets of panic symptoms have been found to cluster together, including respiratory, nocturnal, non-fearful, cognitive and vestibular symptoms[31]. Investigation of the respiratory physiology in panic disorder has been particularly useful in advancing understanding of the neurobiology of the condition[87]. Nevertheless, there is no strong evidence to indicate that any of these subtypes has a distinctive psychobiology, nor is there good evidence that any has a selective treatment response[88]. It is possible, however, that more extensive study will lead to more specific treatment recommendations for panic disorder subtypes.

PTSD is diagnosed in the DSM-5 using twenty symptoms that fall in four symptom subgroups, namely intrusions (five symptoms), avoidance (two symptoms), negative alterations in cognition and mood (seven symptoms), and arousal (six symptoms). While it has long been suggested that different symptom dimensions of PTSD are underpinned by different neurobiological mechanisms[89,90], it seems that there are strong genetic correlations across PTSD symptom dimensions and that efficacious pharmacotherapy for PTSD reduces symptoms across dimensions[91]. As noted earlier, the prescription of anticonvulsants has been linked to avoidance, that of antidepressants to numbing symptoms, that of anxiolytics to intrusions, and that of mood stabilizers to hyperarousal[71], but further work is needed to provide the evidence base for such decision-making.

It has been hypothesized that there is a dissociative subtype of PTSD, with a distinctive neurobiology[92]. This subtype may be characterized by overmodulation of affect, rather than undermodulation of affect with re-experiencing and hyperarousal symptoms. Most clinicians assess dissociation via psychiatric history, but it may be useful to employ a formal tool such as the Dissociative Experiences Scale (DES)[93]. The DES-II is a 28-item self-report measure that assesses the frequency of dissociative experiences through daily life, with scores over 30 considered high[94].

Recording treatment sessions for later review may be helpful for patients with dissociation symptoms, as well as frequent grounding, breaks, and progressing more slowly with traumatic content in order to not overwhelm the patient. Further, in keeping with the hypothesis that dissociation is linked to avoidance,

there is evidence that cognitive processing therapy should include an exposure component when dissociation is present[95]. The ICD-11 construct of "complex PTSD" is marked by increased levels of early childhood trauma and dissociative symptoms, but further work is needed to determine what specific interventions would improve outcomes in this condition[96].

The DSM-IV included a "generalized" specifier for social anxiety disorder, referring to patients with a broader range of social fears. In the DSM-5, this has been replaced by a "performance only" specifier, which is used when the fear is limited to speaking or performing in public. There is a view that social anxiety disorder ranges from single fears through to multiple fears, and that patients with more fears have greater severity and impairment[97]. There is some evidence that patients with "performance only" social anxiety disorder may respond to beta-adrenergic blockers (such as propranolol or atenolol)[98]. SSRIs, on the other hand, may be useful for patients with both more limited or more generalized social anxiety disorder[99]. CBT seems to be effective for all types of social anxiety.

Specific phobias include an animal type (e.g., spiders, insects, dogs), a blood-injection-injury type (e.g., needles, invasive medical procedures), a natural environment type (e.g., heights, storms, water), a situational type (e.g., airplanes, elevators, enclosed places) and "other" types (e.g., phobic avoidance of situations that may lead to choking, vomiting, or contracting an illness). Exposure techniques tailored to particular phobias are helpful for this range of specific phobia types.

The blood-injection-injury type, in contrast to other phobias which result in persistent tachycardia in response to feared cues, may be characterized in some patients by a diphasic response, with an initial rise in heart rate followed by vasovagal bradycardia and, in some cases, syncope[100,101]. If patients faint upon exposure to cues, exposure therapy can be conducted with the patient lying down. It may be useful to teach patients an isometric muscle tensing technique that can help increase blood pressure during exposure to feared cues[102].

The situational type of specific phobia often overlaps with agoraphobia and/or panic disorder and therefore typically requires cognitive techniques in addition to exposure.

SEVERITY

Assessing the severity of anxiety symptoms is an important component of the evaluation of the patient with an anxiety or related condition.

The DSM-5 includes symptom severity measures for each of the anxiety and related disorders, and several standardized symptom measures are widely used in clinical practice and research. These include the GAD-7[38] and the Penn State Worry Questionnaire[53] for GAD; the Y-BOCS[54] for OCD; the Panic Disorder Severity Scale[57] and the Panic and Agoraphobia Scale[58] for panic disorder; the Mobility Inventory for Agoraphobia[56] and the Albany Panic and Phobia Questionnaire-Agoraphobia[55] for agoraphobia; the PCL-5[59] and the CAPS-5[60] for PTSD; the Fear Survey Schedule[63] for specific phobia; and the Social Phobia and Anxiety Inventory[61] and the Liebowitz Social Anxiety Scale[62] for social phobia (see Table 2).

Table 2 Tools to assess severity of anxiety and related disorders

Agoraphobia	
Albany Panic and Phobia Questionnaire-Agoraphobia[55]	Number of items: 27 Scale: 0-8 Subscales: 9
Mobility Inventory for Agoraphobia[56]	Number of items: 26 Scale: 0-5
DSM-5 severity measure[44,47]	Number of items: 10 Scale: 0-4
Generalized anxiety disorder	
Generalized Anxiety Disorder-7 (GAD-7)[38]	Number of items: 7 Scale: 0-3
Penn State Worry Questionnaire[53]	Number of items: 16 Scale: 1-5
DSM-5 severity measure[44,46]	Number of items: 10 Scale: 0-4
Obsessive-compulsive disorder	
Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[54]	Number of items: 10 Scale: 0-4 Subscales: 2
DSM-5 severity measure[44,48]	Number of items: 10 Scale: 0-4
Panic disorder	
Panic Disorder Severity Scale[57]	Number of items: 7 Scale: 0-4
Panic and Agoraphobia Scale[58]	Number of items: 13 Scale: 0-4
DSM-5 severity measure[44,47]	Number of items: 10 Scale: 0-4
Post-traumatic stress disorder (PTSD)	
PTSD Checklist for DSM-5 (PCL-5)[59]	Number of items: 20 Scale: 1-5 Subscales: 4
Clinician Administered PTSD Scale for the DSM-5 (CAPS-5)[60]	Number of items: 30 Scale: 1-5 (frequency) Scale: 1-5 (intensity) Subscales: 4
DSM-5 severity measure[44,50]	Number of items: 10 Scale: 0-4
Specific phobia	
Fear Survey Schedule[63]	Number of items: 51 Scale: 0-6
DSM-5 severity measure[44]	Number of items: 10 Scale: 0-4
Social anxiety disorder	
Social Phobia and Anxiety Inventory[61]	Number of items: 45 Scale: 0-6
Liebowitz Social Anxiety Scale[62]	Number of items: 24 Scale: 0-3
DSM-5 severity measure[44,52]	Number of items: 10 Scale: 0-4

Measurement of symptom severity in anxiety is useful for a number of reasons. First, considering the full spectrum of symptom severity is relevant to stepped care models of treatment delivery. Stratified stepped care offers less intensive treatments (e.g., digital therapies) to those with lower symptom severity, while those with higher symptom severity are offered more intensive treatments[103-105]. Intensive approaches, including home visits or hospital admission, may be necessary for agoraphobia when patients are unable to leave their homes, for OCD patients when rituals make their homes unsafe or prevent clinic appointments or when they are suffering severe self-neglect as a result of their symptoms, or for the PTSD patient who has such severe symptoms that he/she is unable to attend outpatient treatment sessions.

Second, incorporation of symptom severity measures in treatment visits helps guide both the clinician and the patient, allowing them to be responsive to worsening symptoms, and to positively reinforce treatment gains[106,107]. Practical approaches to measurement-based care of both adult and pediatric anxiety have been implemented, and this promises to contribute to improvement in personalized care and optimization of clinical outcomes[108,109].

Third, guidelines for clinical management of anxiety and related disorders may advise treatment choice based on symptom severity. This is consistent with the point made above that mild symptoms may respond to less intensive treatments, while more severe symptoms may require more intensive treatments, including the use of more than one modality of treatment.

In GAD, symptom severity can be reliably assessed by the GAD-7 (patient-rated) and the HAM-A (observer-rated). With the GAD-7, cut points of 5, 10 and 15 can be interpreted as signifying mild, moderate and severe levels of anxiety: increasing scores on the scale are strongly associated with worsening functional impairment and increasing number of disability days[39]. With the HAM-A, scores of 9, 15 and 24 can be interpreted as representing the lower limits of borderline, mild and moderate illness, respectively[110]. Increasing symptom severity on the HAM-A is linearly related to increasing functional impairment in the three domains of the Sheehan Disability Scale (see below)[111].

The NICE guidance on the management of patients with GAD suggests that, if symptoms are mild, a period of active monitoring should initially be undertaken, as symptoms will often resolve without need for intervention. If symptoms have not resolved following a period of active monitoring, a low-intensity psychological intervention (essentially self-help or psychoeducational approaches) should be offered. In the presence of marked functional impairment, or when symptoms have not resolved with low-intensity psychological interventions, either a high-intensity psychological intervention (CBT or applied relaxation) or medication (typically an SSRI) should be offered, depending on the person's wishes[112].

In OCD, symptom severity can be evaluated with the Y-BOCS: in adults, scores of 14, 26 and 35 may indicate the lower limits of moderate, moderate-severe, and severe symptom intensity, respectively[113]. Increasing symptom severity is generally associated with increasing levels of disability. Severity of symptoms is one of several important clinical factors that should be considered when discussing treatment choices and sequencing with OCD patients[69]. Some guidelines indicate that severity is relevant to choosing between pharmacotherapy and psychotherapy (e.g., with psychotherapy a first line of intervention in mild OCD, and pharmacotherapy employed when patients are unable to undergo CBT)[114], but other guidelines indicate that pharmacotherapy and psychotherapy may be used irrespective of the level of symptom severity in OCD[69].

In PTSD, the assessment of symptom severity may be challenging, as a comprehensive evaluation requires systematic enquiries about multiple symptoms in different domains. The most widely used symptom severity measure is the CAPS-5[60], which comprises 30 items assessing symptom severity over the previous week. PTSD patients with severe symptoms may have more difficulty in tolerating CBT. However, intensive outpatient programs in which PTSD patients are seen daily may increase retention rates to over 90%[115,116], with associated decreases in both PTSD symptoms and suicidal ideation[117].

NEUROCOGNITION

Neurocognition represents one of the key mechanisms by which changes in brain structure and function ultimately give rise to clinical signs and symptoms. Lying closer to the putative biological substrate and being measurable on objective tests, neurocognitive markers may be more reliable, consistent and enduring than the variably expressed symptoms of a disorder[118-120]. Neurocognitive testing in patients with OCD and related disorders, for example, has been used to characterize abnormalities of fronto-striatal circuitry compared to controls[121], as well as to identify putative subtypes with different brain structure, function and connectedness[122].

Clinical assessment of neurocognition in anxiety and related disorders has been given impetus by the development of more reliable neurocognitive tasks with adequate specificity and sensitivity for domains of relevance to these conditions, as well as by technological advances such as delivery via the use of concise computerized batteries that are relatively cheap and easy to apply with little burden on patients or staff. Such testing may support evaluation and diagnosis, and may also be used to monitor the impact of treatment (although some neurocognitive deficits do not appear to change when symptoms respond to intervention, representing candidate vulnerability markers which also occur in asymptomatic first-degree relatives of such patients)[8,123].

Cognitive assessments are more commonly used in OCD than in other anxiety and related disorders. In a systematic review and meta-analysis of candidate biomarkers for OCD, only cognitive measures showed convincing or highly suggestive supportive evidence (class 1 or 2 evidence)[124]. Furthermore, assessment using standardized self-report tools such as the Cognitive Assessment Instrument of Obsessions and Compulsions (CAIOC-13)[125], a 13-item scale, shows a wide range of functional deficits in OCD which are thought to be derived from cognitive difficulties that interfere with many aspects of daily life. As these deficits are easily overlooked, a recent expert survey recommended routine cognitive-functional assessment using scales such as the CAIOC-13

in the clinical assessment for patients with OCD[126].

In the future, the hope is that neurocognitive testing may be used for detecting cases of anxiety and related disorders even prior to the onset of symptoms[126], and to predict treatment response *a priori*, improving overall outcomes[124]. Assessment of cognitive inflexibility is likely to be of particular value for predicting treatment outcomes in OCD. However, confirmatory evidence remains highly preliminary, with only a few small studies of OCD showing overall or differential response to pharmacotherapy or CBT depending on the degree of cognitive flexibility on set-shifting tasks[127].

FUNCTIONING AND QUALITY OF LIFE

Assessing functioning and quality of life in patients with anxiety and related disorders is important for several of the reasons discussed in the earlier section on symptom severity. First, the impact of the disorder on these domains helps determine whether standard outpatient management is to be used, or more intensive approaches are required. Second, assessing functioning and quality of life is part of measurement-based care; there is good evidence that treatment of anxiety and related disorders improves these domains[128]. Third, guidelines for treatment of anxiety and related disorders may be based in part on the degree of functional impairment. Although symptom severity, functional impairment and quality of life demonstrate significant correlations, it is important to note that in any particular patient they may not be entirely aligned, and hence each construct needs to be independently assessed[129,130].

According to the World Health Organization, quality of life is an individual's perception of his/her position in life in the context of the culture and value systems in which he/she lives and in relation to his/her goal, expectations and concerns. So, the assessment of quality of life can be distinguished from the measurement of functional impairment and symptom-related disability by its focus on the subjective experience of satisfaction with current functioning and the accompanying sense of general well-being.

The assessment of quality of life should ideally embrace both generic and specific measures, to maximize sensitivity and generalizability. However, studies in anxiety disorders, PTSD and OCD have largely employed generic instruments. The Sheehan Disability Scale[131], the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[132] and the Medical Outcomes Study 36-item Short Form Health Survey (SF-36)[133] have been most commonly employed, with the EuroQoL (EQ-5D)[134] and the Quality of life Inventory (QOLI)[135] also used. Disorder-specific scales include the CAIOC-13[125] for OCD and the Veterans Rand 12 Item Health Survey (VR-12) for PTSD[136].

Some clinical guidelines for treatment of anxiety and related disorders have focused on functional impairment. In the NICE guidelines for OCD, for example, low intensity psychological treatment is suggested for patients with mild functional impairment (or when a patient prefers this type of treatment), whereas SSRIs or more intensive CBT are suggested in the case of moderate functional impairment[137].

PERSONALITY TRAITS

Among the "classic" traits from the five-factor (Big Five) model of personality, neuroticism – which refers to negative emotionality, or the persistent tendency to readily experience strong negative emotions – has shown the most robust association with anxiety[138]. Neuroticism has been linked to increased symptoms of general anxiety, as well as symptoms of OCD, panic disorder, phobias, PTSD, and social anxiety disorder. According to the tripartite model of Clark and Watson[139], neuroticism is a core risk factor shared across anxiety and depressive disorders, with the added component of anxious arousal being more specific to anxiety conditions, and anhedonia being more characteristic of depression[140].

In a clinical context, understanding the patient's degree and history of negative emotionality as a vulnerability factor could help contextualize the initial onset and maintenance of anxiety symptoms. If neuroticism is impacting current coping and functioning, for example by exacerbating anxiety and related distress, its levels can be reduced through psychological therapies based on acceptance-based and cognitive-behavioral approaches that specifically target responses to negative emotions[141].

Another Big Five personality trait, extraversion – which refers to sociability and the tendency to draw energy from interacting with others – has clinical relevance for understanding certain anxiety disorders, including agoraphobia, specific phobia, and social anxiety disorder[138]. Social anxiety has been found to correlate genetically with decreased extraversion, but not with neuroticism[142]. Knowledge of a patient's level of extraversion could be particularly beneficial in informing the treatment of social anxiety, for example the selection of a hierarchy of social exposures.

Patients with generalized anxiety tend to present with higher than average levels of conscientiousness[143], another Big Five personality trait. High conscientiousness may raise both opportunities and challenges for treatment adherence in the course of psychotherapy for an anxiety or related disorder: it may result in higher levels of therapeutic homework completion, but also more worry and preoccupation around assigned practices or tasks. In the latter case, clinical reasoning suggests that explicit discussion around realistic expectations and normalizing incremental progress may be helpful. High levels of conscientiousness can also flag the possibility of an underlying obsessive-compulsive personality disorder, and the potential value of treatments developed for this condition[144].

Some literature has indicated that the Big Five personality traits are best considered in combination when it comes to understanding anxiety, with higher levels of extraversion and conscientiousness linked to lower risk of anxiety disorders among individuals with high neuroticism[145]. Consistent with this, higher levels of conscientiousness have been linked to more rapid recovery from negative emotional information in adults[146], perhaps buffering the effects of neuroticism.

Thus, a clinician may consider where a patient with anxi-

ety falls along multiple personality domains. If a patient demonstrates high neuroticism but low conscientiousness, he/she may be at particularly risk for emotion regulation difficulties, and thus benefit from adjunctive strategies to improve emotion regulation, such as those from dialectical behavior therapy. By contrast, a patient with high neuroticism but also high extraversion and conscientiousness may benefit from standard strategies such as cognitive restructuring or exposure. However, further research is needed to establish whether treatment recommendations can be guided by assessment of the Big Five traits.

In terms of how a clinician should evaluate personality traits in an anxious patient, assessment of the Big Five traits has been the subject of growing attention, and a number of validated scales, such as the NEO Personality Inventory-3[147] and the Big Five Inventory-2[148], are available. However, because these scales are relatively lengthy, clinicians may find it useful to select the most relevant subdomains – such as neuroticism – for assessment, or use brief personality trait scales (e.g., the Ten-Item Personality Measure[149]) with trade-offs of precision and reliability. In assessing personality, clinicians should keep potential bidirectional influences between reported personality traits and anxiety outcomes in mind, as the presence of an anxiety or related disorder may impact the experience and reporting of neuroticism over time[150].

Importantly, each of the Big Five personality traits has been posited to consist of "facets" that could further prove useful for understanding the development and maintenance of symptoms in anxiety patients. For example, recent efforts to probe personality facets within neuroticism have identified five potential subdomains, including anxiety, depression, anger proneness, somatic complaints, and envy[151]. Nuanced assessment of personality facets may point to specific intervention targets that could be productive in the course of psychotherapy, such as addressing somatic issues with mind-body strategies, or anxiety sensitivity with cognitive-behavioral techniques.

Finally, personality traits may manifest in the form of personality disorders as outlined in the DSM-5. In particular, Cluster C personality disorders may be overrepresented in patients with anxiety disorders: these include avoidant personality disorder (characterized by social inhibition and sensitivity to rejection); dependent personality disorder (characterized by separation anxiety and passive behavior); and obsessive-compulsive personality disorder (characterized by strong need for order and control). Cluster C personality disorders that co-occur with anxiety and related disorders may complicate treatment, for example by interfering with treatment engagement in the case of avoidant personality or leading to excessive reliance in the case of dependent personality. These personality disorders can be assessed using the Personality Inventory for DSM-5 (PID-5)[152].

ANTECEDENT AND CONCOMITANT PSYCHIATRIC CONDITIONS

Many persons suffering from an anxiety or related disorder will experience a comorbid psychiatric condition during their life[153]. Anxiety disorders are relatively central in the multidimensional domain of psychopathology[154], and high levels of comorbidity between these disorders and other mental disorders have been consistently reported, especially with depression. As noted earlier, some view anxiety and depressive disorders as expressions of a common internalizing psychopathology, that may be further divided into fear (e.g., panic, phobia) and distress (e.g., GAD, PTSD, depression) disorders[155].

Some authors have expressed concerns that comorbidity may be an artifact of our current diagnostic systems[156], being better viewed as a reflection of the severity and/or magnitude of the underlying problem rather than as the co-occurrence of distinct clinical entities. Such a perspective may emphasize the importance of measuring transdiagnostic constructs such as neuroticism, as above. Notably, in the DSM-5, the presence of panic attacks is now used as a generic specifier (e.g., social anxiety with or without panic attacks), and may be useful in signaling severity across different disorders.

The median age of onset of anxiety disorders is earlier than many other psychiatric disorders, leading to the question of how far anxiety disorders are antecedents of comorbid conditions. In the World Mental Health Surveys, a very early median age of onset (7-14 years of age) was found for separation anxiety and specific phobia, while GAD, panic disorder and PTSD had a much later age of onset (24-50 years of age). Still, in the majority of comorbidity pairs, anxiety disorders are either concurrent or antecedent to the other disorder. The clearest pattern is seen regarding specific phobia: in 75% of comorbidity pairs, specific phobia is antecedent[153]. From this perspective, early recognition and treatment of anxiety disorders may be key for preventing subsequent psychiatric morbidity[157]. Future research is needed to determine whether treatment of specific phobia, a particularly important marker of internalizing psychopathology, prevents the onset of later psychiatric conditions[158].

Several diagnostic interviews can be used to assess comorbidity. The SCID-5 is useful, but its administration takes about 90 min and requires considerable training. The MINI is quicker to administer, but has the disadvantage of being entirely structured. The DSM-5 includes "cross-cutting" symptom measures which may be helpful in screening for a range of comorbid conditions. The Psychiatric Diagnostic Screening Questionnaire (PDSQ)[159] covers multiple psychiatric disorders, including mood, anxiety, substance abuse, eating and somatoform disorders.

In individuals with an anxiety or related disorder, identifying other psychiatric conditions is key in personalizing management. If the two conditions are judged to be independent, then both are likely to require condition-specific treatments. If interdependent, five principal models come into play[6].

First, a sequential model: for example, in a patient with social anxiety disorder and a substance use disorder, stabilizing the substance use disorder may be the priority before addressing the anxiety disorder. Second, a hierarchically-weighted model (a single treatment may address an underlying factor such as neuroticism, and so improve comorbid conditions): for example, an SSRI and/or CBT may be of benefit for comorbid states of anxiety and depression. Third, a severity-weighted model (treatment of a primary anxiety condition might correct any secondary condi-

tions or consequences): for example, if panic attacks lead to agoraphobia, then targeting the panic attacks may be the first step towards managing the agoraphobia. Fourth, a "motivational bypass" model: for example, an individual with a borderline personality disorder leading to severe anxiety may not be motivated to undergo psychotherapy, but may be willing to take medication for anxiety, which may also have a positive impact on impulsive personality traits. Fifth, a risk management model: for example, if an individual with PTSD has developed a substance use disorder and is displaying severe aggression, then hospitalization and other relevant strategies that target patient and family safety may be an immediate priority.

While there is a substantial evidence base on the treatment of anxiety and related disorders, and a growing evidence base on the management of patients with comorbidity, any particular patient requires individualized assessment, weighing up of possible causal models, and clinical judgment to address these optimally.

PHYSICAL COMORBIDITIES

Anxiety and related disorders may arise as a consequence of a physical disorder, be an antecedent of a physical disorder, or be a co-occurring phenomenon.

A broad range of physical disorders may lead to or exacerbate anxiety symptoms, with some evidence of specificity across the anxiety and related disorders. Thus, for example, there are important causal associations between respiratory conditions and panic disorder[87], and it has been suggested (though also disputed) that there are causal links between panic disorder and a range of physical conditions, including mitral valve prolapse[160] and joint hypermobility[161]. Furthermore, there has been particular attention to the causal role of traumatic brain injury in PTSD[162], and to the causal role of some infections in OCD[163].

The majority of studies on the physical comorbidity of anxiety disorders are focused on cardiovascular disease. A meta-analysis showed that persons with a lifetime diagnosis of anxiety disorder have a 60% increased risk of cardiovascular disease onset[164]. Notably, the risk of an anxiety condition increases substantially after an acute illness event, e.g. an acute myocardial infarction. The awareness of the illness event may play a major role, as "silent" myocardial infarction (in which the person is not aware of the cardiac event[165]) is not followed by an increased risk of anxiety disorders, contrary to manifest infarction. Post-myocardial infarction anxiety is in turn associated with negative cardiovascular consequences[166].

Despite considerable attention to the association between anxiety disorders and cardiovascular disease, causality in the association remains to be proven. Perhaps even more important, the association is not specific, as anxiety disorders are associated with a whole range of physical disorders, with hazard ratios in the range of 1.17-1.73 for ten condition groups and between 1.13 and 2.40 for the individual conditions[167]. The strength of the association of anxiety disorders with cardiovascular disease is only in the middle of that range. In other words, the over-specific focus on the comorbidity of anxiety disorders with cardiovascular disease is not warranted, and attention should be extended to other physical conditions.

Given the lack of specificity in the associations of anxiety disorders with physical diseases, we emphasize the importance of screening for and evaluating physical disorders in all patients with anxiety and related disorders, and of paying particular attention to the possibility that physical conditions play a causal role in anxiety and related disorders, particularly in patients with unusual or refractory presentations[168]. More specific recommendations regarding assessment of physical conditions have been provided for depression, which is often comorbid with anxiety and related disorders[6]. These recommendations are consistent with a general emphasis on the integration of mental health into the care of non-communicable diseases, including the identification and management of modifiable risk factors such as tobacco use, unhealthy diet, physical inactivity, and harmful use of alcohol[169,170].

Clinicians should consider how a patient's particular anxiety symptoms may affect the interfaces with physical health care settings. For example, anxiety might lead to patients not seeking help for physical health symptoms, or make it hard for them to attend medical appointments. On the other hand, certain anxiety concerns (e.g., health anxiety) may lead to repeated presentations in particular medical settings where over-investigation can lead to reinforcement of underlying anxiety-related concerns. In these circumstances, measures such as the Short Health Anxiety Inventory[171], and treatments that specifically target health anxiety[172] may be appropriate.

When pediatric acute-onset neuropsychiatric syndrome (PANS) is suspected as the cause of OCD symptoms, a comprehensive psychiatric and physical assessment is required[163], and specific immunotherapies may be considered in addition to standard OCD treatments[173]. Given the high rates of co-occurrence of PTSD and traumatic brain injury, screening for this condition in patients with PTSD may be recommended: there is a growing literature demonstrating that existing treatments for PTSD are efficacious in this population[174], but additional targeting of brain trauma symptoms may be appropriate. Assessing and treating obstructive sleep apnea may improve management of PTSD.

In general, the presence of physical comorbidities requires specific treatment targeting. This may include interventions focused on particular illnesses as well as on healthy lifestyles. Notably, there is growing evidence that engaging in physical activity protects against anxiety symptoms and disorders[175]. Evidence for the efficacy of aerobic exercise – as well as for a range of complementary and alternative medicine approaches – in the management of anxiety and related disorders remains, however, preliminary[176,177].

FAMILY HISTORY

Anxiety and related disorders are known to run in families, and the clustering of anxiety conditions among related individuals, ranging from GAD to OCD, phobias and panic disorder, is well documented in clinical and population-based samples[178].

Knowledge of family history – where possible including the

specific relatives affected, their relationship to the patient, the age of onset and course of the disorder – may inform the clinician's understanding of the patient's presenting condition and help the patient to contextualize his/her current and past challenges with anxiety.

Meta-analytic data indicate that having a first-degree relative with any anxiety disorder may increase a person's odds of developing an anxiety disorder by four- to six-fold. This risk may be similarly elevated regardless of whether the first-degree relative is a parent, sibling or child, suggesting that systematically inquiring about a range of family members may be most informative. This familial aggregation of clinical anxiety has been attributed in large part to genetic factors, with twin studies indicating heritability of anxiety conditions of 30 to 40%[178].

Studies have suggested disorder-specific patterns of familial transmission, in which a family history of a particular anxiety or related disorder is more strongly linked to heightened risk for that same disorder rather than other anxiety disorders or psychopathology more broadly. Where relevant, this disorder specificity can be informative for making a differential diagnosis of anxiety conditions, as a reported history of multiple family members with a given disorder may point to a similar diagnosis to be considered. This specificity has been demonstrated for OCD, panic disorder, social anxiety disorder, and in some cases GAD[179].

Obtaining a family history from adult patients themselves is the most straightforward approach, but such information can also be gleaned from family members when available. Research comparing direct interview with family member reports has indicated satisfactory agreement between informants. Data suggests that, when individuals positively endorse a family history of an anxiety or related disorder in one or more of their relatives, this information can be considered reliable; however, clinicians should keep in mind that it is possible for individuals to be unaware of anxiety and other psychiatric conditions in their relatives, and reporting may be biased by various patient characteristics[180].

Multiple informants have been recommended for optimum accuracy, but this may be challenging in standard clinical contexts. Relatively brief screening tools for family psychiatric history, such as the Family History Screen[181], have been designed to take 5 to 20 min and may be more feasible.

Importantly, a positive family history has not only been associated with the lifetime development of an anxiety or related disorder, but also with meaningful clinical outcomes. For example, a prospective cohort study showed that family history of an anxiety disorder, defined as the weighted proportion of first- and second-degree members in the family with a positive history of any such disorder, was associated with greater recurrence of anxiety and worse functioning, as well as greater service utilization, across adulthood[182]. Thus, assessing family history can inform prognosis and guide the formulation of follow-up treatment plans.

If a family history of an anxiety or related disorder is identified, it would seem appropriate to determine whether specific medications have been useful in the affected relative. However, to date there is little evidence of a high concordance of medication response in members of the same family. A family history of tics may point to the potential value of augmentation with dopamine antagonists in OCD, but further research is needed to validate this clinical suggestion.

EARLY ENVIRONMENTAL EXPOSURES

A broad range of early environmental exposures have been examined in relation to anxiety and related disorders. These include perinatal complications, season of birth, socioeconomic status, parental rearing practices, infections, and traumatic brain injury. Studies have been characterized by methodological limitations, and conclusions remain tentative[183-185]. Nevertheless, a number of early environmental exposures should be specifically assessed, as they may influence treatment planning.

First, there is growing evidence that acute onset of obsessive-compulsive symptoms in childhood may sometimes be due to streptococcal infections (i.e., autoimmune neuropsychiatric disorders associated with streptococcal infections, PANDAS) or to a broad range of other insults (i.e., PANS). As noted earlier, when PANS is suspected, a comprehensive psychiatric and physical assessment is required[163], and augmentation of standard treatments with specific immunotherapies may be considered[173].

Second, a growing evidence base supports an association between early childhood adversity and subsequent anxiety and related disorders. Examples include physical and sexual abuse[186,187], parental separation[188] and emotional maltreatment[189]. More childhood and adolescent major adversities predicted the subsequent onset of anxiety disorders over the next several years in a sample of late adolescents[190]. Data from the World Mental Health Surveys indicate that eradication of childhood adversities would lead to a 31% reduction in anxiety disorders[191]. A range of questions continue to be explored in the literature, including associations of different types of early adversity with anxiety, the timing of early adversity, causal mediators between such adversity and subsequent anxiety, and associations of early adversity with different features of anxiety.

Given the importance of this association, assessing the history of childhood adversity should be part of a comprehensive evaluation of patients with an anxiety or related disorder. As discussed in relation to depression, a number of key issues must be kept in mind when assessing early adversity in a patient with anxiety[6]. First, reports of adversity are largely subjective, and there is the possibility of recall bias. Second, it is important to explore not only the events that occurred, but also key aspects of the subjective experience and meaning assigned. Third, personality and sociocultural background may influence both the experience and reporting of early adversity. Obtaining a history of childhood adversity that also includes a focus on coping and resilience may be useful in helping to address these issues.

The Childhood Experience of Care and Abuse (CECA)[192] is a comprehensive interview measure for the assessment of childhood adversity. It allows for detailed collection of information, but is time-consuming to administer, requires interviewer train-

ing, and information on its clinical utility is limited. Several shorter self-report questionnaires have been used in research settings and can be considered in clinical practice. These include a shorter self-report questionnaire based on the CECA (CECA.Q)[193] and the Childhood Trauma Questionnaire (CTQ)[194]. The short form of the CTQ has 28 items, assessing five domains of childhood adversity: emotional neglect, physical neglect, emotional abuse, physical abuse, and sexual abuse.

A number of measures are available for assessing the parenting patterns of early caregivers. The Young Parenting Inventory (YPI) has been used in schema therapy and provides a useful way of assessing early parenting styles, and how these might be related to an individual's early maladaptive schemas[195]. The inventory has 72 items that retrospectively assess perceived parenting experiences in respect of each key caregiver. This measure is designed to be used in conjunction with the Young Schema Questionnaire (YSQ)[196], which assesses eighteen early maladaptive schemas.

Although much of the potentially relevant evidence base is from work on depression[6], the presence of early adversity may impact treatment planning for anxiety and related disorders in a number of ways. First, the presence of early adversity may be associated with premature treatment termination, perhaps because of a weaker therapeutic alliance. Particular attention to shared decision-making in such cases would seem appropriate. Second, specific evidence-based psychotherapies developed for patients with childhood adversity, such as trauma-focused treatment, can be considered. Third, it is possible that early adversity is associated with a reduced response to treatment, pointing to the need for robust management.

RECENT ENVIRONMENTAL EXPOSURES

A broad range of environmental stressors are associated with increased rates of anxiety and related disorders[197]. These include minority status (especially linked with risk for PTSD, which has been attributed to experiences of discrimination and exclusion), income insecurity, unemployment, homelessness, natural hazards, armed conflict, crime and displacement.

Individuals exposed to childhood adversity are more vulnerable to anxiety and related disorders from proximal stressors (i.e., stress sensitization). For example, data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) indicated that the magnitude of influence of past-year stressful life events upon risk of anxiety disorders and PTSD was amplified by a history of childhood adversity, especially three or more childhood adversities[198]. This pattern was moderated by gender, in that fewer major life stressors were necessary to trigger stress sensitization in liability for PTSD in women compared to men.

Data from twin studies indicate that almost all types of environmental stress are genetically influenced (for example, a genetic propensity for risk-seeking may lead to increased exposure to dangerous environments)[199]. Evidence for diathesis-stress effects is weak thus far, with data from twin studies indicating none to modest interaction effects[200,201]. Genome-wide methods have produced promising initial effects: for example, a genome-wide polygenic score of emotional responsivity to the environment was found to interact with negative parenting to produce higher rates of anxiety-related symptoms[202].

Consideration of proximal life stressors is important in the assessment of anxiety and related disorders. Semi-structured interview measures include the Life Event and Difficulty Schedule (LEDS)[203], which assesses objective aspects of life events and chronic stressors, as well as the person's subjective experience of how threatening or disruptive they were. Another useful tool is the UCLA Life Stress Interview[204], which assesses both chronic and episodic stress and rates severity within the context of other life circumstances. Training is required for both interviews.

A range of self-rated checklist measures for assessing life events and chronic stressors may be suitable for use in clinical practice. These include the Psychiatric Epidemiology Research Interview Life Events Scale (PERI-LES)[205], the List of Threatening Experiences (LTE)[206], and the Questionnaire of Stressful Life Events (QSLE)[207]. All have good to strong psychometric properties. The PERI-LES lists 102 events, and has been widely used in epidemiological research. The LTE was specifically developed in order to be shorter; it assesses twelve recent life events that are associated with long-term threat. The QSLE was developed to cover the lifespan; it assesses eighteen life events that occur during childhood, adolescence and adulthood, noting the age at which they occurred and their impact. Perceived discrimination can be assessed using self-report questionnaires such as the Everyday Discrimination Scale[208].

Stressful life events and chronic stressors may impact clinical management in a number of ways. First, they may hamper self-management and adherence/response to medical care, especially when combined with high personal demands (such as school or job responsibilities)[209]. CBT homework practice, for example, may be completed less often as a function of multiple life stressors and, although cognitive and behavioral skill practice is important to overall success rates, understanding and allowance for personal impedances to practice is essential to continued treatment engagement.

Second, high levels of chronic stress can lead to persistent sensitization of the pituitary-adrenal and autonomic stress response[210], thereby contributing to the physiological and cognitive disruptions already present in persons with anxiety and related disorders. The combination of high arousal and attention deficits can interfere with attending to and encoding treatment-relevant information, whether it be about medications or cognitive and behavioral skills. Arousal regulatory strategies (e.g., breathing retraining, muscle relaxation, mindfulness training) may be of particular value for the person facing significant life stressors.

Third, for some individuals, traumatic experiences may warrant trauma-focused therapies targeting the intrusive and distressing memories and the behavioral and physiological consequences. On the other hand, understanding of contextual factors such as

neighborhood violence can moderate the therapeutic approach to traumatization; for example, *in vivo* exposures to places that are reminders of the trauma will be contraindicated whenever there is a potential for re-traumatization.

Fourth, understanding of recent life stressors can guide tailoring of psychological treatment. For example, patients with panic disorder sometimes report histories of medical trauma in themselves or other family members that prime their fearful response to bodily sensations. Understanding those medical traumas can help the clinician to tailor cognitive restructuring about personal risk or design exposures most effectively[211]. Similarly, patients with social anxiety disorder who were recently laid off from work may experience elevated perceptions of rejection, and that information can inform tailoring of cognitive skill practice.

PROTECTIVE FACTORS / RESILIENCE

Protective and resilience factors can be generally grouped as individual trait characteristics or environmental supports, although the two are likely to interrelate for reasons of "support generation", as individuals with resilient traits may self-select into supportive environments and conduct their lives in ways that increase support.

Extraversion is an individual trait shown to function as a protective factor for anxiety disorders (see above). One aspect of extraversion is positive affect such as happiness, joy, interest, excitement, confidence, and alertness; this has been shown to promote flexibility in thinking and problem solving, reduce the physiological effects of negative emotions, build enduring social resources, promote effective coping strategies and create upward spirals of improved emotional well-being[212].

High levels of trait positive affect functioned as a protective factor in predicting lower rates of anxiety disorders prospectively, and as a protective factor in buffering the effects of stressful life events upon the risk for social anxiety disorder[213]. Related traits that have shown to reduce the risk for anxiety disorders in adolescents include optimism, perceived competence, and self-esteem[214].

In a review of protective factors for anxiety disorders among adults in the general population, individual characteristics of physical activity and coping styles (ways of responding to perceived stressors) were also highlighted[215].

Supportive interpersonal environments may act as a protective factor for anxiety. Interpersonal relationships are presumed to promote well-being by increasing social contacts and interactions as well as access to resources. The protective function of social support for anxiety has been demonstrated in different risk contexts, including childhood adversity[216]. Social support is also associated with reduced risk for anxiety disorders prospectively[214,217] and can mitigate the development of PTSD following exposure to trauma. Given the role of financial strain in anxiety[197], it is not surprising that employment is robustly associated with reduced symptoms of depression and anxiety and decreased suicide risk, especially among men[218-220].

A comprehensive clinical interview for patients with anxiety and related disorders should cover protective factors and resilience. As described in the case of depression[6], the acronym SOCIAL can guide questioning of key protective factors; Social resources, including friends, groups and social influence; Occupation (paid or not); Children and family; Income and sources of material resources; Abilities, appearance, health, time and other personal resources; and Love and sex in intimate relationships[221]. More in-depth questioning around these topics can gauge the personal and environmental strengths to be reinforced and potentially leveraged throughout the treatment process (e.g., engaging a supportive partner in aspects of cognitive behavioral skills practice) as well as the areas of weakness to be improved upon.

There are a number of standardized scales to measure various aspects of resource and protection. Trait positive affect can be measured using the Positive Affect Scale of the Positive and Negative Affective Schedule (PANAS)[222], a widely used 20-item tool. Self-esteem can be assessed using the Rosenberg's Self-Esteem Scale[223], a ten-item scale of overall self-worth or self-acceptance. An alternative to these would be the Patient-Reported Outcomes Measurement Information System (PROMIS)[224] scales for meaning and purpose (the sense that life has purpose and there are good reasons for living, including hopefulness, optimism, goal-directedness, and feelings that one's life is worthy), positive affect (feelings that reflect a level of pleasurable engagement with the environment, such as happiness, joy, excitement, enthusiasm, and contentment), and self-efficacy (the confidence in ability to deal effectively with a variety of stressful situations), all of which have short forms.

A number of self-report scales of perceived resilience, broadly construed, have been developed[225], and parallel those recommended for use in the clinical management of depression. These include the Connor-Davidson Resilience Scale[226], a 25-item measure of personal competence, tenacity, trust in one's instincts, tolerance of negative affect, acceptance of change, secure relationships and spiritual influences, that is sensitive to treatment change. A shortened 10-item version of this scale may be more practical[227]. The Brief Resilience Scale comprises only six items and measures ability to bounce back from life stressors[228].

A large number of scales measure social support. Examples include the Multidimensional Scale of Perceived Social Support[229], a 12-item measure of perceived support from family, friends and significant others. Another option is the Medical Outcome Study Social Support Survey[230], that measures emotional/informational support, tangible support, affectionate support, and social interaction. In addition, the PROMIS[224] scales include measures of companionship, emotional support, informational support, and instrumental support, all with short forms available.

Coping skills can be measured using the Ways of Coping Checklist[231]. Albeit lengthy (66 items), this scale measures thoughts and acts that people use to deal with the internal or external demands of specific stressful encounters. A briefer alternative is the Brief Coping Orientation to Problems Experienced inventory[232] (28 items), which assesses problem-focused coping (e.g., active coping, planning, suppression of competing activities, restraint coping, and seeking of instrumental social sup-

port) and emotion-focused coping (e.g., seeking of emotional social support, positive reinterpretation, acceptance, denial, and turning to religion). These scales provide insight into the type of coping skills, some of which are adaptive and can be reinforced, while others are maladaptive (e.g., wishful thinking, denial) and can be the target of intervention.

Understanding of protective factors, or lack thereof, can guide clinical management in a number of ways. First, those protective factors already present can be reinforced, encouraged and leveraged in treatment. For example, supportive significant others can be incorporated into the treatment process, such as when significant others co-learn cognitive-behavioral skills and facilitate *in vivo* exposure practices for patients with agoraphobia[233]. Supportive family members may be similarly helpful partners for patients with OCD or PTSD as they engage in exposure and response prevention of avoidance or rituals, with care to correct over-accommodation on the part of the family member (e.g., complying with patient requests to wash excessively due to fears of contamination), since such accommodation inadvertently reinforces avoidance behavior[234]. Positive affect can be a facilitator of exposure therapy for phobias[235].

When protective factors are lacking, they can become the target of intervention. In essence, CBT builds greater protection through coping skills for managing internal (i.e., symptoms of anxiety) and external stressors. Building more robust social support networks can become a particular target of intervention, especially when anxious avoidance behavior has diminished social connection and support. Low levels of positive affect can be targeted directly through newer psychological interventions designed specifically to improve reward sensitivity[236,237], with initial results showing effectiveness in both anxious and depressed patients, albeit in need of replication. Mindfulness based practices also improve positive affect[238].

DYSFUNCTIONAL COGNITIVE SCHEMAS

Anxious people display hypersensitivity in recognizing, processing and responding to threat-related information even in the absence of actual threat. Biases towards threat occur within processes of attention and appraisal.

Attentional biases mean that anxious individuals have a tendency to be easily distracted by potential threats at the expense of attending to other, perhaps more important, features of the environment[239]. In clinically anxious groups, the attention bias is often specific to their focus of apprehension (e.g., socially anxious individuals show an attention bias to detect social dangers, whereas individuals with GAD show a broader attentional bias to physical and social threats). Attention biases involve a number of components, ranging from sensory-perceptual processes (early processing and detection of stimuli), to attentional control (ability to attend to some stimuli and ignore others), memory (maintenance and retrieval of information) and executive function (complex integrative and decision-making processes).

Furthermore, anxious individuals tend to show slowed disengagement from threat-relevant stimuli. A particular type of bias in attentional engagement occurs with respect to interoceptive cues. Interoceptive awareness (or awareness of internal bodily states) has been studied mostly in the context of panic disorder, but is elevated in other anxiety disorders as well[240,241]. Notably, heightened awareness of bodily states is not synonymous with heightened accuracy, which may contribute to errors in symptom reporting and misappraisals of threat.

Anxious individuals are likely to position themselves at various points along the continuum of attentional bias, with some showing more bias in initial detection, others showing more bias at the stage of disengagement, and others still showing more strategic avoidance[242,243]. Such attentional biases likely underlie the common complaints of distractibility and poor concentration in persons with GAD and in phobic individuals as they face their feared situations.

Alongside attentional biases toward threat, anxious individuals interpret ambiguous stimuli in a threat-laden manner[244,245]. Attentional biases likely influence interpretation of threat, which in turn is presumed to influence attention to threat. Interpretation biases are most directly observed in response to ambiguous stimuli, such as interpretations given to the meaning of ambiguous sentences.

As with attentional biases, interpretation biases tend to be specific to the foci of apprehension. Thus, persons with panic disorder are more likely to resolve ambiguous stimuli related to physical sensations in a threat-congruent fashion, whereas persons with social anxiety disorder tend to interpret ambiguous social events as more negative, and mildly negative social events as more catastrophic than other anxious patients or controls. Individuals with high trait anxiety or GAD tend to interpret ambiguous events in general as threatening[20].

Aside from disorder-specific interpretation biases, anxiety sensitivity is relevant to most anxiety disorders, although especially panic disorder, and refers to a tendency to interpret anxiety *per se* as harmful physically, socially or mentally[246]. Anxiety sensitivity has been shown to be both a predictor of subsequent anxiety symptomatology and a correlate that contributes to the persistence of anxiety disorders. It is responsive to cognitive, behavioral and pharmacological interventions[246].

Many of the research instruments for evaluating attentional bias are not suitable for clinical practice. Online or web-based programs for attentional bias modification (described below) typically include tests of attentional bias before training, and these may therefore be available. More practical are standardized self-report scales that measure aspects of engagement and disengagement from threat-relevant stimuli. One example is the 20-item Attentional Control Scale[247], assessing attention focusing and shifting.

The Interpretation Questionnaire[248] assesses individuals' interpretation of ambiguous social scenarios. This questionnaire comprises twenty-two ambiguous scenarios (e.g., "You see a group of friends having lunch, they stop talking when you approach") and three interpretations of each scenario (i.e., positive: "They are about to ask you to join"; negative: "They were saying negative

things about you"; and neutral: "They just ended their conversation"). Participants are asked to rank how likely each interpretation would come to mind if they were in a similar situation.

For OCD, the Obsessive Beliefs Questionnaire[249] is a 44-item measure of cognitive biases that lead to misinterpretation of normally occurring intrusive thoughts as threatening. The Multidimensional Assessment of Interoceptive Awareness-2 (MAIA-2)[250] is a state-trait questionnaire with thirty-seven items to measure multiple dimensions of interoception by self-report. The Anxiety Sensitivity Index-3[251] is an 18-item scale with three subscales representing physical concerns (e.g., death, faint), cognitive concerns (e.g., loss of control) and social concerns (e.g., embarrassment) about anxiety and related symptoms.

Cognitive biases towards threat are directly targeted through CBT for anxiety disorders. Psychoeducation, the initial therapeutic strategy, typically includes information designed to correct mistaken beliefs particularly about anxiety symptoms. Cognitive restructuring teaches skills for identifying overestimates of danger and ways of balancing estimates with more evidence-based interpretations. Exposure therapy targets prediction error correction (i.e., violation of negative expectancies) through direct experience. High levels of threat misappraisal may suggest the need for CBT, although there is insufficient evidence for matching the treatment approach (medication vs. CBT vs. other psychotherapies) to such cognitive biases. In fact, one study has shown that higher scores on anxiety sensitivity predicted poorer response to both CBT and medications for panic disorder[252].

Bias modification programs have emerged as a more specifically targeted treatment for cognitive biases. The attention training technique[253] consists of auditory attentional exercises that require individuals to engage in executive control skills including selective attention, divided attention, and attention switching, in order to lessen inflexible self-focused attention, threat-oriented attention biases, and worry and rumination. This technique has demonstrated efficacy for anxiety disorders[254]. Attention bias training (i.e., training attentional bias away from threat-relevant stimuli towards neutral or positive stimuli by reinforcing dot probe selection) and interpretation bias training (i.e., training to interpret ambiguous scenarios in a neutral or positive manner by reinforcing word selection) have also gathered evidence. However, while such training has robust effects upon attentional or interpretation bias *per se*, studies tend to show small effect sizes on anxiety symptoms in clinical samples[255,256].

Understanding cognitive biases is relevant to pharmacotherapy approaches as well, particularly when patients judge their bodily sensations to be indicative of injury or danger, which can lead to excessive fears of medications and their side effects. Graduated approaches to medication may be advised in these scenarios.

Threat-laden cognitive biases can subtly influence the ways in which information is received and encoded, such that what are benign comments from the clinician can be easily misunderstood to involve threat to the patient. Care in presenting information, taking the patient's biases into account, may be beneficial.

There is some evidence that change in cognitive biases mediate therapeutic outcomes, especially for social anxiety disorder[257-259] and panic disorder[64]. Hence, lack of change in cognitive processes may be an indicator of poor treatment response and the need to reevaluate the treatment approach. Evidence regarding cognitive mediation of pharmacotherapy for anxiety disorders remains nascent.

DISCUSSION

This paper has aimed to describe systematically important domains that are relevant to the personalization of management of anxiety and related disorders. Careful assessment of anxiety symptoms to ensure appropriate clinical diagnosis is key, given that the majority of the evidence in this area is based on trials of specific disorders. However, there is growing work supporting the view that the assessment of other domains is also useful in clinical decision-making.

Taken together, the evidence suggests that we are beginning to be able to move from simply recommending that anxiety and related disorders are treated with SSRIs, CBT, or their combination, to a more complex approach which emphasizes that the clinician has an increasingly broad array of management modalities available, and that treatment of anxiety and related disorders can start to be personalized in a number of important respects.

This review of what is currently known, as well as of key areas for future research, seems timely and valuable for a number of reasons. First, it is consonant with a growing re-emergence of interest in the establishment of a personalized psychiatry, and with similar reviews in other important areas of psychiatry[6,260]. Second, it resonates with systematic work on identification of treatment outcomes, and may help identify variables for potential inclusion in complex predictive models, including machine learning approaches[261,262]. Third, the literature suggests a number of clinically feasible measures, including self-report scales, that can potentially be included in future observational or intervention research. Fourth, the review identifies a number of scales that can begin to be employed by clinicians in practice, as they attempt to personalize treatment of anxiety and related disorders, recognizing that additional research is needed to validate their use.

A number of potential criticisms of our approach here deserve discussion. First, it may be argued that clinicians are already aware of the heterogeneity of anxiety and related conditions. While this is certainly true, there is a lack of systematic efforts to provide the clinician with practical ways of assessing such heterogeneity. Second, it may be argued that use of formal assessments is not practical or efficacious in standard clinical practice. However, even if clinicians do not always formally rely on diagnostic criteria, the introduction of a reliable nosological system has usefully impacted clinicians' approach to assessment, and there is a growing evidence base suggesting the value of routine outcome monitoring[106,107]. Third, it may be argued that ultimately a translational neuroscience approach is needed to optimally personalize the management of anxiety and related disorders.

Our aim is certainly not to downplay the importance of such work, but rather to argue that refinement of clinical assessment can usefully contribute to both neurobiological and interventional work in the future.

A key issue that emerges from this and similar reviews is the abundance and complexity of available relevant measures. This abundance presents a number of important problems for the field[263]. First, even if clinicians agree on the importance of assessing a particular construct, the use of different instruments may lead to disagreements about findings. Second, measures may yield information that is difficult for clinicians to interpret, and may therefore reinforce a view that clinical judgment is more helpful than clinical measures. Third, the use of a range of metrics may impede communication between clinicians and consumers, making shared decision-making more difficult. The review here is consonant with calls in the field to develop common metrics[264], to agree on core outcome sets[265,266], and to harmonize measurement results[263].

It may be instructive to compare existing work on personalized approaches to depression and anxiety[6]. At first glance, it seems that the field of depression is much more advanced, with more evidence available on a range of important domains and how these can be used to personalize treatment. By contrast, major depression is an enormously heterogenous condition, whereas some anxiety and related disorders appear more homogeneous. Although no particular anxiety or related condition has received as much attention as depression, the recognition of specific anxiety and related conditions has created the opportunity for more fine-grained work on each of these disorders, and subtyping of specific conditions has contributed towards personalization of management.

Clearly, much further work needs to be done to achieve a detailed and evidence-based approach to the personalization of interventions for anxiety and related disorders. Hierarchical models of self-reported symptoms such as the Hierarchical Taxonomy of Psychopathology (HiTOP) model[155], or the tri-level model of depression and anxiety[267,268], provide useful frameworks for understanding genetic, neurobiological and environmental risk factors and symptom covariation patterns. In the future, it would be useful for clinical trials to include not only anxiety diagnoses and symptom severity, but also more detailed assessment of symptomatology (e.g., evaluation of specific behaviors, physiological parameters, and cognitive appraisals), as well as of the range of other domains reviewed here. Such work will hopefully strengthen the personalization of treatment for anxiety and related conditions.

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DOI:10.1002/wps.20919

Psychiatric symptoms and cognitive impairment in "Long COVID": the relevance of immunopsychiatry

Although precise estimations of the absolute risk are still difficult to provide, it is clear that depression and anxiety are predominant symptoms in post-acute COVID-19, and that they are more pronounced in patients who have been hospitalized for COVID-19 than in those hospitalized for other respiratory tract infections[1]. Also, cognitive impairment has been reported in several people who have had symptomatic COVID-19 infection, which can manifest as difficulties with concentration, memory, receptive language and/or executive function[1]. Psychiatric symptoms and cognitive impairment can develop and persist months after the infection and are therefore part of what is called the "Long COVID" condition, of which fatigue is another paramount manifestation.

The development of depression and anxiety symptoms and of cognitive impairment after COVID-19 may partly be the result of somatic, functional or psychosocial consequences of the disease. Coronaviruses can also induce cognitive, emotional, neurovegetative and behavioral dysregulation due to direct neurological injury through hypoxic damage and neuroinvasion. In addition to this, the systemic immune activation seen in COVID-19 can contribute significantly to the mental health toll even months after the initial disease.

COVID-19 disease has been characterized as a cytokine release syndrome[2]. Elevated serum concentrations of interleukin-6 and other inflammatory cytokines are hallmarks, and correlate in a dose-response manner with respiratory failure, adverse respiratory distress syndrome, and other clinical outcomes. Immuno-inflammatory dysregulation can contribute importantly to acute and post-acute psychiatric and cognition symptoms in COVID-19 patients.

To illustrate, various lines of research indicate a link between immune activation and depression. First, manipulation of the immune system through endotoxin, interferon-alpha or typhoid vaccine interventions induces sickness behavior involving depressive symptoms such as fatigue, low mood and hypersomnia. Second, large-scale studies confirmed that persons with auto-immune conditions, e.g. rheumatoid arthritis, or with inflammation-inducing conditions, e.g. obesity, have an increased risk to subsequently develop depression. Third, meta-analyses of biomarker studies indicate that levels of inflammatory markers, including cytokines – such as tumor necrosis factor, interleukin-1 beta and interleukin-6 – and acute phase proteins – such as C-reactive protein (CRP) – are significantly elevated in depressed patients compared to healthy controls. Low-grade systemic inflammation has also been shown to induce robust pathophysiological abnormalities in the endocrine systems of stress and arousal regulation that further augment neuroimmune reactivity. In addition, human and animal studies indicate that peripheral immune activation is able to induce brain inflammation, and increased inflammatory responses have been indeed reported in post-mortem brain samples of depressed individuals.

Moreover, large-scale genome-wide DNA and RNA studies indicate that depressed persons have more genetic variants and enriched gene expression pathways involved in immune signaling. Such genetic pleiotropy between immuno-inflammatory dysregulation and depression may indicate a genetic vulnerability that might partly explain why persons with a mood disorder history have a higher risk of unfavorable COVID-19 disease outcomes as compared to persons without a psychiatric history[3]. Finally, anti-inflammatory medication approaches have demonstrated efficacy in reducing depression symptoms.

Of note, findings suggesting a pathophysiological link to the immune system have also been reported for other dimensions relevant to COVID-19, such as cognitive impairment and fatigue. In a population-representative cross-sectional analysis of >40,000 adults, a higher CRP level was associated with poorer executive functioning, which was especially true in the presence of depression and even existed in early adulthood[4]. Longitudinally, high levels of inflammatory markers have been linked to long-term cognitive decline, involving deterioration of memory and executive function[5]. A proteome-wide association study of older-adult brain donors indicated increased inflammation in brains of cognitively impaired persons as compared to those of cognitive stable persons[6].

For fatigue, illustration of immune system involvement comes most strongly from studies of chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME), a condition characterized by persistent, unexplained fatigue that is not alleviated by rest. Although CFS/ME has long been indicated as a mystery illness, recent studies suggest that inflammation is central to its pathogenesis in at least a considerable proportion of patients, as suggested by higher levels of inflammatory markers that show a dose-response relationship to disease severity[7].

If even low-grade systemic immune activity increases the risk of depression, cognitive impairment and fatigue, it is obvious that we need to be aware of the role that immune activation can play in the mental health consequences of COVID-19, which involves a massive cytokine storm. A dose-response relationship has been indeed documented between the severity of immune-inflammatory dysregulation in COVID-19 patients and depressive symptomatology three months later[8]. The same study also reported that high baseline inflammation load in COVID-19 patients predicted neurocognitive impairment – involving reduced processing speed, verbal memory and fluency – after three months.

How long the impact of immune activation in COVID-19 patients persists remains to be clarified. However, for infections involving hospital contact, the maximum behavioral effects can take over a year post-infection to fully develop. This suggests that, next to the immediate impact, there may also be priming whereby immune activation triggered by infection (i.e., first hit) may progressively increase sensitivity to common pro-inflammatory stimuli (i.e., second hit), which include other mild infections,

concussions, airborne allergen and pollutant exposure, as well as psychosocial stressors.

Future research goals are to examine how to best monitor, prevent and treat psychiatric, behavioral and cognitive consequences of COVID-19. For clinicians treating depression in patients with SARS-CoV-2 infection, a thorough history and clinical examination are paramount. There is evidence that immune-inflammatory dysregulation is limiting the efficacy of antidepressants, as high plasma levels of CRP and interleukins have been found to be predictors of poor treatment response[9]. Consequently, whether antidepressants are effective in treating COVID-19-related depression deserves specific confirmation.

In the meantime, we can assume that any major advances in vaccines and antiviral treatments targeting SARS-CoV-2, as well as immune targeted therapies (such as anti-cytokines and cytokine receptor blockers), will not only prevent severe illness but also benefit the brain and mental health.

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DOI:10.1002/wps.20913

Learning from the global response to COVID-19 to accelerate innovation in mental health trials

The past two decades have seen an increasing recognition of the contribution of mental disorders to global disease burden. There has also been an awareness that therapeutic innovation based on sound understanding of disease mechanisms has evaded single companies working within a conventional competitive market-based model. Governments, charities and philanthropists are increasingly willing to fund research programmes, and several collaborative initiatives and networks have emerged in recent years. For example, we soon expect the launch of the Health Brains Global Initiative (https://www.hbgi.org), which aims to "address market failures by galvanizing new science and new finance to enable new life trajectories".

Those of us involved in brain health research have a responsibility to take this opportunity, but we need to identify clear objectives and priorities to ensure that we deliver real advances. Inspiration and exemplars can be drawn from many areas of collaborative science. An example is the global response to the COVID-19 pandemic, where, alongside the dreadful death toll and enormous human suffering, we have observed the extraordinary acceleration in research success that is possible when researchers and funders collaborate with shared purpose, and prioritize and coordinate their efforts.

The extraordinary response to COVID-19 has not emerged out of the blue. The global research community had learned from previous inadequate responses to infectious disease outbreaks and created the partnerships and platforms to ensure a state of preparedness for emerging epidemics. The International Severe Acute Respiratory and emerging Infection Consortium (https://isaric.tghn.org) was funded in 2011 to ensure a rapid clinical research response to epidemics. The Coalition for Epidemic Preparedness Innovations (https://cepi.net) was launched in 2017 with a mission to "stimulate and accelerate the development of vaccines against emerging infectious diseases and enable access to these vaccines for people during outbreaks".

What are the key areas in trial design and conduct that have delivered the vaccines? A key area has been the standardization of early phase clinical trials. Vaccine development is not alone here – the critical contribution of phase II trials in providing crucial go-no-go evidence at earlier phases of development (rather than waiting to discover lack of efficacy in highly costly phase III trials) has been recognized for almost two decades[1]. This is most effective when illness mechanism is understood and biomarkers/interim outcomes can be reliably linked to clinical outcomes. Hence, phase II vaccine trials assess immune response rather than clinical outcomes[2].

Pathogenetic understanding of mental disorders is still limited, but the tactic of reverse translation, investigating the effects of treatments of known efficacy on biomarkers, has been productive. For example, antidepressant drugs have rapid effects on emotional bias, and this is a useful experimental measure of potential longer-term therapeutic effect[3]. Emotional bias is now used frequently in early phase studies as an indicator of longer-term clinical benefit of putative antidepressants.

An additional striking feature of the COVID-19 vaccine development has been the disruption of the standard linear sequential approach. Phase II/III trials have been planned and set up – using efficient combination designs – while preliminary studies were just getting underway. We have previously suggested that a non-linear, iterative approach might also be of benefit in drug development in psychiatry[4].

The COVID-19 pandemic also provides an excellent example of the power of embedding a highly simplified, randomized trial platform comparing available and licensed medicines in real world settings. The RECOVERY trial was rapidly designed and set up in March 2020[5]. It randomized over 35,000 patients by February 2021. By that time, it had demonstrated the benefits of dexamethasone

and tocilizumab and, equally importantly, the lack of benefits of hydroxychloroquine, lopinavir-ritonavir and azithromycin in patients hospitalized with COVID-19. The speed and power of the results obtained from a trial of extreme simplicity, with a single-minded dedication to maximizing recruitment across a health system, are impressive.

By radical simplification of procedures to minimize patient and clinician burden, RECOVERY has provided an example of a sustainable rolling trial platform which allows the sequential evaluation of multiple agents. The simplicity and speed of RECOVERY did not come at the cost of sacrificing quality or the short-cutting of ethical or regulatory oversight. Instead, the RECOVERY investigators worked closely with both the ethics committees and the UK regulator in parallel with setting up the trial, achieving a hitherto unimagined speed of trial set-up.

I believe that we urgently need to apply the lessons learned from RECOVERY in mental health trials. We have previously identified the potential for large, streamlined trials in mental health[6], although this approach remains unusual. One exception is the BALANCE trial comparing long-term treatments in bipolar disorder[7]. In this trial, we did radically simplify procedures and achieved a reasonably sized sample with a clear primary outcome. Building on the example of RECOVERY, we now need to scale up trials such as BALANCE by an order of magnitude to allow multiple arms and deliver strong evidence of modest (but worthwhile) treatment effects.

There is no shortage of important clinical questions that need answering via large-scale, streamlined, directly randomized studies. As with RECOVERY, we should initially focus on comparative efficacy of existing, licensed interventions, adding more innovative treatments once the platform is up-and-running. A prime illustrative example is the comparative efficacy of antidepressant drugs. A network meta-analysis reported that there are potentially clinically important differences between 21 available antidepressants, but that nearly all the comparative data are indirect and based on pre-regulatory approval trials[8]. This is a major gap in the evidence base and a substantial barrier to knowing which antidepressant might be most likely to be effective for any specific patient – the goal of precision psychiatry[9].

Large-scale, streamlined trials should be designed in partnership with a broad range of stakeholders, including patients, regulators and industry, and recruiting a broad range of patients from routine clinical settings. Large-scale recruitment can be facilitated by using electronic health records. Progressing this idea using the momentum and learning from RECOVERY seems to be an outstanding opportunity for mental health clinicians, researchers and patients, and needs to be supported by funders.

Finally, the COVID pandemic helps to clarify the relative strengths of randomized and observational studies. Early on, considerable publicity was given to small, uncontrolled reports of the potential benefits of hydroxychloroquine. A report of routinely collected observational data seemed to confirm this, only to be quickly retracted. RECOVERY found no benefit of hydroxycholoquine in severely ill patients, although there remains the possibility that it might be effective in very early or mild cases. This demonstrates the danger of retrospective analyses of data of uncertain provenance as well as the power of large simple randomized controlled trials.

On the other hand, observational data of infection rates following vaccinations were hugely reassuring, given the remaining uncertainties around vaccine efficacy in specific patient subgroups. Observational data can extend and confirm the results of randomized trials, which will always remain smaller and less representative. These data are increasingly available via electronic care records and, although susceptible to residual confounding even after multivariate propensity score matching, may be very valuable for post-marketing safety surveillance and confirmation of treatment effects in larger, more representative datasets.

In conclusion, despite the human tragedy and suffering, the COVID-19 pandemic has inspired some outstandingly creative responses from the international research community. We need to capture this and apply it to the major global challenge of mental illness, building on the developing international collaborative efforts. We should draw inspiration from just how much can be achieved so quickly with a clearly defined objective and common sense of purpose and urgency.

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DOI:10.1002/wps.20918

Metacognition in psychosis: a renewed path to understanding of core disturbances and recovery-oriented treatment

Consistent with early definitions of schizophrenia as marked by a fragmentation of thought, emotion and desire[1], psychosis is currently understood as involving deep disturbances in the sense that persons have of themselves and their connection with the world[2]. Though endemic across psychosis[3], it has remained unclear how to operationalize and measure the processes which underlie and sustain these alterations in self-experience.

One challenge for empirical research is that the sense anyone has of him/herself, given its intimacy, immediacy and elusiveness, is not easily measured. Validated assessments, for example,

of the oddness of thinking, thought disorder, reasoning biases, or the inaccuracy of judgments do not capture how people amidst psychosis experience their purposes, possibilities, and life trajectories differently[4].

Nevertheless, it is possible to evaluate processes that underlie the subjective disturbances that characterize psychosis. The sense anyone has of him/herself is enabled by the integration of experience. A sense of oneself in the world is made possible by the active synthesis of discrete experiences into a larger sense in which the relationship of those discrete experiences lends meaning to one another[2].

One line of research has proposed that metacognition is a process whose disruption could result in alterations of self-experience in psychosis[2]. Metacognition, across disciplines, refers to the awareness of one's own thoughts and behaviors, and the ability to therefore monitor and alter behavior[5]. Applied to subjective experience in psychosis, an integrative model has conceptualized metacognition as a spectrum of activities that range from awareness of discrete cognitive, emotional and embodied experiences to the synthesis of those experiences into a broader awareness of the self, others and one's place in the community[4].

Metacognition, in this integrated model, extends beyond isolated judgments, and involves processes that enable awareness of and reflection upon experience in socially situated and intersubjective contexts[6]. It allows for persons to have available, in a given moment, the kind of sense of self, others, and emergent challenges necessary to adaptation and cooperation with others[2].

Applied to psychosis, this model has offered several significant advances. First, it has been accompanied by the development of a tool for measuring metacognitive capacity as a continuous variable: the Metacognitive Assessment Scale Abbreviated (MAS-A)[4]. The MAS-A differentiates metacognitive capacity according to its focus on the self, others, one's community, and the use of metacognitive knowledge. It provides subscales corresponding to these four dimensions. Higher scores on each subscale reflect a sense which involves greater levels of the integration of information, while lower scores quantify more fragmented experiences[4].

With adequate psychometric properties, the MAS-A has allowed for quantitative studies of subjective experience in psychosis internationally[2,4,6]. Relatively greater metacognitive deficits have been detected in adults diagnosed with multiple phases of psychosis compared to healthy controls, people with non-psychiatric medical adversity, and others with less severe psychopathology.

Illuminated in these studies are qualities of how individuals experience themselves as they seek to make sense of what has happened to them and what they need. Results of these studies indicate, for example, that many individuals with psychosis are able to identify discrete embodied, cognitive and emotional states, but struggle to form a coherent sense of self in which these experiences are cohesively related to one another. Thus, we are afforded a chance to dimensionally measure the experience of fragmentation which may compromise chances of the experience of oneself as an active agent in the world with coherent possibilities and purposes.

The link of these alterations to disturbances in daily life are confirmed empirically by findings that graver metacognitive deficits within psychosis are linked to concurrent and prospective decrements in psychosocial functioning, including social behaviors, negative symptoms, and relatedly intrinsic motivation. Research has also found that changes in metacognition accompany changes in other aspects of function[2].

This work may offer an even more substantial advance as it goes beyond the recognition of a new variable affecting psychosocial functioning in psychosis. Contemporary research has affirmed that complex arrays of social and biological factors create and sustain psychosis[7]. Metacognition not only allows for the study of psychosis as multidetermined, but it offers a view of an underlying process that links social, biological and psychological phenomena in a fluidly interacting network which culminates in any number of possible outcomes.

As supported in a recent network analysis[8], metacognitive capacity may act as a central node in a complex array of heterogenous neurocognitive domains and symptoms in psychosis. In such a network, metacognitive capacity may deeply influence outcome, not only directly, but also via its influence as a node connecting and affecting the relationships among different biopsychosocial elements. Metacognition thus allows for a larger nuanced picture of the forces which shape psychosis, moving from genetics and basic brain function to socio-political issues, to phenomenology of the unique suffering, history and possibilities of a person diagnosed with psychosis.

Finally, maybe most plainly, if deficits in metacognition leave persons unable to make sense of and manage experiences that accompany psychosis, then treatment which ameliorates these deficits may open unique paths to recovery. Here, there are implications for both the general principles of recovery-oriented management as well as the development of unique treatment approaches.

Concerning the common elements of recovery-oriented management, metacognitive research suggests that, in order to promote a personal awareness and approach to managing psychosis, treatment has to be intersubjective in nature and emphasize joint meaning making rather than primarily offering clinician-directed approaches to symptom reduction and skill acquisition[2].

One intervention specifically developed on the basis of this work, metacognitive reflection and insight therapy (MERIT)[9], is an integrative treatment which is responsive to patients' level of metacognitive capacity and explicitly seeks to promote the growth of this capacity over time[6]. With promising initial empirical support[9], this operationalized treatment stands as an example of an innovation that may uniquely address the loss of persons' sense of themselves and promote self-directed recovery.

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DOI:10.1002/wps.20914

The evolving nosology of personality disorder and its clinical utility

There has been increasing consensus that the classification of personality disorder in the DSM-IV and ICD-10 was no longer fit for purpose. There was no good evidence that there are nine to eleven discrete personality disorder categories, the system was too complex, and most categories were not used. The evidence pointed toward the dimensional nature of personality disturbance, with severity being the strongest determinant of disability and prognosis[1].

It was therefore not surprising that the American Psychiatric Association in the DSM-5 and the World Health Organization in the ICD-11 moved toward dimensional models of personality disorder classification. The DSM-5 Work Group proposed a model that included an evaluation of severity (Criterion A) and a description of 25 traits (Criterion B) which were organized into five domains, as well as six individual personality disorders based on DSM-IV categories. The proposal was rejected, but published in the DSM-5 Section III and labelled the Alternative Model of Personality Disorders. Despite not being part of the official classification, the model has acquired an acronym – AMPD – and has received multiple studies evaluating its utility and validity.

The ICD-11 model also involves a dimensional measure of severity (mild, moderate and severe personality disorder) and a subsyndromal condition called "personality difficulty". Once severity has been determined, the personality dysfunction can be further delineated using one or more of the five trait domains labelled negative affectivity, detachment, disinhibition, dissociality and anankastia. The model does not retain traditional personality types, with the exception of a borderline specifier[2].

Research on the AMPD model progressed rapidly once a self-report instrument, the Personality Inventory for DSM-5 (PID-5), was developed. This instrument demonstrated adequate psychometric properties, including a replicable factor structure, convergence with existing personality instruments, and expected associations with clinical constructs[3]. Contradicting the beliefs of the DSM-5 Committee that the AMPD model lacked clinical utility, clinicians reported that the model demonstrated stronger relationships to ten of eleven clinical judgments than the DSM-5 categories[4].

Due to its more recent development, the ICD-11 model has received less clinical scrutiny. However, studies generally report good construct validity and test/retest reliability[5]. Five domains also appear to be the best fitting model for traditional personality disorder symptoms, although the anankastia, detached and dissocial domains may be more clearly delineated than the negative affective and disinhibition domains[6].

It has been documented that the AMPD traits (measured using the PID-5) can describe the ICD-11 trait domains[7]. Despite being derived independently, the AMPD and ICD-11 share four of the five domains; the exceptions are anankastia in the ICD-11 and psychoticism in the AMPD. Both models show relative continuity with traditional personality disorder categories and capture most of their information. The ICD-11 model is superior in capturing obsessive-compulsive personality disorder, whereas the DSM-5 model is superior in capturing schizotypal personality disorder[8].

In addition, both models show some continuity with dimensions of personality in the general population, measured using the Five Factor Model. Negative affectivity is linked with neuroticism, detachment with low extraversion, disinhibition with low conscientiousness, and dissociality with low agreeableness. The ICD-11 anankastia is linked with high conscientiousness, while AMPD psychoticism does not particularly align with any of the five factors[8].

On the face of it, both new models seem more "true" to the existing evidence about personality pathology than the DSM-5 official classification. Yet, the most important rationale for making such a paradigm shift – the development and evaluation of treatments – has not yet been subjected to significant study. It should be noted that there is little justification for retaining the old model of personality disorder classification regardless of how the new model performs. Only borderline personality disorder has an evidence base, and this essentially tells us that a host of treatments are similarly effective and none have shown specific efficacy for this disorder as opposed to general psychological distress and dysfunction[9].

Nevertheless, treatment studies using the new classification are urgently needed. A number of frameworks have been put forward which, on the basis of a careful assessment of severity and trait domains, lead to a coherent and holistic formulation which is usually shared with the patient and results in the adoption of a consensual approach to treatment[9].

A potential problem is the retention of traditional personality disorder categories in both models. In the AMPD model, six individual personality disorders are retained. Since non-personality disorder specialist clinicians generally only use three diagnoses (borderline personality disorder, antisocial personality disorder, and personality disorder not otherwise specified), a danger is that they will simply continue with their current practice. The ICD-11 model only retains one personality disorder – the borderline personality disorder specifier – but its inclusion may also compromise the change to more evidence-based practice. While the old categories have no scientific underpinnings, their familiarity may

hinder clinicians embracing the new classifications.

In summary, the changes in the classification of personality disorder represent the beginning of a paradigm shift in diagnosis. The ICD-11 and AMPD are reasonably consistent with each other. Both place severity of personality disorder at the centre of diagnosis, as the evidence suggests. Both have dimensional trait domains consistent with models of personality such as the Five Factor Model. Both seem to be understood and preferred by clinicians. It is unfortunate that in both models the need has been felt to cling on to traditional categories. The complexity that this created in the AMPD model may be a part of the reason why it was rejected by the DSM-5 Committee. The ICD-11 Committee felt the need to compromise with a borderline specifier in order not to suffer a similar fate[2].

The ICD-11 personality disorder classification is now official and will be required to be used in many countries from January 2022. Whether and when the AMPD, or some form of it, becomes official is unclear. It is hoped that clinicians will see the new classifications as useful and that their use will lead to greater understanding of the concept of personality disorder, resulting in better clinical care.

The importance of personality in the treatment of psychiatric disorders (and physical disorders for that matter) is obvious in most studies which have measured it. Yet, personality is often an afterthought in clinical practice, given to patients when things go awry. If personality pathology can be recorded with relative ease (through brief questionnaires and interviews) and we can let go of traditional categories, then it is my view that its utility in planning and predicting the outcome of treatment will become self-evident.

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DOI:10.1002/wps.20915

"Third-wave" cognitive and behavioral therapies and the emergence of a process-based approach to intervention in psychiatry

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For decades, cognitive and behavioral therapies (CBTs) have been tested in randomized controlled trials for specific psychiatric syndromes that were assumed to represent expressions of latent diseases. Although these protocols were more effective as compared to psychological control conditions, placebo treatments, and even active pharmacotherapies, further advancement in efficacy and dissemination has been inhibited by a failure to focus on processes of change. This picture appears now to be evolving, due both to a collapse of the idea that mental disorders can be classified into distinct, discrete categories, and to the more central attention given to processes of change in newer, so-called "third-wave" CBTs. Here we review the context for this historic progress and evaluate the impact of these newer methods and models, not as protocols for treating syndromes, but as ways of targeting an expanded range of processes of change. Five key features of "third-wave" therapies are underlined: a focus on context and function; the view that new models and methods should build on other strands of CBT; a focus on broad and flexible repertoires vs. an approach to signs and symptoms; applying processes to the clinician, not just the client; and expanding into more complex issues historically more characteristic of humanistic, existential, analytic, or system-oriented approaches. We argue that these newer methods can be considered in the context of an idiographic approach to process-based functional analysis. Psychological processes of change can be organized into six dimensions: cognition, affect, attention, self, motivation and overt behavior. Several important processes of change combine two or more of these dimensions. Tailoring intervention strategies to target the appropriate processes in a given individual would be a major advance in psychiatry and an important step toward precision mental health care.

Key words: Process-based approach, cognitive behavioral therapy, third-wave therapies, processes of change, cognition, affect, attention, self, motivation, overt behavior, precision mental health care

(World Psychiatry 2021;20:363–375)

For a field to progress over the long term, it needs to distinguish clearly its purposes from its strategies, so that new strategies can be adopted when progress bogs down in important areas. Such is the current situation in modern mental health science and practice. By virtually every metric, the incidence and prevalence of mental health problems is increasing worldwide, and our approaches to producing improvement are being challenged. Depression is now the number one cause of disability around the world[1] and rates of common mental health struggles have increased rapidly, especially among the young[2].

At the same time, biomedical treatments are becoming more generic rather than more specific, and effect size improvements for both psychosocial and biomedical interventions are minimal or absent[3]. Concern over side effects and unhealthy physiological opponent processes fostered by the long-term use of common classes of psychoactive medications is growing[4]. Full genomic mapping of hundreds of thousands of persons is failing to support a prominent role of genes in the etiology of common mental conditions[5].

In the context of such challenges, it is wise for the field to refocus on its purpose. If it does so, a large body of work is currently available to guide a new strategic approach.

Intervention science in psychiatry has long sought an understanding of human suffering that is based on the identification of functionally important processes of etiology, development, maintenance and change, so as to help individual clients achieve their goals through targeted and person-sensitive empirical methods. That long-term purpose of scientific analysis has been implicit in the entire field of mental health over the decades, but the strategies for getting there have differed across disciplines and eras. At times these strategies have disguised that ultimate purpose so thoroughly that researchers and providers have virtually forgotten why common practices exist.

In this paper, we briefly review the history of the research and practical program of the cognitive and behavioral therapies (CBTs). Both the cognitive and behavioral wings of CBT began with a person-specific process orientation, which has once again become a central focus as the idea that mental disorder can be classified into distinct, discrete categories has been largely disproved. This transition has been fostered by the so-called "third wave" of CBTs, which has raised a number of new underlying processes of change.

The field appears to be ready to move toward person-focused, evidence-based care models that target core change processes based on testable theories instead of latent disease entities that are moved by evidence-based intervention protocols. If we recognize the opportunity this moment presents, an alternative analytic agenda is available that can help our field, broadly defined, to address its central purpose more effectively.

THE LATENT DISEASE MODEL OF PSYCHIATRY

In traditional psychiatric nosology, the individual's presenting problems and observable characteristics are organized into the "syndromes" that define his/her mental disorder. A syndrome is a set of signs (things the practitioner can see) and symp-

toms (things people complain about) that tend to co-occur. As a set, they are seen as the possible expressions of a latent disease. In other words, it is assumed that people likely share the same syndrome because these sets of signs and symptoms are produced by the same underlying etiological causes, expressed in a characteristic mechanistic course over time, that can be altered in known ways. This is reflected in our everyday language. For example, we often say that a person "has depression" or that she is "suffering from an anxiety disorder", just as somebody "has the flu" or "is suffering from diabetes".

A syndromal strategy is topographical (in the sense that formal differences are its proximal focus), but its purpose is functional. The hope is that a focus on signs and symptoms will ultimately lead to useful categories that will "carve nature at its joints" (a phrase that has been attributed to Plato) by revealing disease entities with known processes of origin, development, maintenance and change. If these can be identified, treatments can then target these underlying disease processes in an increasingly effective manner.

The "clinical utility" of diagnostic categories is the pragmatic end state that in principle validates the entire nosological enterprise. The DSM-5 is clear about this ultimate goal: "The diagnosis of mental disorders should have clinical utility: it should help clinicians to determine prognosis, treatment plans, and potential treatment outcomes for their patients"[6]. The assumption on which this strategy is based, however, is that collections of signs and symptoms reflect similar latent disease processes. If such processes exist but can lead to a myriad of forms, or a myriad of processes can lead to similar forms, the syndromal strategy to reach clinical utility will likely fail, because in such cases topography is poorly linked to underlying processes. If processes of change are normal, they likewise cannot be adequately construed as diseases, latent or otherwise. Aging, for example, is not itself recognized as a disease, even though many processes of aging are known.

Earlier versions of the DSM pursued models of latent disease processes more directly by adopting theories and principles that were popular at the time, and then linking categorization to those ideas. The first two editions of the DSM were heavily grounded in psychoanalytic theory. Until the DSM-III, it was assumed that mental disorders would be shown to be rooted in deep-seated conflicts that needed to be identified and resolved. At a meta-theoretical level, this view was fully consistent with a latent disease model.

Recently, psychodynamically-oriented clinicians have attempted to resurrect this strategy with the notion that personality disorders are at the core of all mental disorders. To complement the DSM, psychodynamically-oriented clinicians developed the Psychodynamic Diagnostic Manual (PDM-2)[7]. The goal is to describe people regarding their personality characteristics, the adequacy of their mental functioning, and the patterns of symptom formation they may show, with particular attention to how they are experiencing these symptoms. The PDM-2 assumes that disorders are embedded in the client's personality structure and manifest in ways that vary with each person's functioning capacities. This too is fully consistent with a latent disease model.

THE ERA OF BEHAVIOR THERAPY

At the same time of the early days of the DSM, an alternative model had considerable impact. The first generation (or "wave") of behavior therapy targeted psychological problems largely based on the idiographic application of behavioral principles to specific cases. While agreeing that private events were legitimate targets of scientific analysis, Skinnerian behaviorism emphasized observable and quantifiable behaviors and their roles in altering the external environment, in part based on the belief that overt behavior, thoughts and feelings were all reflections of the same sets of overt contingencies. It was argued, for example, that the same aversive experiences could lead to fear, thoughts regarding that painful history, or overt attempts to escape or avoid[8]. All of these psychological actions were believed to be reflections of the same history and thus, while all were argued to be scientifically legitimate[8], there was no *requirement* to do the harder work of addressing private experiences over the analysis of overt action. Metaphorically, Skinner opened the door to a scientific analysis of thoughts and feelings but gave no reason to walk through it.

This "direct contingency" functional analytic approach still exists in classic applied behavior analysis, which today is largely deployed for children with developmental disabilities. Early behavior therapists and behavior modifiers also added neo-behavioral principles drawn from associative or social learning to Skinnerian operant principles in an attempt to understand human problems[8-15]. For example, theorists such as Bandura argued that problems could be based on the internalization of social norms or models[9].

For both of these wings of behavior therapy and modification (behavior analytic and neo-behavioristic), traditional diagnostic categories were abstract concepts with little known practical purpose. Instead, early behavior therapists believed that diagnosis should be linked to the individual application of scientifically well-established basic learning principles, leading to the selection of applied methods that were well-specified and empirically tested. This dual commitment is shown in Franks and Wilson's famous definition of behavior therapy as consisting of interventions linked to "operationally defined learning theory and conformity to well established experimental paradigms"[13].

The divisions that existed within behavior therapy at the time, especially between neo-behaviorism and behavior analysis, were papered over by their common frustration with the excesses of psychoanalytic thought and diagnostic strategies based on it. Eysenck and Rachman once put it this way: "There is no neurosis underlying the symptom, but merely the symptom itself. Get rid of the symptom… and you have eliminated the neurosis"[14]. Behavior therapists of all kinds took seriously the bottom line of changes in target behaviors, not a questionable and constructed disease entity[15]. Psychoanalytic fears of re-emergence of symptoms due to underlying conflicts[14] largely failed to materialize[16,17].

Many of the learning principles that were being applied had been identified

through intensive laboratory analysis of small numbers of human or non-human subjects. This origin made it particularly easy for either wing of behavior therapy to maintain its focus on the clinicians' natural analytic agenda: application of knowledge to specific individuals with the purpose of creating analyses and treatment plans that would improve their outcomes. Early behavior therapy was always highly person-focused. Consider, for example, G.L. Paul's formulation of one of the most widely cited questions to guide psychological intervention researchers: "What treatment, by whom, is most effective for this individual with that specific problem, under which set of circumstances, and how does it come about?"[18].

This question encouraged clinical researchers to embrace a new scientific approach to therapeutic intervention. Specifically, Paul's question was intended to guide the field toward empirically supported treatments for specific psychological problem areas that fit the needs of the individual based on known processes of development, maintenance and change. Unlike traditional psychiatric nosology, no assumption of latent diseases was made – the processes involved might be relatively normal and only their combination or contextual sensitivity may be pathological. Despite these differences in assumptions, it should not be missed that, at a deeper level, there was a shared interest in the identification of clinically useful sets of processes that explained the origin, development, maintenance and change of human suffering.

Franks and Wilson's definition of the field shows how heavily the early days of behavior therapy relied on learning principles in a narrower sense, especially those drawn from the animal laboratory[13]. That emphasis contained a strategic assumption that the behavioral principles which applied to non-human animals comprised a relatively adequate beginning set from which to construct functional analyses that explained human suffering and human prosperity.

Well-developed theories of human cognition and emotion were only just forming, but, by the late 1970s, the limitations of a direct contingency approach caused attention to turn to them. Just as behavior therapy began to open up to a wider range of processes that might account for psychopathology, however, the DSM-III system and the funding stream it released began to capture the attention of CBT researchers and treatment developers. This had a significant impact on the strategic vision of the tradition.

THE "SECOND WAVE" OF CBT

Of all psychological treatment approaches, CBT aligned itself most closely to the psychiatric nosology of the DSM/ICD, even though the tradition from which it came was idiographic and process-focused, without any assumption of latent diseases. This dialectic is still the source of considerable controversy within CBT today.

The core premise of the second era (or "second wave") of CBT, as pioneered by A.T. Beck and A. Ellis among others, held that maladaptive cognitions contribute to the maintenance of emotional distress and behavioral problems[19,20]. According to Beck's model, these maladaptive cognitions include general beliefs, or schemas, about the world, the self and the future, giving rise to specific and automatic thoughts in particular situations[19]. The basic model posits that therapeutic strategies to change these maladaptive cognitions lead to changes in emotional distress and problematic behaviors.

The cognitive approach allowed for alternative interpretations of biological models, but a strength in the era of DSM was that they could be aligned with the medical illness model. CBT followed psychiatry by designing specific protocols for syndromes to be tested in randomized controlled trials. Mechanism and process research became somewhat of an afterthought. CBT protocols became increasingly specific, targeting specified DSM syndromes in line with the latent disease model.

A case in point is the story of panic disorder. The original conceptualization of this diagnosis was based on a medical disease model assuming the existence of distinct and mutually exclusive syndromes with an inherently organic etiology and specific treatment indications[21,22]. D.M. Clark introduced his cognitive model by referring to biological studies when he wrote: "Paradoxically, the cognitive model of panic attacks is perhaps most easily introduced by discussing work which has focused on neurochemical and pharmacological approaches to the understanding of panic"[23].

Clark's model conceptualized panic attacks as a consequence of the catastrophic misinterpretation of certain bodily sensations, such as palpitations and breathlessness[23]. An example of such a catastrophic misinterpretation would be that of a healthy individual perceiving palpitations as evidence of an impending heart attack. The vicious cycle of the cognitive model suggests that various external (i.e., a supermarket) or internal (i.e., body sensations or thoughts) stimuli trigger a state of apprehension if they are perceived as threatening: "For example, if an individual believes that there is something wrong with his heart, he is unlikely to view the palpitation which triggers an attack as different from the attack itself. Instead, he is likely to view both as aspects of the same thing – a heart attack or near miss"[23].

This model assumed that biological variables may contribute to an attack by triggering benign bodily fluctuations or intensifying fearful bodily sensations. Therefore, pharmacological treatments can be effective in reducing the frequency of panic attacks if they reduce the frequency of bodily fluctuations which can trigger panic, or if they block the bodily sensations which accompany anxiety. However, if the patient's tendency to interpret bodily sensations catastrophically is not changed, discontinuation of drug treatment is likely to be associated with a high rate of relapse.

In broad terms, this model has empirical support, and cognitive content is indeed known to impact syndromal signs and symptoms[24]. For example, panic patients who were informed about the effects of CO_2 inhalation reported less anxiety and fewer catastrophic thoughts than uninformed individuals[25]. Furthermore, panic patients who believed that they had control over the amount of CO_2 they inhaled by turning an inoperative dial were less likely to panic than individuals who knew that they had no control over it[26]. The cog-

nitive package that was deployed for panic disorder based on these cognitive ideas was easy to standardize and manualize, and there was relatively less need to link specific treatment components to specific individual functional analysis.

More detailed and methodologically adequate research on precisely how change happens was put off to another day and, as a result, CBT packages became more focused on syndromes than processes. Because of diminished need for precision, there was less of an effort to weed out unclear, inconsistent, and even contradictory theoretical and philosophical positions. The golden era of "protocols for syndromes" settled in, with a huge rise in CBT research and funding for CBT laboratories.

Close to 300 meta-analytic studies have examined CBT for a large range of DSM-defined problems, with the strongest support for anxiety disorders, somatoform disorders, bulimia, anger control problems, and general stress[27]. There is much to be proud of in this body of work. With its efficacy proven in many randomized controlled trials, often in comparison to the most effective medications, CBT helped countless people and saved many lives. This has led to the implementation of cost-effective health care policies in many developed countries around the world.

At the forefront currently is the UK initiative called Improving Access to Psychological Therapies (IAPT)[28]. This program has been highly successful: not counting dropouts and refusals, about one in two individuals using an IAPT program for depression, anxiety or other mental health problems recover, and as many as two in three show considerable improvements[29]. At the same time, the relative strength of outcome evidence allowed the assumption that the role of cognitive and emotional content is determinative in psychopathology to cover the open questions about the processes of change underlying CBT strategies. Given the relative success and body of evidence for CBT, these open questions seemed to be a small price to pay.

In the context of the hegemony of syndromal diagnosis, increasingly narrowly focused interventional packages and protocols were assembled within CBT. These fostered ever more fractionated domains of expertise and led to difficulties for students and professionals to consider the progress of the field in a fully cohesive fashion.

THE "THIRD WAVE" OF CBT

Underneath the surface, a set of concerns gathered in the late 1990s and early 2000s, that began to shine a light on the need for both theoretical and philosophical development within the behavioral and cognitive tradition. These included empirical issues such as the unexpected relative success of more narrowly focused and overtly behavioral methods in comparison to full CBT protocols, such as modern forms of behavioral activation in the treatment of depression[30]; the unexpected results from large component analysis studies of CBT[31,32] in which cognitive components were not found to be key to outcomes; and the unexplained response to CBT protocols in early sessions, before putatively critical elements within the model were presented[33]. They also included inconsistent evidence of change processes using measures derived from traditional theoretical models[34,35]. In all of these areas there were counterarguments to be made[36], but the point is that matters that were considered well-settled within CBT were now unexpectedly under scrutiny.

At the same time, the dominance of elemental realist (or "mechanistic") assumptions were challenged by well-known CBT researchers who took a more functional and contextualistic philosophical stance[37,38]. Most traditional CBT models assumed that psychopathology and its treatment could be thought of as being the result of sets of parts, relations and forces that were ontologically preexisting, and thus needed to be modelled much as a machine would be modeled by a construction diagram. In contrast, some CBT researchers began to embrace constructivist assumptions – a more purely descriptive form of philosophical contextualism[38,39] in which the very nature or meaning of events could only be appreciated in their historical and situational context, and in the light of the purposes of scientific analysis itself.

It gradually became clear that some differences within the family of CBT interventions reflected differences in *a priori* assumptions and philosophy of science in such areas as units of analysis or truth criteria[37]. For a contextualist, abstraction of a psychological action required understanding and appreciation of its history and purpose, because the unit of analysis was always the "act-in-context". For an elemental realist, an action and its nature could seemingly be appreciated alone and apart, much as a part taken from a dissembled machine can be examined while sitting on the kitchen table. For instance, for a mechanist, "anxiety" could be viewed as a negative emotion based on its form, frequency or intensity; for a contextualist, across a wide range of forms, frequency or intensity, anxiety could be said to function negatively or positively with reference to its context of occurrence[40].

These different foundational assumptions of "third-wave" CBT methods penetrated the clinical methods they produced and led to a rapid rise of new processes of change that focused on the *function* of cognition and emotion, over and above their form *per se*. For example, instead of trying to change the form, frequency, or situational sensitivity of so-called "negative" emotions or thoughts, as might be done in traditional CBT, "third-wave" methods more frequently targeted the relationship of the client to his/her own experience. A variety of process-oriented models and sets of methods emerged within "third-wave" CBT, including dialectical behavioral therapy (DBT)[41], mindfulness-based cognitive therapy (MBCT)[42], meta-cognitive therapy (MCT)[43], functional analytic psychotherapy (FAP)[44], acceptance and commitment therapy (ACT)[45], modern forms of behavioral activation[46], and several others[47].

The initial shock of the "third wave" has now passed[37,47]. CBT is currently a broader umbrella term that includes different philosophical assumptions, targeted processes, intervention approaches and philosophies, living side by side. The more traditionally behaviorally oriented treatments place a greater emphasis on history and context as it bears directly on overt action. The more cognitively oriented treatments share the basic premise that mental disorders and psychological distress are

maintained by cognitive content. "Third-wave" methods come from both of these wings, but all focus on the person's relationship to his/her own experience.

The amount of research now available on "third-wave" methods is so extensive that it is not possible to characterize it adequately via individual studies, nor even via individual meta-analyses. Just in the area of ACT, there are currently over 420 randomized controlled trials[48] and about 80 meta-analyses[49], covering a wide variety of topics, from mental health to physical health, sport, social change, and high performance.

Some of the "third-wave" methods are as good in terms of outcomes as gold-standard traditional CBT, but research has shown that such a "horse race" question is the wrong one to ask, because different moderators predict different outcomes. Just as one cannot focus on main effects statistically when significant interactions are found, so too it is simply wrong to compare packages in an overall fashion when moderation is regularly present.

Consider for example a series of studies from M. Craske's laboratory at University of California, Los Angeles (UCLA) comparing traditional CBT vs. ACT in people with anxiety disorders. In a study of CBT-based exposure versus ACT-based exposure[50], the focus on "which package is better" initially suggested that ACT was superior on blind clinical ratings from post-treatment to follow-up. Studies soon followed, however, showing that this conclusion would be misleading, because moderation analyses showed a more complex picture. For example, those with anxiety issues alone did better with traditional CBT, while those with both anxiety and depression issues did better with ACT[51]. Several additional studies by the same team identified other significant moderators: for example, in a group of mixed anxiety disorders, ACT was better for those with initial high levels of behavioral avoidance[52], while CBT was better for persons with social phobia if they had very high levels of initial psychological inflexibility[53].

In the context of regular patterns of significant moderation, a question such as "which is better" between "second-wave" and "third-wave" CBT is scientifically and clinically nonsensical. Rather, the moderation results suggest that evidence-based therapists need to know about both types of models and methods.

The second shoe to hit the ground, after regular findings of moderation between various CBT methods across eras and "waves", has been a series of studies showing that the functionally important processes of change identified through mediational analysis sometimes differ and sometimes do not between these intervention methods. Furthermore, these mediational findings do not always line up as expected.

We can stay with the series of studies from UCLA to make this point. In a study on the treatment of social anxiety disorder with either ACT or traditional CBT, rapid decreases in negative cognitions at the beginning of treatment mediated outcomes in both interventions, but an early rapid decrease in "experiential avoidance" (the tendency to avoid difficult private experiences) was a change mechanism specific to ACT[54]. Cognitive defusion (i.e., the ability to experience thoughts with a sense of distance from them, so as to diminish their automatic behavioral impact) mediated worry, behavioral avoidance, and quality of life outcomes in both conditions, but more strongly predicted worry reductions in CBT than in ACT[55].

This same pattern of distinction and overlap has been shown in several studies that have examined the functionally important pathways of change in CBT across eras and "waves". For example, cognitive defusion appears to mediate depression outcome for ACT more than for CBT[56], while outcomes of traditional CBT for chronic pain are mediated by pain acceptance, even though this is not deliberately targeted by traditional CBT protocols[57]. In a multidisciplinary, multicomponent, group-based CBT program for adults with chronic pain, pre-treatment measures of psychological flexibility (the core process target of ACT) predicted ultimate outcomes, and change in each of the aspects of psychological flexibility measured in the study (acceptance, cognitive defusion, values, committed action) separately mediated outcomes[58].

Results such as these have caused a major move toward treatment competencies and processes of change in CBT. It makes little empirical sense to focus on packages for syndromes if the actual sequence of psychological changes that are functionally important to outcomes are not necessarily the putative mechanisms favored by intervention developers and can be moderated by such processes in unexpected ways. Traditional CBT developers might be a bit startled to see that pain acceptance mediates outcomes in chronic pain, despite the fact that it was never targeted explicitly by the therapy they developed[57,58]. Similarly, an ACT developer might be puzzled to see that very high initial levels of experiential avoidance in persons with anxiety problems might suggest the use of traditional CBT over ACT, even though that has always been a key target of ACT but not traditional CBT[53].

A consensus building process launched by the Association for Behavioral and Cognitive Therapies is a clear example of this change in focus within CBT. This association brought together more than a dozen professional societies to develop guidelines for integrated education and training in cognitive and behavioral psychology[59]. Among their recommendations were the key ideas that modern CBT needs to include clarity about philosophical assumptions; understanding of processes of change; the ability to fit intervention methods to the needs of individuals; and competency in delivering a wide variety of helpful kernels across the various CBT wings, eras and "waves".

The lurching quality of "waves" comes from shifts in organizing assumptions that are too narrow: "processes of change can be drawn heavily from non-human animals", followed by "no, cognitive content is key and is left out by that", and then "no, the relationship to experience is key and is left out by a focus on content". All of those assumptions contain some truth, but all are too limited for a mental health field-wide effort to change the trajectory of evidence-based care. For example, all of these strategic assumptions in the generations of CBT under-emphasize genetic, epigenetic and neurobiological processes, or the sociocultural processes, that are involved in human functioning.

The slow progress of evidence-based intervention science, when measured against the magnitude of human needs[60], demands an end to excessively narrow strategic assumptions that cause the field of mental and behavioral health to lurch from one oversimplification to another. While useful knowledge has emerged from each of these eras, it is time to focus on a set of organizing principles that will allow what is most important in our knowledge base to be used by all researchers and practitioners interested in evidence-based care. For that to happen, we need to reconsider what evidence-based care even is.

An integrative cycle has begun that we argue may be able to carry not just CBT forward, but the entire field of evidence-based intervention science. Due in part to the churn of issues raised by "third-wave" methods, modern CBT has recently seen an enormous increase in studies on processes of change, especially in the form of studies on treatment moderation and mediation. Taken together, these findings lay the foundation for a new way forward.

THE "THIRD WAVE" AND PROCESSES OF CHANGE

When the "third wave" of CBT was proposed, it was in recognition of changes that were happening in all of the CBT wings at the time[35]. Five key features were underlined[61]. Much in the same way that cognitive methods were assimilated into behavior therapy as a larger evolution of the tradition, virtually all of these changes have been assimilated over the last 15 years into the core of CBT writ large. They are worth reviewing because they arguably help form the foundation for the process-based change that is now occurring.

A focus on context and function

The newer methods of CBT have virtually all focused on principles of change that deal more with the context and function of psychological events (e.g., thoughts, feelings, and overt action) rather than their content.

From the cognitive wing, examples of this change include MBCT ("unlike CBT, there is little emphasis in MBCT on changing the content of thoughts; rather, the emphasis is on changing awareness of and relationship to thoughts"[62]), and MCT ("MCT does not advocate challenging of negative automatic thoughts or traditional schemas"[63], because while "CBT is concerned with testing the validity of thoughts… MCT is primarily concerned with modifying the way in which thoughts are experienced and regulated"[63]).

In more behaviorally rationalized methods, examples of this change include modern behavioral activation (in which "interventions address the function of negative or ruminative thinking, in contrast to cognitive therapy's emphasis on thought content[30]"), and ACT (in which "the model points to the context of verbal activity as the key element, rather than the verbal content; it is not that people are thinking the wrong thing – the problem is… how the verbal community supports its excessive use as a mode of behavioral regulation"[64]).

The view that new models and methods should build on other strands of CBT

It is the job of a progressive field to carry everything that is useful forward as the field develops. In the case of "third-wave" models, this was described as a core commitment to "transformation of these earlier phases into a new, broader, more interconnected form; thus, while the implications may be revolutionary, the processes giving rise to these developments are evolutionary"[37].

The newer methods of CBT have taken that idea to heart, and well-tested processes and kernels have been included as steps forward were taken. Methods such as exposure, skills training, self-monitoring and behavioral homework were nearly universally included. The larger framework of CBT did change, however, as these processes were assimilated. For example, exposure is now more about values-based new learning than about emotional habituation *per se*. Similarly, rather than using it to challenge and change specific thoughts, thought recording is for decentering or defusion purposes – noting thoughts so as to reduce their automatic impact. Likewise, cognitive reappraisal is now focused more on cognitive flexibility and the utility of a variety of available constructions rather than on noticing and eliminating most or all cognitive errors.

A focus on broad and flexible repertoires vs. signs and symptoms

It is characteristic of the more recent methods that they have been relatively broadly focused. That is evident in the scope of their application and the breadth of their processes of change. The flexible and functional attentional focus of MCT, the values work of ACT, the emotional regulation skills of DBT, the present focus of MBCT, can apply to virtually any life situation, not just narrowly conceived clinical pathology.

In part as a result, a focus on specific syndromes has rapidly broken down in the last 15 years of CBT development, and that in turn has set the stage for the transition we are suggesting is taking place to a process-based model of evidence-based intervention. CBT is rapidly becoming so "transdiagnostic" that even that term is no longer adequate. Indeed, "third-wave" CBT seems to have particular affinity for issues of resilience and positive growth, as much as the alleviation of problems[65].

Applying processes to the clinician, not just the client

Almost all of the newer methods of CBT take time to apply intervention to the practitioner, not just the client. In DBT, the task "is to apply the therapy to one another, in order to help each therapist stay within the therapy protocol"[41]. In MBCT, "perhaps the most important guiding principle is the instructor's own personal mindfulness practice"[66]. In FAP, "in order to best attend to the client's experience, therapists first need to be in touch with their own"[67]. In ACT, "there is no fundamental distinc-

tion between the therapist and the client at the level of the processes that need to be learned"[68].

In part, this is because the methods are arguably more experiential, and there is the belief that you cannot teach what you cannot do. The other part of the picture is that these methods are based more on how normal psychological processes can occur in ways that produce psychological harm, and how these processes can be rearranged to promote greater human prosperity. Empirically, that idea has been borne out by evidence that "third-wave" methods lead to positive psychological outcomes for practitioners and trainees, not just their clients[69].

Expanding into more complex issues

The newer forms of CBT have not hesitated to try to address a wide variety of complex human issues historically more characteristic of humanistic, existential, analytic, or system-oriented approaches than CBT. For example, ACT addresses issues of values and meaning making as might occur more in existential therapy, or of emotional openness and perspective taking as might occur in humanistic or Gestalt approaches. FAP focuses on the qualities of the therapeutic alliance and how to use them to build more supportive relationships, as might be expected in Rogerian psychology. DBT emphasizes interpersonal validation very much as might be done in humanistic approaches.

Indeed, although the theoretical concepts and ways of discussing these phenomena may differ, it would be hard to find any central issue in more depth-oriented clinical work that is still left fully outside of the CBT tradition when all of its generations, eras and "waves" are included. In a few cases this breadth is occurring because modern CBT is simply borrowing methods, but in the majority of these cases it is more that "third-wave" approaches are burrowing into issues that used to be ignored. ACT work focused on values choices, for example, is relatively unique technologically – while being deeply resonant in its focus to other traditions.

INTEGRATING THESE SENSITIVITIES INTO PROCESS-BASED CBT

As these core commitments have been given expression, a large body of evidence has emerged on processes of change. These can be defined as theory-based, dynamic, progressive, contextually bound, modifiable and multilevel mechanisms that occur in predictable, empirically established sequences oriented toward desirable outcomes[70].

These processes are theory-based in the sense that they are associated with clear scientific statements of relations among events that lead to testable predictions and methods of influence; dynamic because they may involve feedback loops and nonlinear changes; progressive because they may need to be arranged in particular sequences to reach the treatment or prevention goals; contextually bound and modifiable so that they directly suggest intervention kernels within the reach of practitioners; and multilevel because some processes supersede or are nested within others.

The literature on processes of change is vast. Much of this is in the form of mediational analyses. If only studies of mediation within randomized controlled trials are examined, more than 1,000 significant findings can be identified, encompassing more than 100 processes of change[71]. While the nomothetically-based pauci-variate, linear and unidirectional nature of mediation needs ultimately to be put aside in favor of idiographic complex network analysis[72], that literature provides an empirical foundation for the steps that are now called for in evidence-based care.

In what follows we summarize the literature on psychological processes of change in CBT, focusing largely on processes with mediational evidence. Our larger point is that, by their progressive work on processes and procedures, the eras and "waves" of CBT have built a foundation that now allows the entire mental health field to move beyond protocols that are focused on syndromal entities into a new, idiographic form of process-based functional analysis[73].

As we will emphasize, this step has indeed been advanced powerfully by the "third-wave" methods and models, and the strategic and assumptive features we have already reviewed, but, in a mature process-based approach, all empirically well-established processes and the intervention kernels that move them need to be included in evidence-based care regardless of origin.

Empirically speaking, psychological processes of change can be roughly organized into six dimensions, which we will consider in turn.

Cognition

The newer forms of CBT have added several processes of change in the dimension of cognition, but all of them focus on changing the relationship of thinker and thought. Particularly well-supported change processes from newer forms of CBT include cognitive defusion[74] (which is the ability to experience thoughts with a sense of distance from them, so as to diminish their automatic behavioral impact) and non-reactivity[75,76] (which is allowing cognitive or other experiences to come and go without reacting in an effort to change them). Both of these processes alter the impact of human cognition by changing the person's relationship to his/her own thoughts, rather than trying to change the form, frequency, or situational sensitivity of thought itself. As such, these are contextually focused processes, rather than being content focused – a key feature of many "third-wave" processes.

Our understanding of traditional more content-oriented CBT cognitive constructs, such as cognitive reappraisal[77], rumination and worry[78], catastrophizing[79], and dysfunctional thoughts[80], have also been impacted by these newer concepts. For example, it is not the mere appearance of worry that is considered negative so much as it is entanglement with worry. Similarly, it is not that reappraisal is a way to get to the "right thought" or to get rid of the "wrong thought", but rather that there are a variety of thoughts available to guide action and the client should notice and retain the

more functional ones.

A consensus appears to be emerging that what is most needed is enough healthy psychological distance from thought, so that beliefs and cognitive constructions are not excessively entangling, either through avoidance and suppression, or attachment and rigid adoption[81,82]. In addition, what is needed is enough cognitive flexibility[81], so that an array of possibly useful constructions are available in a given situation and the person can learn what is most useful in that context.

Affect

The newer forms of CBT have added a variety of affective processes to those targeted by traditional CBT. These new concepts all focus on how the person relates to emotion, in such areas as the openness to affect, the willingness to deepen experience, and the importance of learning from emotional experience[62]. The most frequently supported is acceptance[82,84,85] – the willingness to experience affect without needless escape, avoidance or constraint. Far from resignation, acceptance implies an active embrace of experience and learning from the content of affective events. Other examples of newer affective processes are closely aligned with acceptance, including self-compassion or self-kindness[86], and distress tolerance[87].

The more content-focused concepts found in traditional CBT, such as positive and negative affect[88], loneliness[89] and hopelessness[90], are still important clinical guides, especially when excessive in frequency or intensity, but the newer processes expand on the clinical meaning of these affective contents. For example, negative affect has been shown to be most behaviorally harmful when it kicks off processes of suppression and avoidance[91]. When it does not, the capacity to notice and describe negative emotional experiences can predict positive clinical trajectories even in the presence of stressful emotions as defined by their mere form[92]. These positive trajectories may in turn reduce negative affect over time, and thus to some degree the traditional content-focused processes may also be long-term markers of the mismanagement of more contextual emotional regulation strategies.

Attention

Traditional CBT did not have a rich conceptual language for the regulation of attention, with the exception of a small number of concepts, such as rumination and worry, that are attentional as well as cognitive. In contrast, work on attention has been very dominantly evident in newer forms of CBT. Almost all methods of "third-wave" CBT include forms of mindfulness-based intervention or contemplative practice, and all of these methods thus include training in the flexible, fluid and voluntary control of attentional processes[61,93]. Such training can occur through contemplative exercises, deliberated training in attentional control, guided imagery, or other means of focusing on the now – shifting or persisting in attention, and broadening or narrowing in attention, as the situation demands.

Mindfulness interventions impact a broad collection of change processes that go far beyond attentional processes *per se*[94], and "mindfulness" as a term suffers from the wide varieties of measures and perspectives that reflect its diverse history of origin. Regardless, the link between attention and mindfulness is so strong that sometimes "mindfulness" is used as a virtual synonym for paying attention.

The centrality of this dimension is shown also by how these processes interact. For example, the shift from a focus on the content of thought to the process of thinking itself (as in cognitive defusion) is in part an attentional shift inside the cognitive domain. Similar statements could be made about the "third-wave" processes of change in affect, sense of self, or motivation.

Self

Self-regulation and self-management work began in the behavior therapy era[95], and continued in traditional CBT with concepts such as self-efficacy[96]. The "third wave" brought more spiritual senses of self into evidence-based care, through such concepts as an observing self or "self-as-context"[84], self-distancing[97], decentering[98], or a sense of spirituality[99].

These senses of self are not defined by evaluated content – indeed, in "third-wave" approaches, the conceptualized and evaluated self is commonly viewed as an unhelpful psychological process[84]. Rather, they refer to a sense of pure awareness or perspective taking, that affords or includes conscious experience, but is not defined by its content.

Of all the areas of development, this is perhaps the most empirically difficult, because these deeper senses of self are difficult to measure by self-report. A self that is defined by pure awareness is not so much an object of reflection as it is a marker of human consciousness *per se*[99]. Human consciousness is too central a topic in the history of psychology and behavioral science to avoid, but its complexity can hardly be overestimated. Nevertheless, studies have shown the relevance of these "third-wave" processes to outcome[100].

Motivation

Motivation was a key focus in early behavior therapy, especially in the form of reinforcement and goal setting. These processes are still of known importance[101], along with such traditional motivational concepts as intentions and expectations[102]. The newer forms of CBT, especially ACT, have added an emphasis on chosen values as a key mediator of change[84,103].

The embrace of values choices as a motivational process needs to be seen in the context of the other dimensions added by "third-wave" research and theory. For example, greater emotional awareness and openness itself informs values choices, as does greater cognitive and attentional flexibility.

Overt behavior

A number of targeted skills have emerged in modern CBT, but these are often focused on other processes. For example, DBT skills include methods of self-regula-

tion mediating outcomes of the therapy in the area of suicidality[104]. ACT's focus on a commitment to the creation of patterns of values-based actions has some empirical support[105].

However, the majority of known behavioral targets have roots in early behavior therapy, such as restriction of safety behaviors, behavioral activation, problem-solving, social skills, planning, or reductions in impulsivity[106].

Cross-dimensional concepts

Several of the important psychological processes of change combine two or more of the above evolving dimensions. Self-regulation arguably involves both overt behavior and sense of self. Mindfulness involves affect, cognition and attention – and in some models a transcendent sense of self.

Perhaps the prime example of such clustered processes is psychological flexibility, which combines "third-wave" concepts in each of the six above dimensions, including emotional, cognitive and attentional flexibility, a perspective-taking sense of self, values as a motivator, and construction of overt behavioral patterns of values-based habits. Meta-analyses have shown that psychological flexibility is a common mediator of psychological change especially with "third-wave" interventions such as ACT[107,108].

Processes of change at other level of analysis

It is not possible to move to a process-based era staying entirely at the psychological level. At the bio-physiological level, for example, changes in brain connectivity have already been shown to mediate the impact of some cognitive interventions. It is also known that processes of change such as emotional acceptance are themselves mediated by the connectivity strength between brain areas known to relate to difficult emotional responses[109]. Biologically relevant behavior change is also known to be important in such area, including diet, exercise and sleep[110,111].

In an increasingly diverse world, processes at the socio-cultural level also cannot be forgotten. Social processes that can vary between cultural groups, such as forms of social support, or styles of family functioning, are known empirically to mediate outcomes[112]. Socially focused processes from modern CBT are also important, including such issues as interpersonal compassion, perspective taking, prosociality and empathy[86]. A more controversial but important focus is the therapeutic alliance, which mediates outcomes across a variety of psychosocial interventions, but which also appears to have its impact in part because it promotes internalization of psychological processes of change such as acceptance, non-judgment, or maintaining a values focus[113,114].

ANALYZING PROCESSES OF CHANGE

Processes of change need to be studied in a way that is consciously "idionomic" – i.e., that uses idiographic analysis for ultimately nomothetic purposes[72,115-117]. This approach encourages the clinician to examine the functional connectivity between the various problems the client experiences and the situations in which they occur, emphasizing the use of processes of change to characterize the development and maintenance of the client's difficulties and the limitations on his/her growth.

For example, a person may respond to historically produced social anxiety with social withdrawal in the service of avoiding feelings of inadequacy. Once we understand the functional connections, we can try to modify his/her maladaptive network by establishing greater emotional openness, or increasing the likelihood of compassionate social connection. Another person with very similar historically produced social anxiety may attempt to control negative social outcome by greater vigilance to social threats, and increased rumination and worry. That person may need work in increasing attentional control and training in reappraisal skills so as to dampen ruminative cognitive habits. These cases identify treatment relevant functional analytic patterns that incrementally add to the idionomic research base of process-driven complex network analyses of psychological problems.

The idea of moving away from treating psychiatry labels toward treating the individual patient by understanding the process-based complexity of his/her problems and applying tailored intervention strategies is not new. The use of functional analysis and case formulation is at the core of the behavioral tradition[73,115], but an empirical complex network approach based on ecological momentary assessment data drawn from the last 40 years of process-based research is a substantial expansion, elaboration and further development of this early tradition. In addition, it provides a heuristically valuable model for a treatment-relevant classification system that is based on treatment processes.

We have identified the steps needed in such a process-based form of functional analysis[73]. Unlike classical functional analysis, the steps begin with the consideration of the features of the case in terms of possible complex network formulations, identification of possible change processes within the network, and collection of higher temporal density longitudinal measures to build out the network empirically. Relevant treatment kernels can then target the key elements of the client's empirical network of experiences, actions, bio-physiological, socio-cultural, and situations features, that indicate key processes of change idiographically over time. If the processes are altered in an expected direction, treatment can continue, and outcomes be assessed – which, if successful, then allow idiographic patterns to be identified and sorted into nomothetic grouping, provided the individual pattern need not be distorted to do so. If targeted processes do not change, or expected outcomes do not follow, the cycle of process-based functional analysis could be restarted.

Studies have already suggested the empirical superiority of deploying evidence-based treatment modules or kernels to target person-specific maladaptive processes of change, over global protocols targeting global syndromes[118,119]. Over time, this recursive idionomic process-based functional analytic strategy would build a

body of empirical nomothetic categories with known treatment utility[120-122].

The field still would have to systematize this growing body of findings over time in a clinically accessible way that is not theoretically narrow. That is a tall order, but it does not seem to be beyond our reach. Indeed, we have already proposed such a system based on an extended evolutionary account[123].

CONCLUSIONS

As the controversy over the "third-wave" passes into the rear-view mirror, contemporary CBT has become broader, more flexible, more philosophically responsible, more process-focused and more committed to fitting treatment methods to the needs of people. Data have increasingly emerged that reveal the wisdom of a process approach[61] as it applies to the understanding of traditional and newer-wave CBT methods.

This does not argue that therapists can be merely eclectic, because different models may rely on contradictory philosophical assumptions and theoretical concepts. Rather, therapists need to know how to identify and target central processes of change in a manner consistent with their underlying evidence. This can only fully happen if the field at large moves in a process-based direction.

All of the strategic approaches to evidence-based interventions have an ultimate purpose of understanding the processes that account for the origin, development, maintenance and change of adaptive or maladaptive human functioning. The assumption that mental problems reflect the expression of a latent disease entity has dominated psychiatric nosology, with the distinction being one of tactics, whether it is using psychoanalytic principles as in the early days of the DSM, or identifying syndromes, or developmental neurobiology as in the case of the Research Domain Criteria[124].

This assumption appears to be inhibiting the effective search for processes of change and has significantly altered modern culture in dangerous ways. Consider people in the US who sought treatment for psychological struggles during the years from 1998 to 2007 (the most recent decade with studies having reliable sample sizes). In that time, the number of people using only psychosocial change methods to address their problems fell by nearly 50%, while the number of those persons using psychological approaches along with medications fell by about 30%. What shot up? People using only medications. By 2007 more than 60% of people with psychological conditions were using medication *alone*[125]. There is no body of science that could justify such an unintended outcome of a latent disease construction. Indeed, global health specialists point out that, when this construction enters into the developing world, care can deteriorate rather than improve[126]. A new way forward is needed.

Intervention science has arguably reached a tipping point as a new process-based paradigm is emerging[70]. This paradigm is questioning the biomedicalization of human psychological suffering due to its poor validity and clinical utility. The field appears to be ready to move toward person-focused, evidence-based care models that target core change processes based on testable theories, instead of latent disease entities that are moved by evidence-based intervention protocols.

We believe that a process-based approach represents a paradigm shift in intervention science. The time is ripe for modern psychotherapy and intervention science to focus on a new foundational question that may be viewed as an expanded version of G.L. Paul's original question: "What core biopsychosocial processes should be targeted with this client given this goal in this situation, and how can they most efficiently and effectively be changed?"[18].

Process-based therapy (PBT) is not a name for a new therapy – it is a name for a new approach to evidence-based intervention science that uses contextually specific and evidence-based processes in order to alleviate the suffering and promote the prosperity of people. In contrast to the protocol-for-syndromes approach, PBT targets theoretically derived and empirically supported processes that are known to be responsible for positive treatment change, thus ensuring the treatment utility[127] of the approach.

PBT marks an era that is more open, theoretically coherent, philosophically clear, broadly focused, and idiographic. In some ways this represents a throw-back to earlier days in CBT, but it is occurring now with new concepts, measures, empirical approaches and analytic methods. Like a walk up a spiral staircase, we cover previous ground, but in a more advanced position.

Many of these changes were greatly amplified by the arrival of the "third wave" of CBT, but, for the sake of long-term progress, it is important that the field not stay there. All of the "waves" and eras of CBT, psychiatry, and evidence-based interventions more generally, have a place and a role in the future that is unfolding. Identifying processes of change has been the implicit agenda of intervention science from the beginning – it is time to make that agenda the explicit core of our field.

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DOI:10.1002/wps.20884

A question of continuity: a self-determination theory perspective on "third-wave" behavioral theories and practices

Hayes and Hofmann[1] provide a sweeping history of behavioral approaches to clinical practice, from applied behavior analysis, through cognitive behaviorism, to contemporary "third-wave" approaches. Reviewing their history from my vantage points – as a clinician, a motivational researcher, and a psychological theorist – engenders different reactions, two quite positive and one more skeptical.

As a clinician, and former trainer of therapists, I laud the more "process-oriented" point of view represented by the "third wave", which conveys respect for individuals' perspectives and values, and greater flexibility regarding the directions of treatment. Both applied behavioral analyses and cognitive behavioral approaches (the first "two waves" of behaviorism described by the authors) have traditionally embraced an outcome focus to treatment – applying techniques and interventions to bring about pre-defined targets of behavioral change and involving therapist-directed activities such as teaching, training, shaping and rewarding.

Such outcome-focused approaches often either assume or select for motivation or "readiness" for change, such that patients can "fail the therapy"[2]. In contrast, process-focused approaches conceptualize both motivation and resistance as part of the change process, and are centrally concerned with the client's experience and volition with respect to change. Process-focused therapists emphasize activities of listening, reflecting, empathizing and facilitating. These are empowering, autonomy-supportive and relational activities.

Another important, and laudable, feature in Hayes and Hofmann's depiction of the "third wave" relative to prior behaviorisms is a focus not merely on behavior change, but rather on the "development and use of inner resources" for ongoing adaptive self-regulation. Highlighted is the person's relationship with events, cognitions and emotions, and developing a sense of awareness, value, and volition in reacting to them. A focus on facilitating such self-regulatory resources highlights new assumptions concerning internalized capacities and mechanisms of agency that prior waves of behavioral theory did not acknowledge, but which (in this clinician's view) are essential to maintained change and the enhancement of adaptive functioning amidst the ever changing environments people encounter.

As a researcher, I am particularly struck by the convergence of these "third-wave" ideas – particularly those embedded within acceptance and commitment therapy (ACT) and mindfulness-based cognitive therapy – with research accomplished within self-determination theory (SDT)[3]. SDT studies have, for example, shown that more self-endorsed or autonomous motivations are reliably associated with greater engagement, behavioral persistence, as well as more positive experience[4].

Clinical and applied research within SDT has also shown that a facilitating environment of acceptance and autonomy support enhances treatment motivation, engagement and success[5], offering a promising interface for applying SDT's research methods and concepts to ACT interventions in particular. Such theoretical iteration has been illustrated by work applying SDT to motivational interviewing[6]. Moreover, SDT models of change also suggest that mindful awareness facilitates greater autonomy in functioning, and in turn greater wellness. Indeed, a recent meta-analysis supports SDT's nuanced assumption of graded associations between mindfulness and more internalized and autonomous forms of motivation[7], suggesting that awareness supplies a foundation for improved self-regulation.

In parallel, we see the ACT concept of "psychological flexibility" as entailing both mindful awareness and autonomy, constructs that have been well researched within the SDT tradition. Similarly, ACT appears to converge with SDT in advancing integrative forms of emotion regulation, in which persons approach and understand the meaning of emotional reactions, rather than focusing only on down-regulating or reframing negative experience[8].

However positive my reactions as a clinician and researcher, I am a bit more skeptical regarding Hayes and Hofmann's claims concerning the philosophical coherence or conceptual continuity of the third wave's theoretical constructs with prior behaviorisms, as if they represent a logical next step rather than a leap to a new foundation. Finding a way from Skinnerian positivism to therapies cultivating awareness, choice, and inner resources recalls an old joke involving getting directions from a rural farmer who states: "You can't get there from here".

Classical behavioral theorists actively eschewed and often disparaged concepts such as awareness, volition and autonomy. And, although cognitive behavioral theorists accepted the reality of inner mediators between environments and behavioral outputs, their focus remained on leveraging these mediators toward behavior change, retaining an outcome focus[2]. For example, Bandura explicitly dismissed concepts such as autonomy and basic psychological needs as inconsistent with his views[9].

Hayes and Hofmann do establish some forms of continuity in that, like applied behavior analysis and cognitive behavioral theories, the new wave remains: a) evidence based; b) highly focused on contexts; and c) inconsistent with a medical model. But none of these general attributes is unique to behaviorisms and, more importantly, none establishes a deep theoretical or philosophical coherence of new-wave constructs with these old meta-theoretical foundations. This is not to say that connections cannot be established, but the question is whether these ideas and practices really fit well within such a procrustean bed. The core concepts underlying new-wave therapies involve authentically engaging clients, understanding their perspectives, and helping them build or access inner resources and capacities for reflective, value-based choices, concepts and practices that cannot be parsimoniously derived from earlier behaviorist worldviews.

Although doubtful of the congruence of many "third-wave" concepts with classical or cognitive behavioral theories, I am optimistic that the processes and models of the "third wave" can be both richly theo-

retically described and fruitfully studied within organismic perspectives such as SDT. Because the process-oriented issues of mindful awareness[7], integrative emotion regulation[8], autonomous treatment motivation[5], basic psychological needs[3] and other constructs relevant to new-wave behavioral interventions already have a coherent place within the system of concepts specified in SDT, research using this theoretical framework as either a primary or supplementary guide for research may help illuminate "active ingredients" in "third-wave" techniques.

Perhaps as importantly, the organismic meta-theory underlying SDT brings with it a person-centered sensibility and philosophy that is in itself important in effectively implementing new-wave clinical practices or, for that matter, any truly process-oriented approach. Process-oriented therapy approaches are not merely sets of techniques, but also entail an orientation toward perspective-taking, facilitation, and respect for autonomy. Part of the role of theory is to guide clinicians in developing, refining and implementing such orientations in their relationships with clients. The psychological principles and values forwarded within SDT seem, in this regard, well-matched with many of the "third-wave" sensibilities and values expressed by Hayes and Hofmann, and are integrated into a conceptual framework directly relevant to the innovations of this new movement.

Since the days of classical behaviorism, empirical models of human motivation have seen a "Copernican turn" – a movement away from models of people as pawns to external contingencies, toward a focus on the development and support of people's inner capacities for acting. From this view, it is nice to see this turn within behaviorism away from assumptions that Hayes and Hofmann describe as "too narrow", and toward a more person-centered point of view. Given SDT's past clashes with behaviorists, this openness of the "third wave" to a truly process-oriented perspective affords fresh opportunities for exchanging methods, findings and practices, and ultimately a more convergent clinical science.

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DOI:10.1002/wps.20885

Variation, selection and retention: the evolution of process of change

Hayes and Hofmann[1] argue for the value of "third-wave" cognitive behavioral therapies (CBTs) – with which I heartily agree – and call for a renewed focus on targeting an expanded range of processes of change. They highlight five features of "third-wave" therapies: a) a focus on context and function; b) the view that new models and methods should build on other strands of CBT; c) a focus on broad and flexible repertoires; d) applying processes to the clinician; and e) expanding into more complex issues that historically were addressed by humanistic, existential and dynamic perspectives.

Variation is always to be desired and, if we have learned anything over the last century, it is that "one size does not fit all". We have made some marvelous strides in the field (we have doubled the efficacy of treatments for depression since the 1970s), but we are only about halfway to where we want to be. Midway through the second year of my "internship" at the University of Pennsylvania, in 1976, I was called into the office of the associate director of the training program and told "Steve, we have a problem". When I asked what the problem was, he told me that I was discharging my patients too fast. When I said that they were better, he told me that what I was observing was a "flight into health" and that I risked pushing my patients into psychotic decompensations if I insisted on treating their symptoms. We now know that any of several different types of psychotherapy are as efficacious as antidepressants for depression, and that both cognitive therapy ("second wave") and perhaps behavioral activation ("third wave") have enduring effects that medications lack.

Nothing works for everyone, and the more different "arrows in our quiver", the better for all. We now have tools at our disposal that can tell us what works best for whom, and the early indications are that some people will respond to one treatment who will not respond to another[2]. Hayes and Hofmann criticize the application of treatment packages to diagnostic categories, and I appreciate their critique. That being said, two-thirds of the patients meeting criteria for major depressive disorder in the trials that I do also meet criteria for other Axis I disorders, and half meet criteria for at least one Axis II disorder. While I do attend to the content of my patients' beliefs (more than their context) and often encourage them to use their own behaviors to test their accuracy, what I do and how I do it varies from one patient to the next. Most patients see themselves as either unlovable or incompetent, but precisely how that came to be and what tests they find compelling varies across patients. If Hayes and Hofmann can help lay that out, I am all ears.

I am a huge fan of D. Clark and his colleagues at Oxford and wrote a paper recently in which I speculated about how it is that they have been so successful in the approaches they have developed[3]. Clark essentially cured panic disorders, and a recent network meta-analysis found his approach to individual cognitive therapy to be the single most efficacious treatment for social anxiety[4]. He also found time to reshape the mental health care system in the UK to increase access to empiri-

cally supported treatments[5]. His partner A. Ehlers has a "kinder gentler" cognitive approach to the treatment of post-traumatic stress disorder that is as efficacious as prolonged exposure, with considerably less attrition. P. Salkovskis knows more about the treatment of obsessive-compulsive disorder than anyone else I am aware of and would be my "go to" person for a really tough patient that I did not fully understand. C. Fairburn generated the single most crushing defeat for another therapy in the literature when 20 weeks of his CBT for eating disorders was more than twice as efficacious as two years of dynamic psychotherapy[6]. D. Freeman is doing some very innovative work with virtual reality in the treatment of paranoid ideation in the schizophrenias[7]. As best I could surmise, the crux of what these colleagues all do is to talk with their patients to get a sense of the idiosyncratic beliefs shaping their problematic behaviors and of what kind of experiences would be required to produce change. The approach they seem to share is to move from open-ended conversations with their patients to identifying possible mechanisms that they then use to develop intervention strategies that they test first in analogue studies and then in clinical trials[8]. This process is anything but formulistic and it is incredibly successful.

If Hayes and Hoffman can improve on this record for even some, I am all for it and I would not bet against them. As the authors suggest, the "second wave" (cognitive) stood on the shoulders of the "first wave" (behavioral), and it seems right and fitting that the "third wave" should do the same. I wholly agree that we want to follow principles, not protocols, and that the processes that generate and maintain the problems our patients encounter will provide guidance along the way.

I have become enamored with an evolutionary perspective in recent years, and I understand from our conversations that this is true of the authors too. I have come to think of most high-prevalence low-heritability psychiatric "disorders" that revolve around negative affect, such as depression and anxiety, as adaptations that evolved to serve a function in our ancestral past[9]. I put the term "disorders" in quotes because these adaptations are neither diseases (there is nothing "broken in the brain") nor "disorders"; rather, they coordinate an integrated but differentiated array of whole-body responses to various environmental challenges that increased the reproductive fitness of our ancestors. These evolved adaptations are at least as well treated with psychosocial interventions that facilitate the functions that they evolved to serve as they are with medications, and the former often have an enduring effect that medications simply lack. The low-prevalence high-heritability disorders like the schizophrenias or psychotic bipolar disorder likely are "true" diseases in the classic sense of the term and at this time are best treated with medications.

Not all that comes down to us from the past is necessarily wrong, but I do think that any "good idea" tends to be taken too far. When you have a hammer, everything becomes a nail. Variation, selection and retention are the essence of evolution. Mutations produce variation, some of which is selected if it outperforms its competition and, if it does, it is then retained in the genes. This process that differentiates and improves the species can do the same for treatment interventions. The authors are to be congratulated for thinking outside the box (introducing variation). If what they produce can outperform the competition, "third wave" processes will thrive and be retained.

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DOI:10.1002/wps.20886

Process-based and principle-guided approaches in youth psychotherapy

We appreciate the rich, thought-provoking paper by Hayes and Hofmann[1], including their inspiring account of the work of so many intervention scientists on whose shoulders we all stand. The directions they propose warrant close attention by all of us who seek to strengthen psychotherapies. Here, we focus specifically on how their ideas may apply to youth psychotherapy and idiographic treatment of youth mental health challenges.

Youth and adult psychotherapy have obvious similarities, but differ in ways relevant to Hayes and Hoffman's analysis: a) caregivers' involvement in accessing and participating in their children's treatment highlights the salience of caregiver support and "styles of family functioning", which Hayes and Hofmann identify as mediators of outcome; b) youths, unlike adults, often begin treatment at the behest of their caregivers and teachers, not for intrinsic reasons, and this can make motivational processes especially critical to success in youth therapy; c) youth developmental stage may impact the accessibility and efficacy of some therapeutic processes (e.g., recursive reasoning about one's own cognitions; regulation of attention and emotion through mindfulness and sense of self, prominent in some "third-wave" therapies).

These caveats notwithstanding, much of the authors' analysis is directly relevant to youth psychotherapy. For example, they stress that, although psychotherapy protocols have often outperformed comparison conditions, advances in efficacy to date have "been inhibited". This perfect-

ly characterizes the youth psychotherapy literature. In a recent meta-analysis[2], we synthesized findings of 453 randomized controlled trials of youth psychotherapies, spanning five decades. Across time, mean effect sizes have not changed significantly for treatment of anxiety and attention-deficit/hyperactivity disorder (ADHD), and have *declined* significantly for depression and conduct problems.

Those worrisome findings were complemented by an analysis of the potential for improvement of current psychotherapies[3]. Using a meta-analytic copula approach with 502 randomized trials, we predicted youth psychotherapy effect size as a function of therapy quality. Our results indicated that a currently available therapy of "perfect quality" would have an estimated effect size of Hedges' g=0.83, conferring (via common language effect size) a 63% chance – only 13% better than a coin-flip – that the average treated youth would improve more than the average control group youth. This suggests, consistent with Hayes and Hofmann, that truly major improvements in therapy benefit may require fundamental changes in our interventions.

But, aren't new and different therapies being designed every year? Yes, but the challenge has been to create new therapies that are not skeuomorphic – new in some respects but retaining unnecessary and potentially counterproductive features of their predecessors[4]. Optimizing advances may require both building on strong foundations and breaking the mold. Hayes and Hoffman wisely note the value of leveraging the strengths of existing therapies when innovating, making intervention development evolution, not revolution. We agree. The challenge may lie in striking the delicate balance between incorporating decades of evidence on what works, and shedding structures that are based in tradition or habit, rather than evidence.

Achieving the right balance could involve, as the authors suggest, focusing on change processes and making treatment more idiographic, less standardized. They suggest "moving away from treating psychiatry labels toward treating the individual patient by understanding the process-based complexity of his/her problems and applying tailored intervention strategies". Our efforts, and those of our colleagues, to apply such an approach in youth psychotherapy have led to the creation of treatments that are modular, transdiagnostic, and personalized using measurement-based care. In one version, called MATCH[5,6], 33 components (i.e., "modules") of evidence-based treatments for anxiety, depression, trauma, and conduct problems – all derived from decades of research by our predecessors – are organized into a menu of treatment options. Clinicians use this menu to design treatment idiographically, guided by decision tools and an individual dashboard showing each youth's treatment response, updated weekly. Although decades of research inform its content, MATCH departs from traditions such as treating just one psychiatric disorder and using a standardized sequence of sessions – potential skeuomorphs but, at a minimum, not features that research has shown to be essential for beneficial outcomes.

In a second step of idiographic design, we have organized youth psychotherapy around empirically supported principles of change, honoring ideas previously proposed by many leaders in the field[7]. The resulting FIRST protocol[8,9] synthesizes treatment procedures within five principles: calming and self-regulation, cognitive change, problem-solving, positive opposite behaviors (e.g., exposure, behavioral activation), and motivation for change. This principle-guided approach rests on the rationale that learning specific procedures is useful, but perhaps *most* useful to therapists who understand *why* they are using certain techniques – i.e., which change processes need to be set in motion to produce real benefit. In FIRST, as in MATCH, treatment is fully idiographic, with individualized intervention guided by clinician decision tools and repeated measurement of each youth's functioning and treatment response.

Early evidence on these idiographic approaches has been both encouraging and revealing, highlighting what youth psychotherapy research suggests may be three key challenges for process-based psychotherapy. One challenge is clinical decision-making. As treatments become less standardized and more idiographic, clinicians will be required to decide, for each youth, which processes to target, in which order and in which combinations, and with which specific procedures, given multiple options supported by evidence. A critical long-term task for intervention science will be developing strategies for guiding such decision-making, and determining the optimal blend of data-driven and clinician-guided judgment.

A closely-related challenge will involve enriching and deepening clinical assessment to capture the underlying processes that need attention in treatment – processes that may be key to therapeutic success. Our field has a long history of assessment focused on diagnosis and symptoms, and a respectable track record within some of the process dimensions identified by Hayes and Hofmann – for example, cognitive reappraisal, rumination, worry, and catastrophizing. However, the newer, deeper, contextually-focused processes identified by the authors – such as cognitive diffusion, flexibility, non-reactivity, and "healthy psychological distance from thought" – may well require new measures, and possibly entirely new assessment strategies.

A third challenge will be discerning the implications of process-based psychotherapy for what many consider the holy grail of intervention science: identifying mechanisms of change. There is a long history in our field, well-documented by Hayes and Hofmann, of efforts to elucidate mediators of therapeutic change. Documenting mediators is a statistical step toward identifying mechanisms that account for treatment benefit – the switches that, when flipped, make therapy successful.

An implicit assumption historically has been that we will eventually discover *the* mechanisms of change (or perhaps a small number of them) for treatment of each psychiatric disorder. A process-based analysis turns this thinking upside down in at least two ways: a) treatment focuses not on disorders but on underlying processes, and b) treatment is tailored to each individual, targeting complex underlying processes that matter for that individual. Under these conditions, do we continue the search for mechanisms of change and, if so, are we searching for "flip switches" as diverse and distinctive as the individuals our interventions are designed to support?

Taken together, there is much that intervention scientists – including those of us immersed in youth psychotherapy –

can learn from the perspective offered by Hayes and Hofmann. Clearly, exciting challenges lie ahead in process-based psychotherapy.

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DOI:10.1002/wps.20887

Trans-theoretical clinical models and the implementation of precision mental health care

Hayes and Hofmann's paper[1] provides a new framework to conceptualize psychological therapy as a process-based clinical intervention. The authors describe the history of cognitive behavioral therapy (CBT) in three waves and formulate the process-based orientation as the step beyond theoretical orientations. They outline a shift from protocols treating syndromes to idiographic approaches using process-based clinical strategies to adapt treatment to the complexity of patients' problems.

The main idea is to use knowledge derived from empirical findings on psychological change processes in CBT to tailor treatments to patients and include new evidence as it becomes available. Therefore, process-based therapy is presented as a conceptual framework open to new, empirically tested processes identified in international research on diverse samples and dedicated to the goal of evidence-based psychotherapy.

Overall, we welcome the development of process-based psychological therapy within the context of a larger trans-theoretical and integrative trend in clinical practice, training, and theory building. There is no general agreement on the conceptualization of psychological therapies, and clinical services differ largely between and within countries. Furthermore, treatment models are often combined intuitively in clinical practice. The task for psychotherapy research is to improve this clinical decision-making process by grounding it in empirical data[2].

Hayes and Hofmann observe that, despite the many theoretical developments, the practice of psychological therapies has not seen a large improvement in success rates over the last decade. This conclusion of outcome research is receiving increasing attention and acceptance in the field[2]. Therefore, it is no wonder that new modular and integrated concepts have emerged. The idea is to combine elements within or between different treatment orientations based on sound empirical data, with the goal of tailoring treatments to specific patient problems and needs[1-4].

Such trans-theoretical treatment concepts are complemented by recent trans-diagnostic psychopathology research – for example, the Research Domain Criteria, the multivariate Hierarchical Taxonomy of Psychopathology, and network models. Psychological disorders are no longer seen as categorical entities, but as elements of a multidimensional and transdiagnostic model of psychopathology.

Beyond Hayes and Hofmann, we argue for a trans-theoretical perspective facilitated by data-informed clinical practice, research and training, and focusing particularly on patients not profiting from psychological therapies. Some recent and ongoing research trends can be delineated in this respect[2]. These include the development of improved, standardized, freely available, and easy-to-apply measures; new efforts in replication; new statistical methods (e.g., machine learning) to analyze large cross-sectional as well as intensive longitudinal datasets; improved research on processes and mechanisms of change; a better dissemination and cross-cultural adaptation of interventions, including Internet services[5]; and a better implementation of outcome monitoring and clinical navigation systems to support therapists to identify and treat patients at risk for treatment failure.

We see the chance for psychotherapy to become characterized by trans-theoretical, personalized, and evidence-based clinical practice and training. Implementing continuous multidimensional assessments in routine care and identifying negative developments early in treatment are particularly crucial. Given that the knowledge about moderators and mediators in our field is limited, any treatment application needs to be evaluated by its actual progress for the individual patient[2].

This development has the potential to help the field mature and to empower clinical interventions. The goal could be to move away from concepts based on average differences and broad clinical assumptions that are difficult to operationalize, and towards concrete outcomes and studies on subgroups of patients not profiting from treatment.

In recent years, concepts from precision mental health research and precision medicine have been introduced, driving these advancements forward[6,7]. Rather than choosing between treatment protocols, the aim of these developments is to tailor treatment to individual patients using empirical data. Evidence-based personalization in clinical practice might be improved by combining research on treatment prediction and selection with research on digital feedback and the application of decision support systems[8].

At treatment onset, therapists are provided with prognostic information, for exam-

ple based on machine learning approaches applied to large datasets in order to recommend the optimal treatment, treatment strategy, or therapist for an individual patient[6]. During treatment, therapists are made aware of patients at risk for treatment failure, dropout or self-harm by adaptive decision tools. Additionally, therapists are provided with feedback and clinical problem-solving tools to support treatment for these patients.

Currently, the implementation and prospective evaluation of such systems are rare. However, such studies and new developments are already on their way. For example, more than a decade of our department's research activity has resulted in the development of a digital decision support and navigation system called the Trier Treatment Navigator (TTN). The system combines outcome tracking, prediction, and prescription tools, providing continuous feedback to clinicians and supporting them to apply targeted clinical strategies at the onset of and during treatment.

The online navigation system includes two components of patient-specific treatment recommendations: a) a pre-treatment clinical strategy recommendation and b) adaptive recommendations and support tools for patients at risk for treatment failure. The prospective evaluation on 538 patients showed an advantage in outcomes, with an effect size of about 0.3, when patients were treated with the recommended strategy during the first ten sessions. Furthermore, therapist symptom awareness, attitude, and confidence using the system were found to be significant predictors of outcome, while therapist-rated usefulness of such feedback moderated the feedback-outcome association[2,8].

A similar approach, the Leeds Risk Index (LRI), was developed based on a sample of 1,347 patients and prognostically tested on 282 patients in the Improving Access to Psychological Therapies (IAPT) programme, to recommend either low or high intensity treatments[7]. Results indicated that such stratified care improves efficiency by generating comparable outcomes with less treatment sessions.

The goal of these developments is the timely translation of research into clinical practice. Of course, many more prospective studies are necessary. However, in the future, the field might be better able to operationalize change processes, regarding both how patients experience them and how therapists induce them. These developments could be the basis of a trans-theoretical, process-based, personalized and data-informed psychological treatment approach, which includes both an idiographic (e.g., intensive longitudinal assessments on single cases) and a nomothetic (e.g., large databases of patients and therapists) perspective. Such advancements could finally make a difference for patients previously not profiting from psychological interventions.

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DOI:10.1002/wps.20888

Do we really need a process-based approach to psychotherapy?

Hayes and Hofmann[1] discuss the neglect of processes of change in psychotherapy and the lessons we can learn from process research in the context of "third-wave" cognitive behavioral therapies (CBTs). They criticize the notion of psychiatric syndromes and argue that these newer therapies should be considered in the context of an idiographic approach to process-based functional analysis.

Although I do agree upon several of the arguments the authors put forward, there are a few issues on which my views are somewhat different. As to their critic to the latent disease model of psychiatry, they do not discuss the progress which is now being made by the network approach. This approach to psychopathology posits that mental disorders can be conceptualized as causal systems of mutually reinforcing symptoms[2]. The model has been used over the past decade to examine psychiatric comorbidity and developmental psychopathology, and is being applied to a variety of specific disorders, such as anxiety disorders, autism, depression, post-traumatic stress disorder, eating disorders, psychosis and psychopathy.

Hayes and Hofmann argue that in the 1980s the golden era of "protocols for syndromes" settled in, with an ignorance of the therapeutic processes involved in these CBT protocols. This observation may be partly correct, but it is important to note that the CBT movement has always emphasized the role of theory, and of basic research supporting this theory[3]. Nevertheless, the dominant paradigm has indeed been evidence-based treatment. Expert committees have been providing guidelines for evidence-based treatment of mental disorders, thus "certifying" a given treatment for a given population based on its proven efficacy for that specific mental disorder in randomized controlled trials (RCTs).

It should be acknowledged that this approach has led to a number of evidence-based CBT treatments for many mental disorders[4]. At the same time, about 30-40% of patients cannot be successfully treated with current CBT protocols, including "third-wave" CBTs, such as acceptance and commitment therapy (ACT), compassion-focused therapy, mindfulness-based cognitive therapy (MBCT), meta-cognitive therapy, and functional analytic psychotherapy. Although "third-wave" therapies

are more experiential and "may lead to positive outcomes for trainees and practitioners"[1], there is no robust evidence that they are more effective than classic behavior therapies or "second wave" CBTs[5,6].

One important way to investigate mechanisms of change is mediation. Several potential mediators have been proposed in the literature in relation to depression. Cognitive theory states that depression is caused and maintained by dysfunctional cognitions and maladaptive information processing strategies, and depression severity can be reduced by altering the function, content and structure of cognitions associated with negative affect, as is done in CBT. Changing the content of thoughts is seen as an unnecessary step in ACT, as it is assumed that distancing oneself from thoughts is a sufficient and more productive way to diminish the influence of thoughts on behavior. Distancing is achieved through the process of defusion or decentering.

In an RCT[7], manualized CBT was compared with ACT, and patients in both conditions reported significant and large reductions of depressive symptoms aa well as improvement in quality of life up to 12 months after treatment. Interestingly, dysfunctional cognitions did not only mediate treatment effects of depressive symptoms in CBT, but also in ACT. On the other hand, decentering mediated not only treatment effects in ACT, but also in CBT. Thus, both treatments seem to work through changes in dysfunctional cognitions and decentering, even though the treatments differ substantially.

Another interesting issue for further research is the role of the therapeutic alliance in CBT and "third-wave" therapies. In an RCT[8], the alliance-outcome association in CBT vs. MBCT was evaluated in diabetic patients with depressive symptoms. Because both CBT and MBCT therapists aim to form a therapeutic bond by adopting an open, empathic, accepting, and nonjudging attitude towards patients, it was hypothesized that the therapeutic bond was going to predict the subsequent symptom change in both treatments. The results showed, however, that patients' ratings of the therapeutic alliance predicted depressive symptom improvement in CBT, but not in MBCT. There is a clear need for further studies into the role of the therapeutic alliance in "third-wave" therapies.

Although the empirically supported treatment approach is currently still followed by a majority of CBT researchers and practitioners, a growing minority argues for the need to put greater emphasis on individual case formulation based on empirically tested theories instead of treatment protocols. Hayes and Hofmann suggest to study processes of change in therapy using idiographic analysis for nomothetic purposes and to treat the individual patient "by understanding the process-based complexity of his/her problem and applying tailored intervention strategies"[1]. But, what is the evidence that individualized treatment based on functional analysis and case formulation is more effective than standard protocolized treatment?

Hayes and Hofmann cite two studies to support the notion that treatment modules to target person-specific maladaptive processes of change are more effective than global protocols. In one of these studies[9], an individualized approach was found to be more effective than standard treatment in children with behavioral problems. However, only about one half of children in the control condition actually engaged in behavioral health services. To test the study hypothesis, the individualized approach should be compared with an evidence-based treatment for behavioral problems.

Actually, there is no robust evidence for a superior effectiveness of treatment based on functional analysis compared with manualized evidence-based treatments[2]. Although there are clear advantages associated with an individualized approach, if proven effective, there are also disadvantages. First, the success of the therapy will largely depend upon the therapist's creativity. Moreover, an individualized treatment approach is certainly much more difficult to learn and practice than a manual-based, standardized, evidence-based intervention.

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DOI:10.1002/wps.20889

Challenges in the evolution toward process-based interventions

Hayes and Hofmann's paper[1] is much welcome. As they argue, there is a need to re-evaluate assessment and treatment practices that are solely or primarily based on psychiatric diagnoses. Diagnoses do not sufficiently account for individual differences, and additional information is usually needed to implement a psychological intervention. In one of our clinical trials aimed at decreasing the symptoms of depression[2], participants with an ICD-10 diagnosis of a depressive condition reported 5 to 15 additional psychological problems.

Several significant behavioral problems can be overlooked and left untreated if the treatment providers only focus on one or two syndrome categories. Diagnostic categories could be used, for example, when making decisions regarding financial support in the case of sick leave. However, alternative behavioral assessment models should be used when making decisions about the type of intervention methods that are needed.

If we complete an individual behavioral assessment, for example by applying a case formulation model, it appears that several factors have contributed and continue to contribute to symptoms of depression. Logically, this leads to the conclusion that there are several potential ways to treat depression, and that the treatment could focus on several maintaining factors. However, in the field of behavioral science, progress is not facilitated by increasing the number of behavioral treatment models; rather, it is linked to identifying the essential processes that explain the beneficial changes that occur due to psychological interventions.

As Hayes and Hofmann[1] point out, we have seen a considerable increase in the number of studies on psychological processes of change in cognitive behavioral therapies (CBTs). Thus, the focus on intervention studies has turned more toward the question of why psychological interventions are effective instead of just asking if they are effective. However, psychological processes of change appear to be a very complex issue. Several processes may explain why psychological interventions are effective for reducing certain symptoms, and there can be different combinations of processes that are essential when treating symptom X in comparison to symptom Y.

In a study exploring – by the Five Facet Mindfulness Questionnaire (FFMQ)[3] – which of the mindfulness facets (observing, describing, acting with awareness, nonjudging, and non-reacting) mediated the effects of a mindfulness-, acceptance-, and value-based intervention on three burnout dimensions (exhaustion, cynicism, and reduced professional efficacy), we found that a large spread of mindfulness facets mediated changes in all the burnout dimensions during the intervention[4]. However, only improvement in non-judging skills mediated the reduction in all burnout dimensions during the follow-up. So, the identification of the psychological processes that mediate changes in symptoms not only during but also after any intervention can help us increase the impact of that intervention and allow a more cost-effective use of resources.

The newer forms of CBT should include an individual behavioral assessment of psychological processes. This procedure is far more complex and sophisticated than labeling (or naming) individuals according to diagnostic categories. As Hayes and Hofmann state, the field needs to move towards a process-based functional analysis.

The authors also mention that recent findings would require a major shift in the competences needed for practicing CBT. At present, there is limited evidence of the relationship between therapeutic competence and outcome of psychotherapies, and this relationship is usually found to be weak[5,6]. The focus on packages for syndromes, the difficulties in measuring competence, and the limited knowledge about and understanding of the processes of change may have contributed to this. Given the emerging consensus on empirically-established psychological processes of change, we need methods to assess whether the relevant competences have been acquired during training; for example, whether therapists are capable of identifying and targeting central processes of change. There is also a need to develop assessment procedures to evaluate whether professionals are capable of delivering process-based treatments.

Hayes and Hofmann review a significant number of studies identifying processes of change. They propose that it is useful to organize the large number of psychological processes into dimensions, and they classify them into six dimensions. However, it is challenging to limit the classification to so few dimensions. The following are examples of the possible challenges. The dimension "cognition" is suggested to include the process of non-reactivity. This is somewhat problematic, since in the FFMQ[3] the subclass of non-reactivity also includes items regarding emotions (e.g., "I perceive my feelings and emotions without having to react to them"). The dimension "affect" is proposed to include distress tolerance. However, this has also been considered to be a behavioral measure of avoidance[7]. Thus, it remains to be seen whether empirically established psychological processes of change can be organized into the proposed six dimensions.

Overall, Hayes and Hofmann argue that the field is ready to move toward person-focused, evidence-based care models. Thus, more attention needs to be devoted to answering the question: why do we do the things we do? This evolution involves several opportunities (including the possibility to consider psychological skills training in prevention efforts at the level of the school environment), but also a variety of challenges.

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DOI:10.1002/wps.20890

Cognitive behavioral therapy, process-based approaches, and evolution in the context of physical health

Hayes and Hofmann[1] describe how the context around cognitive behavioral therapy (CBT), a context that has supported significant success for many years, may now be stifling progress[1]. They say that it is now time for a new strategic approach. In their words, a focus on syndromes, diagnostic categories, and the development of treatment protocols based on studies of group data, has dominated the field of mental health, perhaps for too long. New developments in CBT provide the chance to

refocus on the unique problems that individual people face, and on custom-delivered methods targeting empirically-based processes of change, rather than packages of methods prescribed by a protocol. This evolution of CBT toward more person-specific and process-focused delivery presents an opportunity to transform mental health care. Clearly this ought to apply to physical health care as well.

While there is no quibbling with the authors' reminder that depression is one of the world's leading causes of disability, it is also worth pointing out that the top ten contributors to the global burden of disease in adults include low back pain, headache disorders, ischemic heart disease, and stroke[2]. In fact, each of these conditions actually surpasses even the substantial disease burden of depression in people aged 25 to 49, and, excluding headache, in people aged 50 to 74.

What makes this relevant is that each of these conditions involves a substantial role for modifiable cognitive and behavioral processes. In each case, risk factors that lead to the development and maintenance of these conditions, and the processes that translate the experience of these conditions into impacts on daily functioning, and years lived with disability, can be substantially modified with forms of CBT. These include newer, "third wave", forms[e.g.,3,4].

The point is that, even with the great need for improving mental health worldwide, we should not lose sight of the need for cutting across the assumed border between mental and physical health, to consider the opportunity for world health as a whole. This boundary is called "assumed" because so-called mental and physical health conditions are highly comorbid, certainly share many risk factors, worsen under many of the same influences, and improve with application of many of the same kinds of treatment methods. Individual behavior is an extremely powerful common pathway toward general health and well-being, as well as an outcome or indicator of these, more so than we often think.

In some ways, the contexts of physical health provide easier access for person-specific and process-focused approaches. The door is already open to a degree. When people have chronic pain, headache, heart disease, cancer or diabetes, as examples, they already have a diagnosis and clearly their focus and the focus of clinicians, at least in part, is on addressing the impacts of these conditions. That being the case, there can be less an urgency around assigning another diagnosis in the realm of mental health. Also, a focus on multiple outcomes, on healthy behavior, on functioning well and well-being, and not just on symptom reduction, is already a relatively ordinary focus in the domain called clinical health psychology or behavioral medicine, essentially the domain where CBT operates in physical health. This appears particularly true in the context of chronic diseases.

Seizing the opportunity for enhancing physical health through the application of new CBT methods is not without potential impediments. For example, in chronic pain management, particularly in specialty centers, CBTs are traditionally delivered in groups. Also, in most health care research, studies are based on group data, normally collected at relatively infrequent intervals, before treatment, immediately after treatment, and at a later follow-up. This focus on groups clearly presents significant difficulties, if the aim is highly individualized treatment. Group delivery and a focus on group means are not likely to yield the knowledge needed, if the need in knowledge is how to customize the delivery of treatment components and to selectively target only relevant process of change for each person[5]. The infrequent assessment of outcomes, and presumed mediators of outcome, if included, is unlikely to detect complex, multivariate, bidirectional, and highly individual processes of change[6].

In the future, we will need to more frequently employ single case experimental designs with intensive longitudinal data gathering. As well as needing to build a library of theoretically derived and empirically-based therapeutic processes of change, we will also need to harness new technologies for data gathering and analysis. These data will most likely be collected by hand-held "smart" devices that include a new generation of outcome and process measures which are brief, individually-relevant, and sensitive to change. Analyses of these data will then allow analyses of potential mechanisms of change in highly individual ways, and meta-analyses of these case data will allow the development of new general principles, and a science of truly personalized therapy will finally emerge[6].

Another possible impediment to change in CBT for physical health resides in the predominantly interdisciplinary context of much of this work. When working in interdisciplinary teams, it seems necessary that all members know what the others are doing and why. With the appearance of new approaches, some members of teams may express frustration, such as to say that now we must train colleagues all over again. While this frustration might be understandable, change will come, approaches will evolve. And this is not a break from past learning, but an extension. Moreover, the alternative – staying the same – is both undesirable and ultimately impossible.

Important steps are already being made. Implementation of "third wave" therapies well-suited to process-based delivery is expanding rapidly in physical health contexts, as demonstrated in published randomized controlled trials dealing with bowel disease, cancer, chronic pain, dialysis, diabetes, epilepsy, exercise, headache, HIV, multiple sclerosis, sleep, smoking, tinnitus, and weight loss[7]. A focus in research on predictors and mediators of outcome is becoming common[e.g.,8]. And in the wider field of CBT there are now an increasing number of studies that employ single case approaches. These studies are now able to analyze processes of therapeutic change, using methods for gathering data daily, including ecological momentary assessment. They can also apply methods for analyzing process and outcome data that allow individualized targeting of key functional processes of change, including factor analysis and network analyses of individual data[9].

While there is progress, at the same time there is much to do so that these developments will continue. We need to produce new knowledge, new applications of current technology and new technology, and we need to educate and train. Perhaps in small steps, process-based therapy designed around the specific needs of individual people, for both mental and phys-

ical health, is becoming a reality.

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DOI:10.1002/wps.20891

The coming revolution in intervention science: from standardized protocols to personalized processes

Intervention science has set for itself a noble goal. How do we reduce mental health problems, promote happiness, and help people to engage in behaviour that is effective and in their best interest? The scientific community has now spent hundreds of millions of dollars and decades to answer this question. The good news is that we have made excellent progress. Meta-analyses suggest that a wide variety of interventions are effective in reducing mental illness[1], increasing well-being[2], and promoting effective health[3] and work behavior[4].

Despite this success, Hayes and Hofmann[5] argue that the dominant approach to intervention research may no longer be adequate. Meta-analytic research supports their view. Psychotherapy effect sizes are modest (about .30), when compared to placebo or treatment as usual[6]. Perhaps most concerning, effect sizes appear to have stagnated[7]. The authors argue that the lack of progress is not due to a lack of effort. Rather, they identify some major problems with the "protocol-for-disease" research paradigm, which seeks to identify effective clinical protocols to treat latent diseases.

Decades of research have failed to identify psychological diseases that exist independently of their so-called symptoms. We diagnose depression in individuals because they report feeling extremely sad and inactive, and then we say that they are inactive because they are depressed. In medicine, the physical disease can exist independently of symptoms: someone can have cancer with or without symptoms of fatigue and nausea. If we abandon the assumption that a latent disease causes depression, we can free practitioners from the medical model and all its assumptions about suffering being caused by some internal abnormality.

We can open up to the role of context, and see that people display patterns of depressive symptoms that are causally related in different ways. For example, two clients have both received a diagnosis of depression. With only this knowledge, the practitioner might apply the same treatment protocol to both of them. What if we assume that they do not have the same disease? Instead, we look at the pattern of symptoms and how they interrelate in context. Imagine we discover that one of the depressed clients has just lost her partner, which is leading to intense sadness that drives social withdrawal, while the other client has been bullied at work, leading to social anxiety, which drives social withdrawal and intense sadness. Though we diagnose both clients with depression, we will presumably not give them the same intervention.

The protocol-for-disease approach does not recognize the role of contextual factors in therapeutic outcome[5]. Therapeutic procedures are not effective across all people and contexts. Some clients may love structured mindfulness practice, whereas others find such practices anxiety provoking and decidedly unhelpful[8]. Moreover, the protocol-for-disease approach focuses excessively on trademarked packages rather than evidence-based processes. It also fails to recognize the common effective processes shared by different protocols. A protocol is not a single thing, like a 50 mg dose of penicillin. Some processes are useful to a particular individual, some useless.

Hayes and Hofmann propose a radically new way forward, which, if correct, would lead to a revolution in intervention science. Rather than focusing on protocols for diseases, they focus on individualized processes of change for promoting broad and flexible behavioural repertoires. Their unifying framework allows people from any therapeutic approach to share a common process language focused on cognition, affect, attention, self, motivation, and overt behaviour.

Importantly, the framework shows how to tailor interventions for a particular person, in a particular context. Rather than assuming that a process, say emotional openness, has the same beneficial effect on everybody, it seeks to identify how different processes function, or drive well-being for different people. The practitioner identifies, through functional analysis, what processes are helping the client, and what processes are inert and harmful, and emphasizes the effective processes. This means that some aspects of an evidence-based protocol may be discarded, at least for a particular client.

Hayes and Hofmann are trying to entirely change the rules of the game. Shifting to their new process paradigm will not be easy. Improvements will not be immediate, just as the shift from Ptolemaic to Copernican system did not immediately result in better predictions[9]. We should expect null results and missteps along the way. Making matters worse, the current academic environment is not conducive to revolution. Academia pressures scientists to publish fast and efficiently in the top journals, and this usually means staying within accepted and safe paradigms, such as evaluating protocols for hypothesized latent diseases. The alternative path is uncertain and could be inefficient, at least initially. Yet it may lead to something new and potentially exciting.

The scientific community must decide

whether to spend 20 more years showing that standardized protocols perform better than placebo, but not better than other protocols. Or to take risks, make some mistakes, and see if it can create personalized interventions that help each individual reach his/her full potential.

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DOI:10.1002/wps.20892

Initial treatment choices to achieve sustained response in major depression: a systematic review and network meta-analysis

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Major depression is often a relapsing disorder. It is therefore important to start its treatment with therapies that maximize the chance of not only getting the patients well but also keeping them well. We examined the associations between initial treatments and sustained response by conducting a network meta-analysis of randomized controlled trials (RCTs) in which adult patients with major depression were randomized to acute treatment with a psychotherapy (PSY), a protocolized antidepressant pharmacotherapy (PHA), their combination (COM), standard treatment in primary or secondary care (STD), or pill placebo, and were then followed up through a maintenance phase. By design, acute phase treatment could be continued into the maintenance phase, switched to another treatment or followed by discretionary treatment. We included 81 RCTs, with 13,722 participants. Sustained response was defined as responding to the acute treatment and subsequently having no depressive relapse through the maintenance phase (mean duration: 42.2±16.2 weeks, range 24-104 weeks). We extracted the data reported at the time point closest to 12 months. COM resulted in more sustained response than PHA, both when these treatments were continued into the maintenance phase (OR=2.52, 95% CI: 1.66-3.85) and when they were followed by discretionary treatment (OR=1.80, 95% CI: 1.21-2.67). The same applied to COM in comparison with STD (OR=2.90, 95% CI: 1.68-5.01 when COM was continued into the maintenance phase; OR=1.97, 95% CI: 1.51-2.58 when COM was followed by discretionary treatment). PSY also kept the patients well more often than PHA, both when these treatments were continued into the maintenance phase (OR=1.53, 95% CI: 1.00-2.35) and when they were followed by discretionary treatment (OR=1.66, 95% CI: 1.13-2.44). The same applied to PSY compared with STD (OR=1.76, 95% CI: 0.97-3.21 when PSY was continued into the maintenance phase; OR=1.83, 95% CI: 1.20-2.78 when PSY was followed by discretionary treatment). Given the average sustained response rate of 29% on STD, the advantages of PSY or COM over PHA or STD translated into risk differences ranging from 12 to 16 percentage points. We conclude that PSY and COM have more enduring effects than PHA. Clinical guidelines on the initial treatment choice for depression may need to be updated accordingly.

Key words: Major depression, treatment choice, maintenance treatment, sustained response, psychotherapy, pharmacotherapy, combination therapy, cognitive behavioral therapy, network meta-analysis

(World Psychiatry 2021;20:387–396)

The two mainstays of acute treatment of major depression in adults are antidepressant medications and psychotherapies, each backed by several hundred randomized controlled trials[1,2]. After remission from the episode, it is also well documented that continuing pharmacotherapies[3,4] or psychotherapies[5], or sequentially introducing psychotherapies as add-on to pharmacological treatments[6], can reduce the depressive relapse rate in the maintenance phase.

Antidepressants are currently among the most frequently prescribed medications worldwide, being taken by 10% or more of the general population annually in some high-income countries[7]. More and more patients seem to be on longer-term antidepressant treatment: in the US, 44% of the current recipients had been on antidepressants for more than five years in 2015, compared with only 13% in 1996[8].

Three types of trial designs have been used in the literature to assess the efficacy of maintenance treatments in depression[9]. The most commonly used is the "enrichment design" (type A in Figure 1), in which patients who have responded to an acute treatment are subsequently randomized to various maintenance treatments. The second (type B) is the "continuation design", in which patients with depression are randomly allocated to receive an intervention or a control and then the entire cohort is followed up into the maintenance phase. A variant of the latter is the "extension design" (type C), in which only participants who have responded to the acute treatment are followed up. In both type B and C studies, the follow-up maintenance therapy is by design the same as in the acute phase, or a new treatment, or is left to the therapist's discretion in a naturalistic fashion.

Systematic reviews of maintenance treatments to date have focused on type A trials to determine what should be done after successful acute treatment of depression[3-6]. While such information is clinically important, it cannot answer the clinically more pertinent question that faces every patient starting treatment for a depressive episode: "Which therapies can get me well and keep me well?". Type A trials are enriched for, and therefore potentially biased in favor of, the first active therapy[10,11]. Only type B and C trials, in which randomization takes place at the beginning of the acute phase, can inform the initial treatment choice.

We hereby present the first systematic review and network meta-analysis (NMA) to determine which of the available therapies for depression chosen at the beginning of the acute phase are more likely to lead to sustained response in the maintenance phase. The NMA preserves the randomized structure of the evi-

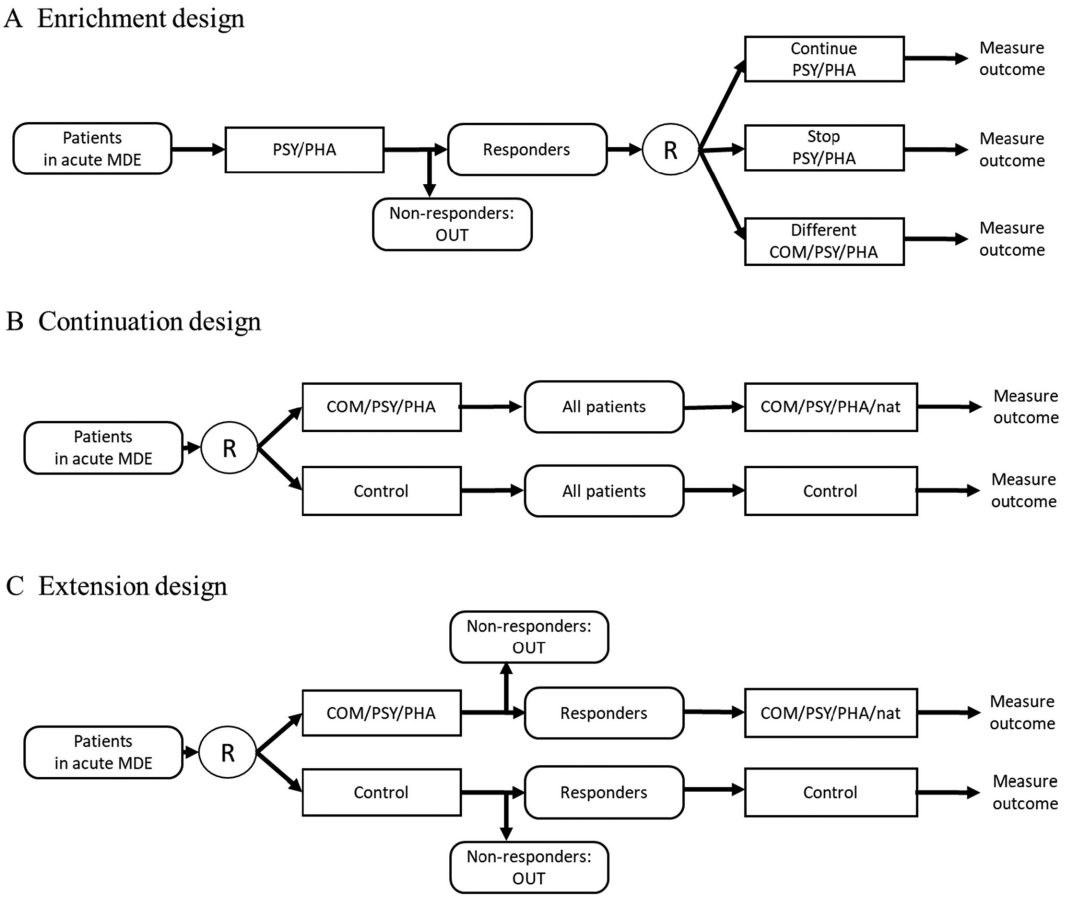

Figure 1 Trial designs to examine maintenance treatment for depression. MDE – major depressive episode, COM – combination therapies, PHA – pharmacotherapies, PSY – psychotherapies, nat – discretionary treatment, R – randomization

dence network, i.e. treatment effects are first estimated separately for each study and then such study-specific estimates are synthetized for each treatment comparison and across the network, assuming constancy of the relative effect at each stage of the synthesis. This assumption of constancy is duly examined while conducting NMA.

METHODS

We followed the PRISMA guideline for NMAs[12]. The protocol has been registered at the Open Science Framework (https://osf.io/5qfuv/).

Data search

We identified relevant studies from three databases covering PubMed, EMBASE, PsycINFO, Cochrane Library, major trial registries, and regulatory agency websites. The first is a database of randomized trials of psychotherapies for depression, described at www.osf.io/825c6 and continuously updated[13] (the last search was conducted on January 1, 2020). The second is a database of randomized trials of psychotherapies focusing on relapse prevention[14] (the last search was on October 13, 2019). The third is a database of randomized trials of antidepressant pharmacotherapies in relapse prevention[9] (the last search was on January 3-5, 2019). The search strings used in each database are provided in the supplementary information. Two independent raters judged the eligibility of the included studies.

Study selection

We included randomized controlled trials in which any of the relevant interventions (see below) were compared with each other or with control conditions (see below) in the maintenance treatment of major depression, in type B or C studies (see Figure 1). We defined maintenance treatment as the continuation of treatment for six or more months. Because the distinction between a continuation phase to prevent relapses (re-emergence of the index episode) and a maintenance phase to prevent recurrences (appearance of a new episode)[15] is more theoretical than pragmatic[3], we use the term maintenance therapy to refer to the longer-term treatment phase after the acute phase.

We included patients aged 18 years or older, of both genders,

with unipolar major depression diagnosed on the basis of standard operationalized criteria. We excluded studies that relied on a cutoff on a screening scale as an eligibility criterion and did not ascertain the diagnosis of depression. Studies in which 20% or more of the participants suffered from bipolar disorder, psychotic depression, treatment resistant depression or subthreshold depression were excluded. We also excluded RCTs which focused on patients with another concurrent primary psychiatric diagnosis or with a concomitant medical illness.

Among psychotherapies, we included any intervention involving "the informed and intentional application of clinical methods derived from established psychological principles to assist participants with their behaviors, cognitions and emotions, in directions that the participants deem desirable"[16]. Interventions could be delivered by any therapist, including psychiatrists, psychologists, nurses, social workers, and also lay health counsellors as long as they were trained to deliver the therapy, either in individual or group format, face-to-face or by Internet. We excluded unguided self-help interventions as they have been documented to be inferior to other delivery modalities for major depression[17-19]. Psychotherapies were further subcategorized into the following major types: cognitive behavioral therapy (CBT), behavioral activation therapy (BA), problem-solving therapy (PST), third-wave cognitive behavioral therapies (3W), interpersonal therapy (IPT), psychodynamic therapy (DYN), non-directive supportive therapy (SUP), and life review therapy (LRT)[20-22].

Among pharmacotherapies, we included fixed or flexible dose regimens of antidepressants that have shown greater efficacy than placebo in acute treatment[1]. Only arms within the accepted dose ranges were included.

Controls included pill placebo; standard non-protocolized treatment in primary or secondary care, typically with pharmacotherapies (STD); and no treatment (NT) if the care as usual in the trial context involved virtually no intervention (operationally defined as less than one third of patients receiving any antidepressant).

The primary outcome was "sustained response", defined as the proportion of patients who had responded in the acute treatment and who subsequently did not have depressive relapses during the maintenance phase. The proportion of sustained response, therefore, represented those who had responded to the acute phase treatment and maintained the response through the maintenance treatment, divided by the total number of patients randomized at the beginning of the acute phase treatment. We extracted the data reported at the time point closest to 12 months.

In some type B studies, when above-defined sustained response was not reported, we used the number of responders at the follow-up, either reported as dichotomous outcomes or imputed from the continuous outcomes using a validated imputation method[23,24]. We regarded all the dropouts as not showing sustained response. We examined the effect of this assumption by a sensitivity analysis limiting to studies with >90% follow-up.

The secondary outcome was all-cause discontinuation of treatment, as a proxy measure of treatment acceptability. We had originally intended to also evaluate discontinuation due to adverse events (tolerability) and suicidality. However, too few studies reported these harm outcomes through the maintenance phase, and we present only narrative summaries for these outcomes.

Data extraction and quality assessment

Two independent researchers extracted the data using a standardized form. Two independent raters assessed the risk of bias in included studies using Cochrane's revised risk of bias tool for randomized trials[25]. We assessed the risk of bias for each comparison within the included studies referring to the primary outcome. Any disagreement between the two raters was resolved through discussion or in consultation with a third reviewer.

Data synthesis and analysis

We evaluated psychotherapies (PSY), protocolized pharmacotherapies (PHA), and their combinations (COM), each of which could be continued into the maintenance treatment, switched to another treatment, or followed by discretionary treatment (nat). Controls were treatment as usual in primary or secondary care followed by the same discretionary treatment (STD), and pill placebo used through the acute and maintenance phase. Psychotherapies combined with protocolized pharmacotherapy or with non-protocolized primary or secondary care pharmacotherapy were counted towards COM. The influence of including the latter was examined in a sensitivity analysis.

We estimated the comparative efficacy and acceptability of these alternative treatments using the NMA methodology, by combining direct and indirect evidence for all relative treatment effects. We conducted contrast-based NMA to estimate odds ratios (ORs) with their 95% confidence intervals (CIs)[26-28]. Given the likely clinical and methodological heterogeneity among the included trials, we used the random effects model.

To examine the transitivity assumption that effect modifiers are distributed evenly across comparisons in the network (a primary requisite of NMA), we first made a table of important trial characteristics of the studies per comparison. We also examined transitivity statistically for the closed network by checking its consistency with the side-splitting test[29] and the design-by-treatment interaction test[30]. We evaluated the heterogeneity in the network with tau-squared in comparison with empirically derived evidence[31]. We further conducted a multivariate meta-regression analysis on age, proportion of women, baseline depression severity and total duration of treatment in order to examine if such factors affected constancy of ORs in the network.

We assessed small study effects, including publication bias, through visual inspection of the contour-enhanced funnel plot[32] and Egger's test[33] of the aggregated pairwise comparisons between active interventions and control conditions.

We also performed several sensitivity analyses: a) limiting to studies which reported narrowly defined sustained response (see above); b) limiting to studies which followed up more than 90% of the randomized patients in all of their arms; c) limiting to studies in which the total duration of treatment was 12 months or longer; d) excluding studies at high risk of bias; e) excluding arms with non-protocolized primary or secondary care pharmacotherapy, because its contents may vary greatly; f) excluding arms with pill placebo, because they may change the nature of the trials[34]; and g) distinguishing all the subcategories of interventions or control conditions. We used CINeMA[35] to evaluate certainty of evidence for the network estimates.

The absolute benefits of the therapies were calculated from the ORs and the control event rate (CER) using the following formulae: RR=OR/(1–CER+OR*CER); EER=CER*RR; RD=EER–CER, where RR is the relative risk, EER is the event rate in the intervention group, and RD is the risk difference (absolute benefit)[36-38].

We employed the package netmeta 1.2-1 and dmetar 0.0.9 in R 4.0.3 (R Core Team, Vienna, Austria, 2020). Network meta-regressions were conducted with the network package[39] in STATA 16.1 (StataCorp, Texas, USA, 2020).

RESULTS

Studies selected and their characteristics

After examining 89,087 references in the three databases and 878 full text articles in detail, we included 81 studies (N=13,722). The PRISMA flow chart is presented in Figure 2. The references for the included trials and the reasons for exclusion of the others are provided in the supplementary information.

Table 1 summarizes the baseline characteristics of the included trials and their participants. The participants' weighted mean age (reported for 12,940 people) was 43.4±10.1, and 68% of the participants (8,668 out of 12,749 people for whom gender was reported) were women. The patients' baseline total score on the 17-item Hamilton Rating Scale for Depression[40] was 21.8±5.4 in the 42 studies (N=7,918) that used this scale. The average total duration of treatment was 42.2±16.2 weeks (range: 24-104 months) for the 81 studies. The average duration of the acute phase of treatment was 10.4±4.8 weeks for 79 studies (two studies only provided the total length of acute plus maintenance phase and continued the same treatment through both phases). The weighted mean follow-up rate was 74.5%.

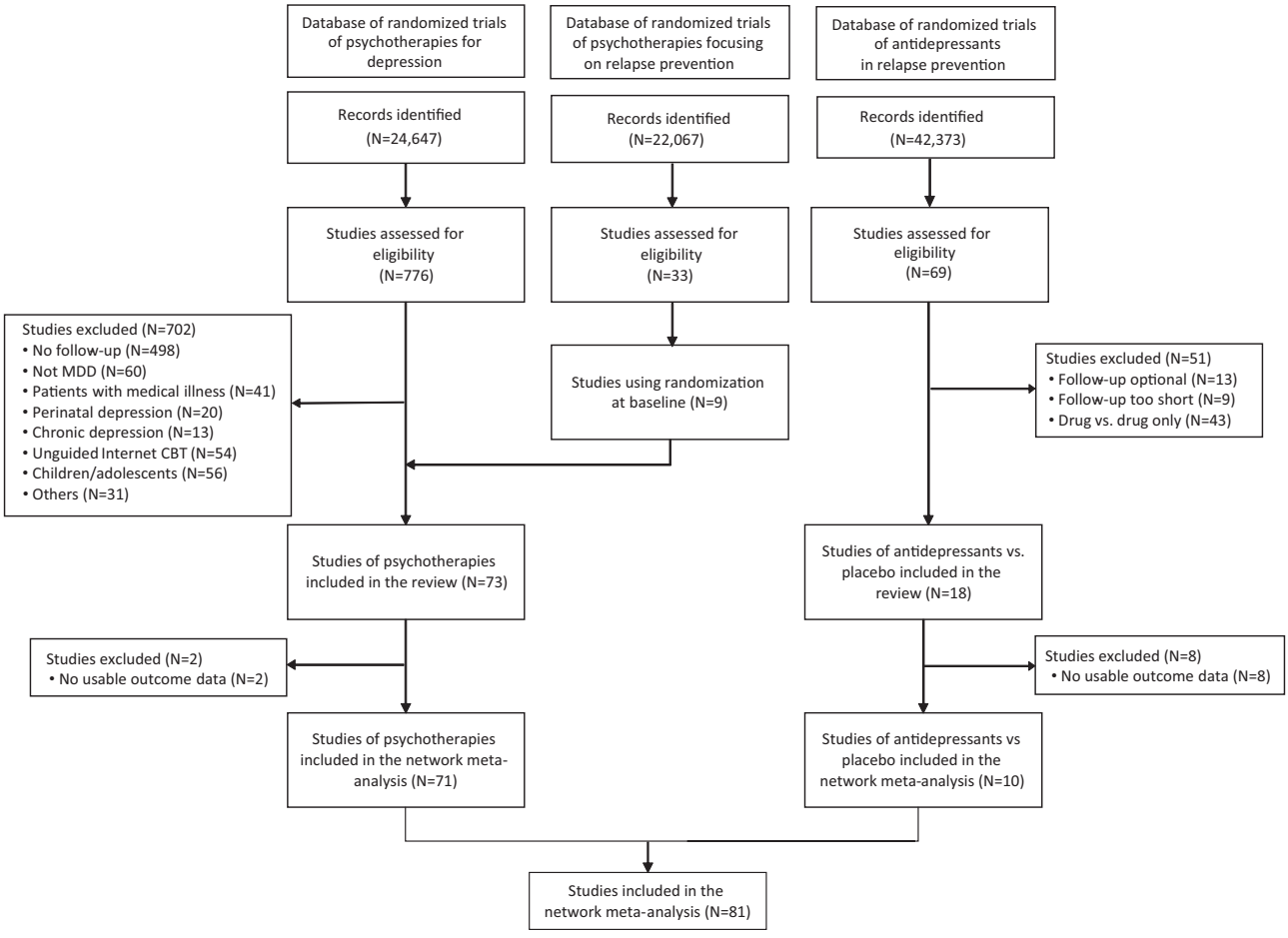

Figure 2 PRISMA flow chart. MDD – major depressive disorder, CBT – cognitive behavioral therapy

Table 1 Summary characteristics of the 81 included studies

Study design	
Type B	64
Type C	17
Number of arms (total=211)	
Two	44
Three	26
Four	10
Six	1
Publication year	
Earliest	1981
Median	2008
Latest	2019
Region	
North America	28
Europe	37
Asia	7
Cross-continental/Other	9
Randomization	
Individual	78
Cluster	3
Number of study centers	
Single	30
Multiple	51
Patient status	
Outpatients	59
Community	12
Inpatients	6
Others/Unclear	4
Treatment setting	
Community	11
Primary care	15
Secondary/Tertiary care	41
Others/Unclear	14
Diagnostic criteria	
DSM-5	2
DSM-IV	47
DSM-III-R	9
DSM-III	4
ICD-10	7
Research Diagnostic Criteria	8
Feighner criteria	4
Patients' gender, N women (%)	8,668/12,749 (68.0)
Patients' age (years, mean±SD)	43.4±10.1
Depression baseline severity (mean±SD)	
HAMD-17 (42 studies)	21.8±5.4
BDI (8 studies)	24.9±7.6
BDI-II (7 studies)	26.8±9.3
Recurrent depression, % (32 studies)	62.6
Length of acute treatment (weeks, mean±SD) (79 studies)	10.4±4.8 (range: 4-30)
Length of total treatment (weeks, mean±SD) (81 studies)	42.2±16.2 (range: 24-104)
Follow-up rate, %	74.5

HAMD-17 – 17-item Hamilton Rating Scale for Depression, BDI – Beck Depression Inventory, BDI-II – Beck Depression Inventory, 2nd version

The 81 studies included 211 arms, which could be classified into 10 types and 34 subtypes of interventions. The most frequently examined intervention types included COM followed by naturalistic follow-up (COM→nat, 65 arms), PHA continued into the maintenance phase (PHA→PHA, 34 arms), PSY followed by naturalistic follow-up (PSY→nat, 30 arms), and treatment as usual in primary or secondary care through the acute and maintenance phase (STD, 25 arms).

The most frequently used types of psychotherapies in PSY and COM included CBT (59 arms), SUP (16 arms), IPT (11 arms), BA (8 arms), and DYN (7 arms). The most frequently used antidepressants were duloxetine (N=906 of 5,714 reported, 15.8%), agomelatine (N=836, 14.6%), paroxetine (N=644, 11.3%), venlafaxine (N=583, 10.2%) and fluoxetine (N=296, 5.2%).

Of the 155 comparisons, 40.6% were rated low for susceptibility bias, 49.4% for performance bias, 37.4% for attrition bias, 53.5% for assessment bias, and 1.3% for reporting bias. Overall, 89 (60.5%) were rated at high, 49 (33.3%) at moderate and 9 (6.1%) at low overall risk of bias.

Network meta-analyses

Figure 3 presents the network of the interventions for the primary outcome. The nodes are well connected. Table 2 presents the network meta-analysis results for the primary outcome (sustained response) and the secondary outcome (all-cause discontinuation), and Figures 4 and 5 illustrate their ranked forest plots in comparison with STD.

COM brought about more sustained response than PHA, both if these treatments were continued into the maintenance phase (COM→COM vs. PHA→PHA: OR=2.52, 95% CI: 1.66-3.85) and if they were followed by discretionary treatment (COM→nat vs. PHA→nat: OR=1.80, 95% CI: 1.21-2.67). The same applied to COM when compared with standard therapy through the acute and maintenance phases (COM→COM vs. STD: OR=2.90, 95% CI: 1.68-5.01; COM→nat vs. STD: OR=1.97, 95% CI: 1.51-2.58)

(see Table 2 and Figure 4).

PSY was also more efficacious than PHA, both if these treatments were continued into the maintenance phase (PSY→PSY vs. PHA→PHA: OR=1.53, 95% CI: 1.00-2.35) and if they were followed by discretionary treatment (PSY→nat vs. PHA→nat: OR=1.66, 95% CI: 1.13-2.44). The same applied to PSY when compared with standard therapy through the acute and maintenance phases (PSY→PSY vs. STD: OR=1.76, 95% CI: 0.97-3.21; PSY→nat vs. STD: OR=1.83, 95% CI: 1.20-2.78) (see Table 2 and Figure 4).

PHA, continued or followed by discretionary treatment, did not differentiate from STD (PHA→PHA vs. STD: OR=1.15, 95% CI: 0.69-1.92; PHA→nat vs. STD: OR=1.10, 95% CI: 0.70-1.73) (see Table 2 and Figure 4).

Given the average sustained response rate on STD of 29% at 12 months (367 of 1,283 reported), the advantage ("absolute benefit") of COM→nat over PHA→nat and STD would translate into a risk difference, respectively, of 14% (95% CI: 4 to 24%) and 16% (95% CI: 9 to 22%), while the advantage of PSY→nat over PHA→nat and STD can be calculated, respectively, as 12% (95% CI: 2 to 20%) and 14% (95% CI: 4 to 24%).

In terms of all-cause discontinuation, all the treatments appeared more acceptable than pill placebo. COM, PHA or PSY followed by discretionary treatment were generally as acceptable as STD. By contrast, stricter follow-up regimens, either by COM, PHA or PSY, tended to lead to more dropouts than STD (see Table 2 and Figure 5).

Transitivity of the network was preserved in terms of age, gender, and baseline depression severity. The global test of transitivity assumption was not suggestive of network inconsistency (p=0.98); none of the side-splitting tests revealed inconsistency beyond chance. The common heterogeneity parameter tau-squared was 0.196, within the empirically expected range for subjective outcomes for non-pharmacological interventions[31]. In network meta-regressions to examine sources of heterogeneity, age, proportion of women, baseline severity of depression and total duration of treatment, alone or in combination, did not show statistically significant effect modifications for any of the interventions. Funnel plots of active interventions against control conditions were not suggestive of small study effects (p=0.84 and p=0.21, respectively).

The overall proportions of dropouts due to adverse events or suicidality through the long-term treatment were 10.3% (64 out of 619 reported in 6 studies) and 3.7% (29 out of 777 reported in 8 studies), respectively.

The sensitivity analyses sometimes had wide confidence intervals but generally produced results convergent with the primary analysis for sustained response. The results were more variable with regard to all-cause discontinuation (see supplementary information).

We also conducted NMA distinguishing all intervention subtypes. There was suggestive evidence that combining DYN, CBT, IPT or BA with antidepressant pharmacotherapy or treatment as usual led to more sustained response than STD. The same was true for CBT (either continued in the maintenance phase or followed by discretionary treatment), and for BA (followed by discretionary treatment) compared to STD (see Figure 6).

The certainty of evidence was rated as moderate for COM→COM and COM→nat vs. STD; as low for PSY→PSY and PSY→nat vs. STD; as low for PHA→PHA vs. STD, and as moderate for PHA→nat vs. STD. It was high only for COM→COM and COM→nat vs. pill placebo (see supplementary information).

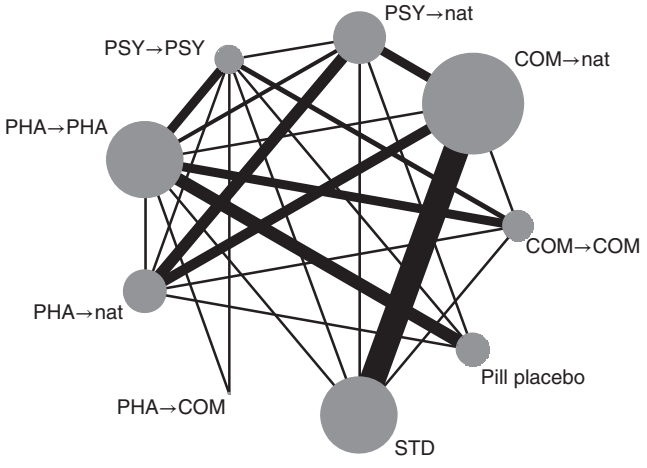

Figure 3 Network diagram for sustained response. COM – combination therapies, PHA – pharmacotherapies, PSY – psychotherapies, STD – standard treatment in primary or secondary care, nat – discretionary treatment. The size of the node is proportionate to the number of participants allocated to that node; the width of the line is proportionate to the number of studies examining that comparison.

DISCUSSION

We conducted the first systematic review and network meta-analysis of the initial intervention choices for major depressive episodes aimed to maximize the chance of not only getting the patients well but also keeping them well. We identified 81 relevant studies (13,722 patients), which constituted a well-connected network of pharmacotherapies, psychotherapies and their combinations with little overall evidence of intransitivity, inconsistency, heterogeneity or publication bias. Various sensitivity analyses corroborated the primary findings.

There were two major findings of this study. First, acute phase combination therapies, either continued into the maintenance phase (COM→COM) or followed by discretionary treatment (COM→nat), outperformed both acute phase pharmacotherapies, continued or followed by discretionary treatment (PHA→PHA and PHA→nat), and standard therapy through the acute and maintenance phases (STD). Given the average sustained response rate of 29% on STD, the advantages of COM over PHA or STD translated into risk differences ranging from 14 to 16 percentage points. Second, psychotherapies, continued into the maintenance phase (PSY→PSY) or followed by discretionary treatment (PSY→nat), also outperformed pharmacotherapies and standard

Table 2 Network meta-analyses for sustained response (efficacy) and all-cause discontinuation (acceptability) of various treatment modalities

COM→COM	**1.92 (1.04-3.54)**	1.31 (0.68-2.51)	0.95 (0.57-1.58)	0.68 (0.43-1.07)	1.43 (0.75-2.75)	0.81 (0.19-3.55)	1.45 (0.78-2.68)	**0.33 (0.18-0.60)**
1.47 (0.85-2.53)	COM→nat	0.68 (0.44-1.07)	**0.50 (0.25-0.97)**	**0.35 (0.20-0.64)**	0.75 (0.48-1.16)	0.42 (0.09-1.95)	0.76 (0.56-1.02)	**0.17 (0.08-0.35)**
1.59 (0.91-2.76)	1.08 (0.74-1.56)	PSY→nat	0.73 (0.36-1.45)	**0.52 (0.28-0.94)**	1.09 (0.70-1.70)	0.62 (0.13-2.88)	1.11 (0.68-1.81)	**0.25 (0.12-0.51)**
1.65 (1.04-2.61)	1.12 (0.62-2.03)	1.04 (0.57-1.88)	PSY→PSY	0.71 (0.45-1.14)	1.50 (0.74-3.04)	0.85 (0.20-3.57)	1.52 (0.78-2.99)	**0.34 (0.19-0.64)**
2.52 (1.66-3.85)	**1.72 (1.04-2.84)**	1.59 (0.98-2.60)	**1.53 (1.00-2.35)**	PHA→PHA	**2.11 (1.13-3.91)**	1.20 (0.29-4.99)	**2.13 (1.19-3.84)**	**0.48 (0.32-0.73)**
2.64 (1.46-4.76)	**1.80 (1.21-2.67)**	**1.66 (1.13-2.44)**	1.60 (0.85-3.02)	1.05 (0.61-1.81)	PHA→nat	0.57 (0.12-2.65)	1.01 (0.62-1.67)	**0.23 (0.11-0.48)**
2.97 (0.71-12.45)	2.02 (0.46-8.79)	1.87 (0.43-8.13)	1.80 (0.45-7.26)	1.18 (0.29-4.76)	1.12 (0.25-4.98)	PHA→COM	1.78 (0.39-8.21)	0.40 (0.09-1.78)
2.90 (1.68-5.01)	**1.97 (1.51-2.58)**	**1.83 (1.20-2.78)**	**1.76 (0.97-3.21)**	1.15 (0.69-1.92)	1.10 (0.70-1.73)	0.98 (0.22-4.27)	STD	**0.23 (0.11-0.46)**
5.05 (3.00-8.51)	**3.44 (1.91-6.18)**	**3.18 (1.79-5.66)**	**3.06 (1.81-5.18)**	**2.00 (1.47-2.73)**	**1.91 (1.02-3.57)**	1.70 (0.41-7.13)	1.74 (0.96-3.16)	Pill placebo

Values are odds ratios (ORs) with 95% confidence intervals. OR>1 in the lower-left half indicates that the treatment in the column is more effective than the treatment in the row. OR<1 in the upper-right half indicates that the treatment in the row is more acceptable than the treatment in the column. COM – combination therapies, PHA – pharmacotherapies, PSY – psychotherapies, STD – standard treatment in primary or secondary care, nat – discretionary treatment

therapy. The expected advantages were 12% for psychotherapies followed by discretionary treatment (PSY→nat) over the corresponding pharmacotherapies (PHA→nat), and 14% over STD.

In the current systematic review, pharmacotherapies, while demonstrably superior to pill placebo, did not differentiate from standard treatment either if continued into the maintenance phase or followed by discretionary treatment.

This study provides strong answers to two long-held questions about psychotherapies[11]. First, it shows that the effects of acute phase psychotherapies are enduring. There was suspicion that, even when those responding to acute phase psychotherapies but receiving no further psychotherapy did as well as those responding to acute phase pharmacotherapies and receiving maintenance pharmacotherapies[5], this would not constitute proof that the acute effects of psychotherapies were enduring. The assumption was that those responding to acute phase psychotherapies may be systematically different from those responding to acute phase pharmacotherapies[11,41]. In this study, we only included trials that randomized participants into psychotherapies or pharmacotherapies at the beginning of the acute treatment and took these numbers as denominators in the analyses according to the intention-to-treat principle. The results clearly show that

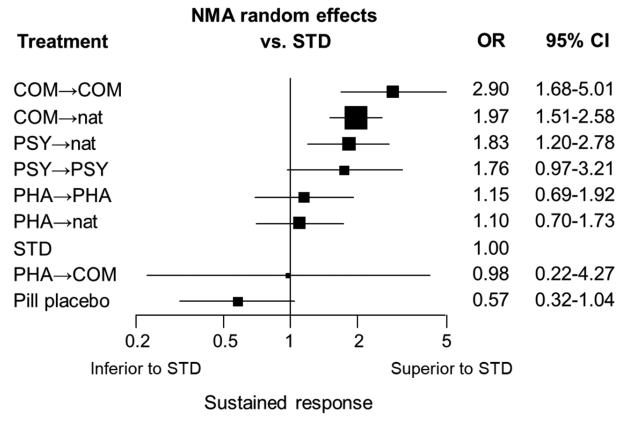

Figure 4 Ranked forest plot for sustained response. NMA – network meta-analysis, OR – odds ratio, CI – confidence interval, COM – combination therapies, PHA – pharmacotherapies, PSY – psychotherapies, STD – standard treatment in primary or secondary care, nat – discretionary treatment

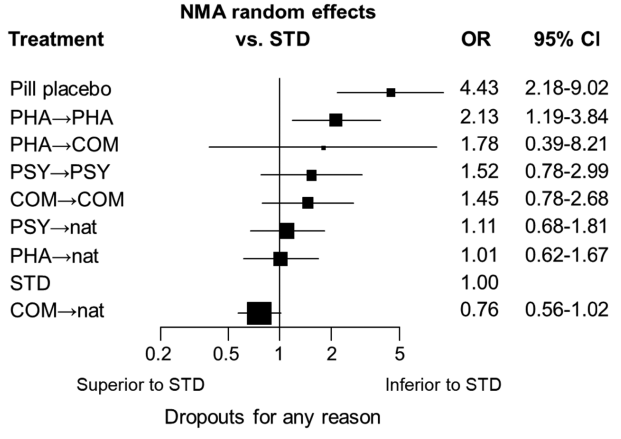

Figure 5 Ranked forest plot for all-cause discontinuation. NMA – network meta-analysis, OR – odds ratio, CI – confidence interval, COM – combination therapies, PHA – pharmacotherapies, PSY – psychotherapies, STD – standard treatment in primary or secondary care, nat – discretionary treatment

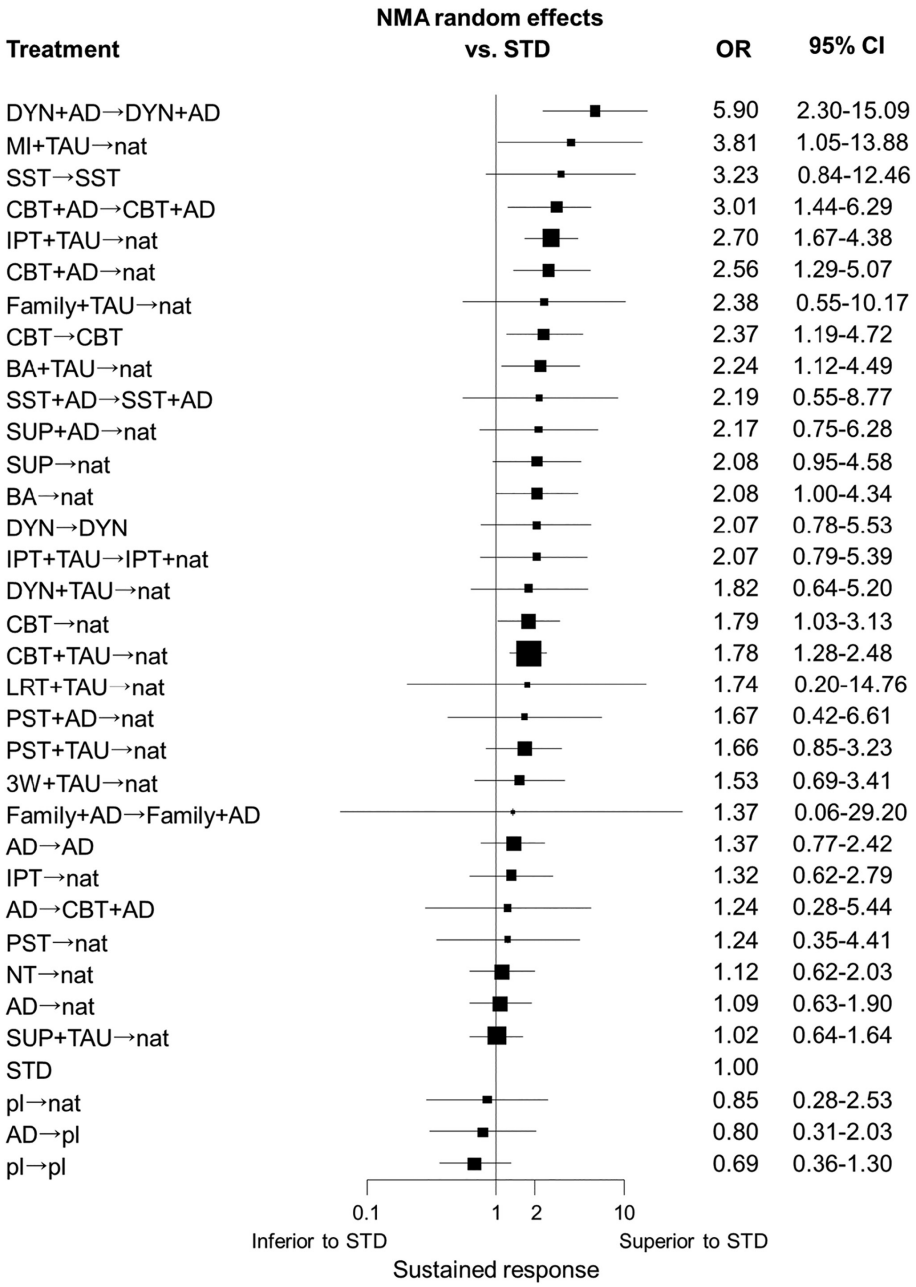

Figure 6 Ranked forest plot for sustained response with intervention subtypes. NMA – network meta-analysis, OR – odds ratio, CI – confidence interval, STD – standard treatment in primary or secondary care, DYN – psychodynamic therapy, AD – protocolized antidepressant pharmacotherapy, MI – motivational interviewing, TAU – treatment as usual, nat – discretionary treatment, SST – social skills training, CBT – cognitive behavioral therapy, IPT – interpersonal therapy, Family – family therapy, BA – behavioral activation therapy, SUP – non-directive supportive therapy, LRT – life review therapy, PST – problem-solving therapy, 3W – third-wave cognitive behavioral therapy, NT – no treatment, pl – pill placebo

acute phase psychotherapies, even when not followed by maintenance psychotherapies, outperformed protocolized pharmacotherapies, standard treatment, and pill placebo.

Second, the findings suggest that adding pharmacotherapies does not interfere with the enduring effects of psychotherapies. The combination therapies followed by discretionary treatment were as effective as the corresponding psychotherapies (OR=1.08, 95% CI: 0.74-1.56), although the confidence intervals are relatively wide and cannot completely exclude the interference hypothesis (according to which the OR should be smaller than 1.0)[11,42].

The duration of total treatment ranged between 6 and 24 months. However, heterogeneity among the relative treatment effects was within empirically expected ranges[31]. Moreover, network meta-regression showed no evidence of an influence of the timing of the follow-up on ORs for any treatment comparisons.

A sensitivity analysis limiting studies to those in which the duration of treatment was 12 months or longer also produced similar results. It is therefore safe to assume that the obtained ORs for sustained response remain reasonably constant for total lengths of treatment ranging between 6 and 24 months. Such constancy of relative effect indices is in line with findings from pharmacological maintenance therapies for depression[3] and, more generally, across medical interventions[36].

There are many types of psychotherapies and pharmacotherapies. While there is only limited evidence supporting differences within each category[1,2], it would be helpful for clinical purposes to have insight as to which particular therapies are backed by stronger evidence. When we conducted the network meta-analysis for different subtypes of psychotherapies, there was consistent evidence that CBT (in combination or alone) and BA led to more sustained response than standard treatment. There were less consistent but similar trends for DYN and IPT. For other psychotherapies, there were too few studies and the corresponding confidence intervals were wide. With regard to pharmacotherapies, we were unable to examine the subtle differences among individual antidepressants in their ability to achieve sustained response. There were too many antidepressants used in the current network (hence too few patients for individual drugs) and several studies allowed use of several different antidepressants within their arms.

This study has several limitations. First, the maximum duration of the included trials was 24 months. The relative performance of the initial treatment choices if followed up for longer periods remains unknown. Second, many trials used a naturalistic follow-up after their protocolized acute treatment phase, and the exact content of treatment in the follow-up phase was seldom reported. Differences in this phase may have affected sustained response rates. However, such concerns are mitigated as the rankings among COM, PSY and PHA were similar when they were followed by discretionary treatment or when each was continued into the maintenance phase, as well as in a sensitivity analysis excluding trials using the discretionary follow-up.

Third, the weighted mean follow-up rate was 74.5%. The superiority of COM or PSY by 12-16% could be counterbalanced by whatever may have happened to the 25% who were lost to follow-up. However, a sensitivity analysis limiting to studies with 90% or greater follow-up confirmed the superiority of PSY and COM over STD. Fourth, only trials comparing PHA versus placebo could have been double-blind, which may have disadvantaged PHA in comparison with other treatments which were examined only in single-blind or open studies. The network without placebo-controlled trials, however, produced essentially similar efficacy estimates for all comparisons.

Fifth, the adverse effects of the available treatment choices were not well documented in the original studies and were therefore not amenable to systematic comparisons in the current network meta-analysis. Rare but critical events such as suicidality, and more common yet subtle downsides such as withdrawal symptoms from antidepressants should be more systematically measured and reported to appropriately inform our treatment choices[43].

Lastly, we did not examine studies that randomized the remitted patients to completely new treatments after successful acute therapies[6]. Wisely sequencing different treatments has a potential to perform even better than simply choosing the best initial treatment[44-46].

CONCLUSIONS

Initiating the treatment of a major depressive episode with combination therapies or psychotherapies alone may lead to 12-16% increments in rates of sustained response at one year, relative to protocolized pharmacotherapies or standard treatment in primary or secondary care. Psychotherapies with the greatest support for such superiority include CBT, BA, and to a lesser degree DYN and IPT. Patients and their therapists may be well advised to seriously consider these psychotherapies as their initial treatment choices. However, availability and affordability of quality psychotherapies may be a major obstacle[47-49].

Combining psychotherapies with pharmacotherapies has an edge in terms of sustained response but has risks of side effects and potential withdrawal symptoms. Such combinations may be reserved for those who value faster relief or who may be deemed difficult to treat[22]. Others may wish to consider them as sequenced treatments when initial therapies fail.

Findings from this study are robust enough to put the currently dominant practices relying on antidepressants into perspective, especially in the context of increasingly prevalent and protracted prescriptions[7,8]. Clinical guidelines may need to be updated accordingly. We also call for appropriately designed and adequately powered studies that examine alternative and sequential strategies to both get patients well and keep them well. Such studies need to consider cost-effectiveness and monitor suicidality and withdrawal symptoms systematically.

ACKNOWLEDGEMENTS

This study was supported by the Japan Society for the Promotion of Science (grant no. 17K19808). E.G. Ostinelli is supported by the National Institute for Health Research (NIHR) Oxford Cognitive Health Clinical Research Facility, and by the NIHR Oxford Health Biomedical Research Centre (grant no. BRC-1215-20005). A. Cipriani is supported by the NIHR Oxford Cognitive Health Clinical Research Facility, by an NIHR Research Professorship (grant no. RP-2017-08-ST2-006), by the NIHR Oxford and Thames Valley Applied Research Collaboration, and by the NIHR Oxford Health Biomedical Research Centre (grant no. BRC-1215-20005). Supplementary information on the study is available at https://osf.io/5qfuv/.

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DOI:10.1002/wps.20906

Repetitive transcranial magnetic stimulation for smoking cessation: a pivotal multicenter double-blind randomized controlled trial

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Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation method increasingly used to treat psychiatric disorders, primarily depression. Initial studies suggest that rTMS may help to treat addictions, but evaluation in multicenter randomized controlled trials (RCTs) is needed. We conducted a multicenter double-blind RCT in 262 chronic smokers meeting DSM-5 criteria for tobacco use disorder, who had made at least one prior failed attempt to quit, with 68% having made at least three failed attempts. They received three weeks of daily bilateral active or sham rTMS to the lateral prefrontal and insular cortices, followed by once weekly rTMS for three weeks. Each rTMS session was administered following a cue-induced craving procedure, and participants were monitored for a total of six weeks. Those in abstinence were monitored for additional 12 weeks. The primary outcome measure was the four-week continuous quit rate (CQR) until Week 18 in the intent-to-treat efficacy set, as determined by daily smoking diaries and verified by urine cotinine measures. The trial was registered at ClinicalTrials.gov (NCT02126124). In the intent-to-treat analysis set (N=234), the CQR until Week 18 was 19.4% following active and 8.7% following sham rTMS (X^2=5.655, p=0.017). Among completers (N=169), the CQR until Week 18 was 28.0% and 11.7%, respectively (X^2=7.219, p=0.007). The reduction in cigarette consumption and craving was significantly greater in the active than the sham group as early as two weeks into treatment. This study establishes a safe treatment protocol that promotes smoking cessation by stimulating relevant brain circuits. It represents the first large multicenter RCT of brain stimulation in addiction medicine, and has led to the first clearance by the US Food and Drug Administration for rTMS as an aid in smoking cessation for adults.

Key words: Smoking cessation, repetitive transcranial magnetic stimulation, cigarette consumption, cigarette craving, lateral prefrontal cortex, insula, addiction medicine

(World Psychiatry 2021;20:397–404)

Transcranial magnetic stimulation (TMS) non-invasively stimulates neuronal tissue in awake humans and has been used in research since 1985 and in clinical practice since 2008[1]. Brief electric pulses are delivered using an electromagnetic coil placed over selected brain areas, which induce electrical currents in the underlying cortical tissue and neuronal depolarization[2].

Repetitive TMS (rTMS) pulses applied in daily sessions can induce long-term modification in mood and behavior[1]. Following multicenter randomized controlled trials (RCTs) that demonstrated both safety and efficacy, specific rTMS coils and protocols have been used in the treatment of depression and obsessive-compulsive disorder[3-5]. In these conditions, rTMS can serve as an alternative for patients who cannot tolerate medication side effects, or who do not sufficiently benefit from pharmacological or psychotherapeutic options.

Substance use disorders affect hundreds of millions of people globally. Treatment options are limited, despite advances in neuroscience that have started to elucidate the brain regions involved[6,7]. Tobacco use disorder is the most common substance use disorder in many countries worldwide. It is characterized by craving and withdrawal, compulsive use despite negative consequences, and repeated relapses, and is associated with multiple health problems and failed attempts at cessation[8-11].

Animal and small sample size human studies have demonstrated that rTMS of the prefrontal cortex affects the neural substrate of substance use disorders and reduces craving and consumption of substances of abuse, including nicotine[12-18]. The majority of studies applied focal rTMS over the dorsolateral prefrontal cortex, while a previous pilot study from our group targeted deeper layers of the lateral prefrontal and insular cortices of subjects with tobacco use disorder[19,20]. In that study, 15 active rTMS sessions (20 min/weekday for three weeks), compared to sham, induced a significantly higher quit rate and reduced cigarette consumption. Increased inhibitory control over the compulsive desire to smoke and disruption of circuits associated with craving were proposed as mechanisms accounting for the therapeutic effect[19].

Here, we report the results of a prospective multicenter double-blind RCT, which was based on our pilot study and followed the recommendations of a consensus paper outlining the criteria for brain stimulation studies in substance use disorders[21]. This trial has led to the first clearance by the US Food and Drug Administration (FDA) for rTMS as an aid in smoking cessation for adults.

METHODS

Study design and participants

The study was conducted in the US (12 sites) and Israel (two sites), with active enrollment from August 2014 through August 2019. The trial protocol was approved by local institutional review boards and registered at clinicaltrials.gov (NCT02126124).

We included adults aged 22-70 years who were chronic smokers (at least ten cigarettes/day for at least one year) and met the DSM-5 criteria for tobacco use disorder[8]. In addition, participants had to be motivated to quit (replying "very likely" or "somewhat likely" to a motivation questionnaire) and with no period of abstinence of more than three months in the past year. All subjects provided informed consent for participation in the study, and gave satisfactory answers on a safety screening questionnaire for TMS[22].

Key exclusion criteria were current treatment for smoking, use of nicotine other than through cigarettes, any other active psychiatric disorder diagnosed according to the DSM-5, any other substance use disorder during the last 12 months before recruitment, use of any psychotropic medication on a regular basis, history of epilepsy or seizures (except those therapeutically induced by electroconvulsive therapy) or increased risk of seizures for any reason, any significant neurological disorder or insult, history of any metal in the head (outside the mouth) or metallic implant, and known or suspected pregnancy or lactation.

Procedures

Eligible participants were randomized and allocated to treatment groups (1:1). A central interactive web-based randomization system assigned a unique participant randomization code, which matched pre-programmed cards maintained at the centers and determined the nature of rTMS (active or sham), such that participants, operators and raters were blinded to the treatment condition.

The timeline for treatment and assessments is provided in Figure 1. Following randomization and selection of a target quit date within the first two weeks of treatment ("grace period"), daily rTMS (active or sham) was applied for three weeks (five sessions/week), while subjects provided daily smoking diaries and (once a week) urine samples for assessment of cotinine levels. At each visit, the number of cigarettes smoked was recorded through the Nicotine Use Inventory (NUI), and adverse events were monitored. The Tobacco Craving Questionnaire (TCQ)[23] and the Fagerström Test for Nicotine Dependence (FTND)[24] were administered weekly.

An additional three weeks of once-weekly rTMS were then delivered, while participants continued to provide daily smoking diaries. Urine samples were collected, adverse events monitored, and the TCQ and FTND administered at each visit. Participants who were abstinent at the last visit (Week 6) were invited for a long-term follow-up, with an additional visit four months after the "grace period" (Week 18). Abstinence was defined as a self-report of no smoking (zero cigarettes/day) confirmed by urine cotinine levels lower than 200 ng/ml[25,26]. During the long-term follow-up, subjects kept on providing daily smoking diaries. Urine samples were collected, adverse events monitored, and the TCQ and FTND administered at Week 18.

The Minnesota Nicotine Withdrawal Scale (MNWS)[27] (both self-reported and observer-reported), the Mini-Mental State Examination (MMSE)[28] and the Buschke Selective Reminding Test (BSRT)[29] were administered at baseline and at Weeks 6 and 18 to assess withdrawal symptoms and cognition.

Treatment was delivered using a Magstim Rapid2 TMS stimulator (Magstim, UK) equipped with the H4-coil (BrainsWay, Israel). The H4 coil has been shown to bilaterally stimulate neuronal pathways in the lateral prefrontal cortex and insula with an in-

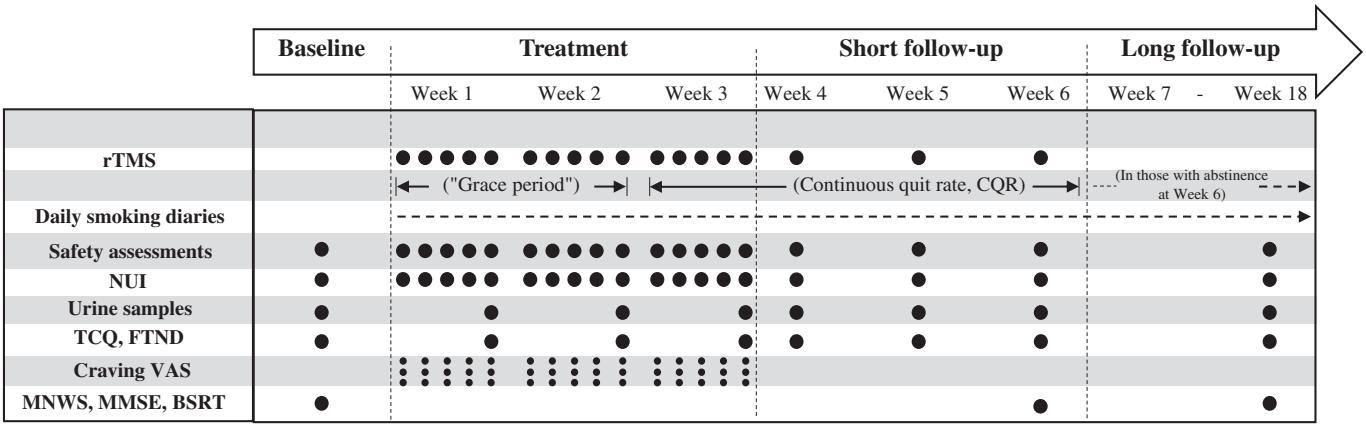

Figure 1 Timeline for treatment and assessments. rTMS – repetitive transcranial magnetic stimulation (active or sham), NUI – Nicotine Use Inventory, TCQ – Tobacco Craving Questionnaire, FTND – Fagerström Test for Nicotine Dependence, VAS – Visual Analogue Scale (before provocation procedure, after provocation procedure, and after rTMS session), MNWS – Minnesota Nicotine Withdrawal Scale, MMSE – Mini-Mental State Examination, BSRT – Buschke Selective Reminding Test

tensity above the neuronal threshold for activation[19,30] (see supplementary information).

For each participant, the rTMS intensity was set using the individual's minimal motor threshold, which was obtained by localizing the optimal helmet position on the scalp for activation of the right abductor pollicis brevis muscle[19]. The helmet was then aligned symmetrically and moved 6 cm anteriorly. Each participant was assigned a unique magnetic card that, when inserted into the TMS machine, determined which coil within the helmet (active or sham) would be used. The sham coil (encased in the same helmet) induced acoustic and scalp sensations similar to those induced by the active coil, but without electromagnetic penetration into the brain and without neural activation[4,19]. The intensity of the stimulator was set to 120% of the minimal motor threshold. Sixty rTMS trains of 30 pulses (i.e., a total of 1,800 pulses) were applied at 10 Hz (3 sec each train) with 15 sec intertrain intervals.

Participants were instructed to refrain from smoking for at least two hours prior to each visit. Each rTMS session was preceded by a 5-min provocation procedure, which included participants imagining their greatest trigger for craving, listening to an audio script with instructions to handle a cigarette and a lighter, and viewing pictures of smoking (see supplementary information). Craving was assessed three times: before the provocation procedure, after the provocation, and after the rTMS session (Visual Analogue Scale, VAS – respectively, VAS1, VAS2 and VAS3). Following each rTMS session, a short (~2 min) motivational talk based on the booklet "Clearing the Air", and supporting the decision to quit, was read to each participant[31] (see supplementary information).

Outcome measures

The primary outcome measure was the four-week continuous quit rate (CQR) until Week 18 among participants composing the intent-to-treat efficacy set (i.e., the percentage of quitters among all randomized participants who met eligibility criteria and had at least one post-baseline assessment). Secondary endpoints included the CQR until Week 18 in the completer analysis set, the CQR until Week 6, and changes in cigarette consumption and craving.

Criteria for discontinuation included missing three consecutive sessions or four total sessions, or the occurrence of a serious adverse event.

Statistical analysis

The weighted average of our pilot study and former pharmacological studies resulted in a difference of about 20% in abstinence rates between the treatment and control groups[19,32-35]. Aiming at this difference between groups and a 80% power with a two-sided level of significance of 5%, and allowing for a potential 40% drop-out, a total of about 270 participants were required.

The CQR was compared between the study groups by a chi-squared test and modeled with logistic regression. The number of cigarettes smoked and TCQ scores were presented over time and analyzed with a repeated measures analysis of covariance model. Craving VAS scores were presented over time and analyzed with a repeated measures analysis.

For comparison of means, the two-sample t-test or the Wilcoxon rank-sum test was used. For comparison of proportions, the chi-squared test or Fisher's exact test was used, as appropriate. The hierarchical approach was adopted for the planned endpoints to control for type I error (i.e., analyzing the next endpoint in the hierarchy only if the previous endpoint analysis was found significant). Nominal p values are presented.

A detailed description of the statistical analysis is provided in the supplementary information.

RESULTS

Characteristics of the patients

A total of 262 participants were enrolled in the study, with 123 randomized to receive active rTMS and 139 sham rTMS. The intent-to-treat efficacy sample included the 234 randomized participants who had at least one post-baseline assessment. The completer analysis sample included the 169 randomized participants who completed the three weeks of treatment and the measures relevant to the four-week CQR determination (following the "grace period") at Week 6. The CONSORT diagram is provided in the supplementary information.

No statistically significant differences were found between the study groups with respect to baseline demographic or clinical data, including nicotine withdrawal and craving assessment scales, except for the MNWS observer-reported scores (see Table 1). Participants in the active group had been smoking for an average of 27.1±13.0 years, while those in the sham group for an average of 26.2±13.7 years. All participants had made at least one prior failed attempt to quit using various methods, with 68% having made at least three failed attempts, and 27% having made more than five failed attempts (see Table 1).

Efficacy analysis

The CQR was significantly higher in the active group until both Week 6 and Week 18 (Figure 2). The CQR of completers until Week 6 was 25.3% for the active group and 6.4% for the sham group (X^2=11.885, p=0.0006). Only participants who were abstinent at the Week 6 visit were followed up to Week 18. Of these participants, 63% (active group) and 50% (sham group) remained non-smokers until Week 18 (X^2=8.46, p=0.003). In the intent-to-treat set, the CQR until Week 18 was 19.4% for the active group and 8.7% for the sham group (X^2=5.655, p=0.017), while in completers it was 28.0% and 11.7%, respectively (X^2=7.219, p=0.007).

The number of cigarettes smoked and the TCQ total score (crav-

Table 1 Demographic and clinical features of patients randomized to receive active or sham repetitive transcranial magnetic stimulation

	Active (N=123)	Sham (N=139)	p
Gender (% female)	48.8	47.5	0.834
Age (years, mean±SD)	45.0±13.0	44.8±13.4	0.946
Years of education (%)	45.0±13.0	44.8±13.4	0.946
<9	0	1.4	0.074
9 to 12	33.3	23.0	
>12	66.7	75.5	
Marital status (%)			
Married	23.6	28.8	
Single	54.5	39.6	0.091
Divorced	17.1	26.6	
Widowed	4.9	5.0	
Age started smoking (years, mean±SD)	16.9±4.0	17.4±5.3	0.390
Total years smoking (years, mean±SD)	27.1±13.0	26.2±13.7	0.597
N. cigarettes/day (mean±SD)	18.3±7.7	18.2±7.2	0.874
Desire to quit (from 1 - low to 10 - high, mean±SD)	8.8±1.4	9.0±1.3	0.238
N. tries to stop (%)			
One	14.3	21.9	
Two	10.9	16.1	
Three	23.5	18.2	0.283
Four	11.8	9.5	
Five	12.6	7.3	
More than five	26.9	27.0	
Longest period without smoking (%)			
1 week or less	26.7	26.1	
>1 week to 1 month	19.2	13.8	
>1 month to 6 months	25.0	26.1	0.728
>6 months to 1 year	12.5	12.3	
Longer than 1 year	16.7	21.7	
Previous stopping methods			
Bupropion	12.4	10.1	0.566
Varenicline	24.0	25.4	0.795
Nicotine patch	33.9	35.5	0.784
Nicotine gum	27.3	26.8	0.934
Nicotine lozenge	9.1	10.1	0.774
Nicotine oral inhaler	5.8	4.3	0.597
Cold turkey	73.6	76.8	0.544
CBT or other psychotherapy	3.3	2.9	1.000
Hypnosis	10.7	5.8	0.146
Other	21.5	18.1	0.496
Tobacco Craving Questionnaire total score (mean±SD)	44.9±15.8	42.7±18.1	0.291
Fagerström Test for Nicotine Dependence (mean±SD)	5.5±2.0	5.3±2.0	0.268
Minnesota Nicotine Withdrawal Scale, self-reported (mean±SD)	7.6±5.4	8.1±6.1	0.450
Minnesota Nicotine Withdrawal Scale, observer-reported (mean±SD)	0.8±1.4	1.4±1.9	0.005

CBT – cognitive behavioral therapy

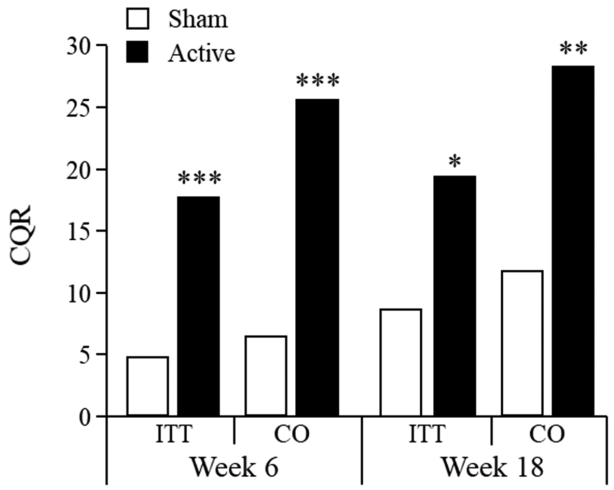

Figure 2 Four-week continuous quit rate (CQR) until Week 6 and Week 18 in patients receiving active or sham repetitive transcranial magnetic stimulation. Only participants who were abstinent at Week 6 were followed up to Week 18. ITT – intent-to-treat set, CO – completer analysis set. *p<0.05, **p<0.01, ***p<0.001.

ing levels) decreased significantly more in the active than in the sham group at each week following the target quit date, in both the intent-to-treat and the completer analysis sets, with the only exception of the TCQ total score at Week 5 in the intent-to-treat set, for which statistical significance was only approached (see Table 2).

The average difference in total number of cigarettes smoked from baseline until Week 6 between the active and the sham groups was –79.9 (95% CI: –136.69 to –23.05, p=0.0061) in the intent-to-treat set and –95.5 (95% CI: –159.16 to –31.91, p=0.0035) in the completer analysis set. The average weekly reduction in cigarette consumption was significantly greater in the active group (adjusted mean weekly difference between groups = 15.01, 95% CI: 2.17-27.85, p=0.022).

The average weekly reduction in TCQ total score was also significantly greater in the active group (adjusted mean weekly difference between groups = 5.71, 95% CI: 0.62-10.81, p=0.028). The changes in all four TCQ domain scores also indicate significant differences between groups following the target quit date, which were durable for the expectancy, compulsivity and purposefulness domains, but not for the emotionality domain (see supplementary information).

At the first treatment visit, craving VAS scores following provocation increased in both groups (before the rTMS session), but the reduction in craving following rTMS (VAS3 minus VAS2) in the active group was significantly greater than in the sham group ($F_{1,253}$=4.85, p=0.028) (see Figure 3). Of note, this acute reduction in craving (VAS3 minus VAS2 in the first treatment visit) significantly predicted eventual quitting in the active, but not the sham, group (odds ratio: active = 1.57, p=0.004; sham = 0.85, p=0.46). The effect of active rTMS on craving was also noted when comparing VAS1 scores on the second vs. the first day of treatment, or over all treatment visits (see Figure 4).

No statistically significant differences between the groups were detected for the change in FTND (dependence) or MNWS self-report or observer-report (withdrawal symptoms) scores (see supplementary information).

Safety analysis and blinding

No differences between groups were observed in vital signs, weight or cognition (measured by the MMSE and BSRT) at any time point (see supplementary information). The blinding as-

Table 2 Differences (active minus sham) in number of cigarettes smoked and change from baseline in Tobacco Craving Questionnaire (TCQ) total score at each week of treatment

	Number of cigarettes smoked		Change from baseline in TCQ total score	
Week	**Adjusted mean difference (95% CI)**	**p**	**Adjusted mean difference (95% CI)**	**p**
Intent-to-treat set				
2	–16.64 (–27.91 to –5.37)	0.004	–3.94 (–8.63 to 0.76)	0.100
3	–19.14 (–31.14 to –7.14)	0.002	–7.17 (–12.16 to –2.18)	0.005
4	–18.02 (–30.22 to –5.82)	0.004	–6.44 (–11.52 to –1.35)	0.013
5	–18.87 (–31.27 to –6.48)	0.003	–4.83 (–9.99 to 0.33)	0.067
6	–16.14 (–28.79 to –3.48)	0.012	–5.56 (–10.70 to –0.42)	0.034
Completer analysis set				
2	–20.35 (–32.73 to –7.98)	0.001	–5.50 (–10.56 to –0.43)	0.033
3	–19.18 (–31.66 to –6.69)	0.003	–7.69 (–12.78 to –2.61)	0.003
4	–16.56 (–29.08 to –4.05)	0.010	–5.97 (–11.04 to –0.89)	0.021
5	–18.55 (–31.15 to –5.95)	0.004	–5.61 (–10.71 to –0.50)	0.031
6	–15.01 (–27.85 to –2.17)	0.022	–5.71 (–10.81 to –0.62)	0.028

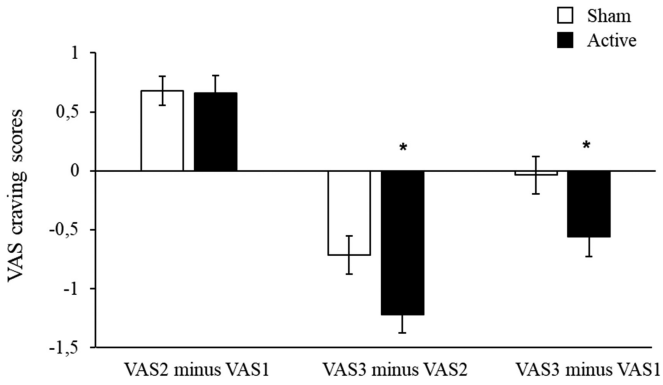

Figure 3 Acute changes in Visual Analogue Scale (VAS) craving scores following provocation (VAS2 minus VAS1) and following repetitive transcranial magnetic stimulation (VAS3 minus VAS2) in patients receiving active or sham treatment in the first session. Overall changes in craving during the first session (VAS3 minus VAS1) indicate that craving in the sham group returns to baseline, whereas it is reduced in the active group ($F_{1,253}$=5.00, p=0.026). *p<0.05.

sessment (in which subjects were asked to guess whether they received active or sham treatment) indicated that the majority of subjects in each group did not know which treatment they received, with no significant difference between the groups (p=0.65).

Adverse events were typical to those of similar rTMS systems and other TMS devices and were at least comparable to those of medications[21,36-38]. The most frequent adverse event was headache (24.4% and 18.0% in the active and sham groups, respectively). Various forms of pain or discomfort (application site pain/discomfort, pain in jaw, facial pain, muscle pain/spasm/twitching, neck pain) were usually reported as either mild or moderate and resolved after treatment. In most of the participants the discomfort or pain disappeared once the participants became accustomed to the treatment.

Although a significant difference was found between the active and sham groups concerning the proportion of participants reporting any adverse event (53.7% vs. 36.0%, X^2=8.274, p=0.004), there were no significant differences between the treatment groups for any specific adverse event, except for application site discomfort (see supplementary information).

One serious adverse event of tinnitus (which resolved) was reported as possibly related to treatment, and participation was terminated by the investigator. The drop-out rate (at Week 6) was 39% for the active group and 32% for the sham group, without a significant difference between groups.

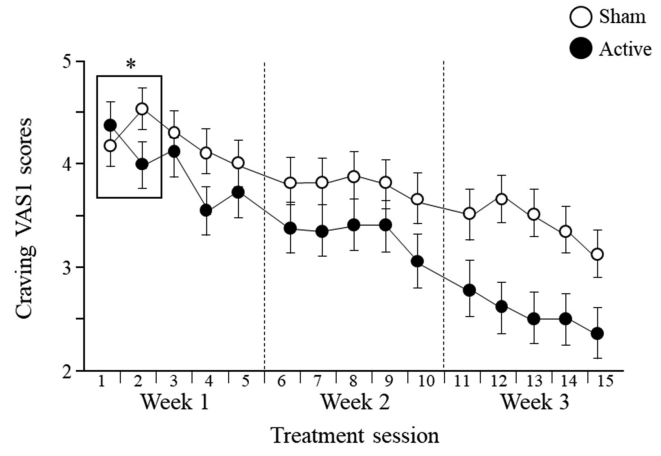

Figure 4 Daily changes in baseline craving (VAS1) scores during the first three weeks of treatment in patients receiving active or sham repetitive transcranial magnetic stimulation. ANOVA comparing VAS1 scores on the second vs. the first day of treatment (see box) revealed a significant interaction effect ($F_{1,165}$=3.70, p=0.025). Repeated measure ANOVA during the treatment period revealed main effects for group ($F_{1,159}$=4.50, p=0.035) and time ($F_{14,2226}$=16.79, p<0.0001), as well as for group x time interaction ($F_{14,2226}$=1.79, p=0.034). *p<0.05.

DISCUSSION

This study is the first large multicenter RCT to examine the safety and efficacy of brain stimulation in addiction medicine. We found that three weeks of daily rTMS targeting the lateral prefrontal cortex and insula during cue-induced craving, followed by once weekly rTMS for three weeks, was a safe and effective intervention in chronic smokers with a DSM-5 diagnosis of tobacco use disorder who had made at least one prior failed attempt to quit (with 68% having made at least three failed attempts). Active treatment more than doubled the quit rate and significantly reduced craving and cigarette consumption, relative to sham control.

Since there are no previous medical devices that aid smoking cessation, the safety and efficacy of this treatment can only be compared to those of FDA-approved medications, including bupropion and varenicline[38]. Yet, there are several limitations to such comparison, as the sample sizes were larger and the follow-up period longer in the pharmacological studies than in the current one. On the other hand, confirmatory testing in most those studies was done using exhaled breath testing for carbon monoxide levels rather than urine testing for cotinine levels, therefore confirming abstinence for a duration of hours instead of days.

In this study, the safety profile was not worse than smoking cessation medications and was similar to that observed in other multicenter rTMS trials, while efficacy was at least similar to medications in terms of relative improvement and effect sizes (active vs. sham). For example, in the bupropion studies, the quit rates of the treatment groups (300 mg/day) were 28% vs. 16% for placebo from Week 4 to 7[35], or 44% vs. 19% for placebo at Week 7[33]. In another study[32], bupropion, varenicline and placebo induced an abstinence rate from Week 9 to 12 of 29%, 44%, and 18%, respectively. As stated, those studies did not use urine testing for cotinine levels.

A recent large-scale study which utilized urine cotinine levels as an objective measure for confirming abstinence (as in the present study, rather than just exhaled carbon monoxide measures), found that the most effective intervention – includ-

ing both medications and monetary incentives – produced a 6-month sustained abstinence rate of 12.7% among actively-engaged and motivated participants, while the abstinence rate among those receiving smoking cessation medications without monetary incentives was only 2.9%[9].

An important feature of our trial was the combination of the pre-rTMS provocation and the post-rTMS motivational talk (in both active and sham groups), although we did not test whether and to what degree these were necessary for the rTMS therapeutic effect. However, previous studies suggest that activation of the addiction circuitry by provocation makes it more amenable to modulation, where rTMS may open a "plasticity window" and behavioral intervention can be more effective[39].

In our study, craving levels of both groups were equally affected by the provocation at the first visit, but active rTMS targeting the lateral prefrontal cortex and insula led to greater acute reduction of VAS craving scores, and the magnitude of this reduction predicted eventual quitting. A possible interpretation for this finding is that effective interference with an activated craving circuit may be an important element in the rTMS mechanism for addiction treatment, and that individual's neural excitability in these regions following induction of craving may affect the clinical outcomes.

The suggested direct influence of rTMS on these brain areas is further highlighted by the attributed role of the lateral prefrontal cortex and insula in functions measured by the TCQ domains. Both areas are implicated in anticipation of rewarding outcomes (expectancy), intention to smoke (purposefulness), and control over use (compulsivity)[40,41], while the emotionality domain is more restricted to the insular cortex, which – due to its deeper location – may require higher rTMS dosage to implement long-term modifications[42]. All these TCQ domains were significantly affected by active as compared to sham treatment in our trial.

In conclusion, this study extends the evidence supporting the use of rTMS for the treatment of substance use disorders by showing that it is a safe and effective treatment for tobacco use disorder. The trial represents the first large multicenter RCT of brain stimulation in addiction medicine and has led to the first clearance by the FDA for rTMS as an aid in smoking cessation.

This study suggests that rTMS directly affects neurocircuitry implicated in craving and might be effective in treating other addictions as well. The clinical benefits, including the fast onset and minor side effects, outweigh the minimal risks involved. The treatment may be particularly of help in patients with a DSM-5 diagnosis of tobacco use disorder who have a long history of smoking and have made several failed attempts to quit using currently available options.

ACKNOWLEDGEMENTS

This trial was financially supported by an unrestricted grant from Brainsway Ltd. This company had no role in data analysis, that was conducted by an independent agency (A. Stein - Regulatory Affairs Consulting and Biostats). A. Zangen and Y. Roth are inventors of deep TMS coils and have financial interest in Brainsway Ltd. A. Tendler is the chief medical officer of Brainsway Ltd. M.S. George is a member of the Brainsway Scientific Advisory Board (uncompensated) and his role as co-principal investigator of the trial was uncompensated. A. Zangen and M.S. George are joint corresponding authors of this paper. The authors would like to thank K. Brady and K. Hartwell for help with initial design of the study and training of investigators in the symptom provocation and motivational talks. Supplementary information on the study is available at https://itonline.co.il/data/.

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DOI:10.1002/wps.20905

Dopamine and glutamate in individuals at high risk for psychosis: a meta-analysis of *in vivo* imaging findings and their variability compared to controls

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Dopaminergic and glutamatergic dysfunction is believed to play a central role in the pathophysiology of schizophrenia. However, it is unclear if abnormalities predate the onset of schizophrenia in individuals at high clinical or genetic risk for the disorder. We systematically reviewed and meta-analyzed studies that have used neuroimaging to investigate dopamine and glutamate function in individuals at increased clinical or genetic risk for psychosis. EMBASE, PsycINFO and Medline were searched form January 1, 1960 to November 26, 2020. Inclusion criteria were molecular imaging measures of striatal presynaptic dopaminergic function, striatal dopamine receptor availability, or glutamate function. Separate meta-analyses were conducted for genetic high-risk and clinical high-risk individuals. We calculated standardized mean differences between high-risk individuals and controls, and investigated whether the variability of these measures differed between the two groups. Forty-eight eligible studies were identified, including 1,288 high-risk individuals and 1,187 controls. Genetic high-risk individuals showed evidence of increased thalamic glutamate + glutamine (Glx) concentrations (Hedges' g=0.36, 95% CI: 0.12-0.61, p=0.003). There were no significant differences between high-risk individuals and controls in striatal presynaptic dopaminergic function, striatal D2/D3 receptor availability, prefrontal cortex glutamate or Glx, hippocampal glutamate or Glx, or basal ganglia Glx. In the meta-analysis of variability, genetic high-risk individuals showed reduced variability of striatal D2/D3 receptor availability compared to controls (log coefficient of variation ratio, CVR=–0.24, 95% CI: –0.46 to –0.02, p=0.03). Meta-regressions of publication year against effect size demonstrated that the magnitude of differences between clinical high-risk individuals and controls in presynaptic dopaminergic function has decreased over time (estimate=–0.06, 95% CI: –0.11 to –0.007, p=0.025). Thus, other than thalamic glutamate concentrations, no neurochemical measures were significantly different between individuals at risk for psychosis and controls. There was also no evidence of increased variability of dopamine or glutamate measures in high-risk individuals compared to controls. Significant heterogeneity, however, exists between studies, which does not allow to rule out the existence of clinically meaningful differences.

Key words: Schizophrenia, dopaminergic dysfunction, glutamatergic dysfunction, clinical high risk, genetic high risk, thalamic glutamate, presynaptic dopaminergic function, dopamine receptor availability

(World Psychiatry 2021;20:405–416)

Disruption of dopaminergic and glutamatergic neurotransmission has been proposed to be central to the pathophysiology of schizophrenia[1-4]. Single photon computed emission tomography (SPECT) and positron emission tomography (PET) allow the dopamine system to be studied *in vivo*, while *in vivo* quantification of glutamate levels is possible using proton magnetic resonance spectroscopy (^{1}H-MRS).

Meta-analyses of available studies have found consistent evidence of higher striatal dopamine synthesis and release capacity in schizophrenia, and shown that this is greatest in the associative region of the striatum[5,6]. In contrast, meta-analyses of studies investigating dopamine D2/D3 receptor availability have not shown significant patient-control differences in schizophrenia, although reporting increased variability in receptor availability[6-9].

Meta-analyses of studies examining glutamate function have shown that, in individuals with psychosis, glutamate levels are higher in the basal ganglia, the glutamate metabolite glutamine is higher in the thalamus, while glutamate in combination with glutamine (Glx) is higher in the hippocampus[1]. In the frontal cortex, a recent meta-analysis of 7-Tesla studies reported lower glutamate in patients[10].

These findings indicate that dopamine and glutamate dysfunction occurs in schizophrenia, but raise the question of whether it predates the onset of the disorder. It is possible to investigate neurochemical changes prior to the onset of schizophrenia by studying people at increased risk for developing the disorder.

The presence of sub-clinical symptoms prior to the development of psychosis has long been recognized[11]. People with schizotypal disorder experience sub-clinical psychotic symptoms, and are at increased risk of developing psychotic disorders, predominantly schizophrenia, with a risk of 25-48% over long-term follow-up[12-14]. The introduction of structured clinical assessments has also allowed the identification of individuals at clinical high risk (CHR) for psychosis, in whom the risk of transition to psychosis is around 20-30% over two years[15]. To meet criteria for CHR, a person is required to show one or more of the following at or above threshold levels: schizotypal disorder plus recent onset functional impairment, and/or brief intermittent psychotic symptoms, and/or attenuated psychotic symptoms[16].

In addition to studying individuals at increased clinical risk, research has also been undertaken to quantify neurochemical functioning in individuals at genetic high risk (GHR) for schizophrenia. These studies have either investigated non-psychotic relatives of individuals with schizophrenia, or individuals with copy number variants, such as the copy number deletion of 1.5-5 megabases at 22q11.2, which is associated with a ~45% lifetime risk of developing psychosis and ~35% lifetime risk of developing schizophrenia[17,18].

There is some evidence that neurochemical dysfunction may primarily exist in a subgroup of high-risk individuals who subsequently develop psychosis[19,20]. If neurochemical alterations occur only in a subgroup of high-risk individuals, this would be expected to lead to increased variability of the parameter in question in the high-risk group[21]. Novel meta-analytic techniques now allow for the quantification of variability across studies[22-24]. It is therefore possible to test meta-analytically the hypothesis that greater variability of dopamine and glutamate measures exists in high-risk individuals compared to controls.

A number of ^{1}H-MRS, PET and SPECT studies have investigated dopamine and glutamate functioning in CHR and GHR groups[25-28], but to our knowledge no meta-analyses of the dopamine findings has been undertaken, and an earlier meta-analysis of the glutamate findings[29] is now outdated, since six new studies have been published after it was conducted[30-35], increasing the sample size by 574 subjects. Moreover, variability has never been investigated for either dopamine or glutamate studies.

In the present paper, we meta-analyze neuroimaging studies of the dopamine and glutamate systems in individuals at high clinical or genetic risk for psychosis to provide the best estimate of the magnitude and variability of group differences across samples and settings.

METHODS

Search strategy and study selection

EMBASE, PsycINFO and Medline were searched from January 1, 1960 to November 26, 2020. Titles and abstracts were searched for the words ("schizophrenia" OR "psychosis" OR "schizophreniform" OR "prodrom*" OR "at risk mental state" OR "high risk" OR "22q" OR 16p OR "vcfs" OR "velocardiofacial") AND ("positron emission tomography" OR "PET" OR "single photon emission tomography" OR "SPET" OR "single photon emission computed tomography" OR "SPECT" OR "MRS" OR "spectroscopy") AND ("dopamine" OR "glutamate").

We included studies of: a) subjects meeting established research criteria for having an at risk mental state for psychosis determined using a structured assessment instrument (the Comprehensive Assessment of At-Risk Mental States[36] or the Structured Interview for Prodromal Symptoms[37]); b) subjects meeting DSM or ICD criteria for a diagnosis of schizotypal personality disorder/schizotypal disorder; and c) non-psychotic people at increased genetic risk for schizophrenia (for example, relatives of individuals with schizophrenia, or non-psychotic individuals with a diagnosis of 22q11.2 deletion syndrome or 16p11.2 duplication syndrome). These studies had to report one or more imaging measures of striatal presynaptic dopaminergic function, striatal D2/D3 receptor availability, glutamate or Glx concentrations, for patient and control groups. As in previous meta-analyses[5,6], studies of striatal presynaptic dopamine function included those of dopamine synthesis capacity, dopamine release capacity, and synaptic dopamine levels. Furthermore, studies had to provide data enabling the estimation of standardized mean differences between patient and control groups for the relevant parameter.

We excluded data in individuals with comorbid substance dependence, as this may have significant effects on the dopamine system[38-40].

Data extraction

The primary outcome of interest was the imaging parameter reported for patient and control groups. In addition, first author, year of study, number of participants, participant age, participant gender, antipsychotic treatment, transitions to psychosis observed over clinical follow-up, and symptom scores were extracted.

Where dopamine measures for the whole striatum were not provided, but data for the caudate and putamen were reported, whole striatum values were calculated by weighting these values by their volumes as reported in the Oxford-GSK-Imanova Structural-Anatomical Striatal Atlas (43% and 57% respectively). If data for ventral striatum were reported, the following weightings were used to derive a summary outcome for the whole striatum: 36% for caudate, 48% for putamen, and 16% for ventral striatum[41]. If only functional subdivisions were reported, the following weightings – based on templates used in previous imaging studies[25,42] – were used to derive a summary outcome for the whole striatum: 12.1% for limbic striatum, 61.9% for associative striatum, and 26.0% for sensorimotor striatum.

Data analysis

For the meta-analysis of mean differences, standard effect sizes (Hedges' g) for individual studies were estimated.

The relative variability of imaging measures in high-risk individuals compared to controls can be quantified using the variability ratio (VR), where ln is natural logarithm; $\hat{\sigma}_h$ and $\hat{\sigma}_c$ are the unbiased estimates of the population standard deviation for the high-risk and control groups; S_h and S_c are the reported standard deviations, and n_h and n_c are the sample sizes.

$$\mathrm{VR} = \ln\left(\frac{\hat{\sigma}_h}{\hat{\sigma}_c}\right) = \ln\left(\frac{S_h}{S_c}\right) + \frac{1}{2(n_h-1)} - \frac{1}{2(n_c-1)}$$

In biological systems, however, variance often scales with mean[22,23], and we therefore used the log coefficient of variation ratio (CVR) as our primary outcome measure in this analysis, where $\bar{x}_h$ and $\bar{x}_c$ are the mean symptom scores of high-risk and control groups.

$$\mathrm{CVR} = \ln\left(\frac{\hat{\sigma}_h / \bar{x}_h}{\hat{\sigma}_c / \bar{x}_c}\right) = \ln\left(\frac{S_h / \bar{x}_h}{S_c / \bar{x}_c}\right) + \frac{1}{2(n_h-1)} - \frac{1}{2(n_c-1)}$$

All statistical analyses were carried out using the 'metafor' package (version 2.0.0) in the statistical programming language

R (version 3.3.1). Separate meta-analyses were conducted for GHR and CHR individuals. For dopamine studies, a distinction was made between studies of presynaptic dopaminergic function and those of D2/D3 receptor availability. Glutamate studies were analyzed separately both on the basis of the region studied and on whether they assessed glutamate or Glx. Meta-analysis was only performed if at least three eligible studies were available. Egger's test, funnel plots and trim and fill analyses were conducted to test for publication bias, and the I^2 statistic was used to quantify study inconsistency.

In both the meta-analysis of standardized mean differences and that of CVR, individual study effect sizes were entered into a random effects meta-analytic model using restricted maximum likelihood estimation.

The time period of risk is longer in people with schizotypal disorder compared to individuals meeting criteria for an at-risk mental state. Sensitivity analyses were therefore conducted to determine the effect of excluding the studies of schizotypal disorder on the findings.

Meta-regressions were undertaken to investigate potential associations between study effect sizes and age, gender composition and publication year. These analyses were performed in all instances where there were at least five eligible studies.

A significance level of $p<0.05$ (two-tailed) was used for all analyses.

RESULTS

A total of 5,454 papers were identified. Forty-eight of these met inclusion criteria, reporting data on 1,288 high-risk individuals and 1,187 controls (Figure 1). The average age of study participants was 26.5 years, and 52.6% of participants were male.

Striatal presynaptic dopaminergic function in clinical high-risk subjects

Eight studies of CHR individuals met inclusion criteria[18,42-48] (see Table 1). The studies included a total of 188 CHR individuals and 151 controls. The two groups did not differ significantly in terms of striatal presynaptic dopaminergic function (Hedges' g=0.28, 95% CI: –0.03 to 0.59, p=0.07) (see Figure 2). The I^2 value was 46%, indicating moderate between-study inconsistency. Neither Egger's test (p=0.75) nor trim and fill analysis suggested publication bias.

A sensitivity analysis excluding the two studies of schizotypal disorder was conducted, and provided similar results (Hedges' g=0.25, 95% CI: –0.10 to 0.60, p=0.17). When the six studies reporting functional subdivisions were analyzed on a by-subdivision basis, there was no evidence for differences in striatal presynaptic dopaminergic function for any subdivision (associative: g=0.20, p=0.20; sensorimotor: g=0.20, p=0.12; limbic: g=0.21, p=0.26).

The meta-analysis of variability did not show differences in variability for CHR individuals compared to controls (CVR=0.13, 95% CI: –0.01 to 0.27, p=0.06) (see Figure 3).

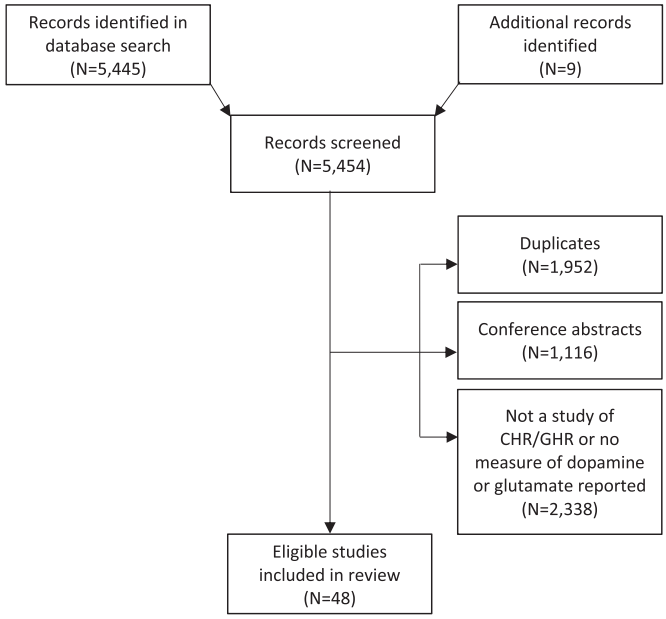

Figure 1 PRISMA flow chart. CHR – clinical high risk, GHR – genetic high risk

Striatal presynaptic dopaminergic function in genetic high-risk subjects

Six studies reported findings in individuals at increased genetic risk for schizophrenia, four of which examined relatives of individuals with schizophrenia[27,28,49,50], and two reported findings in individuals with 22q11 deletion syndrome[51,52] (see Table 1). These studies reported data on 81 GHR individuals and 105 controls. There was no significant difference in striatal presynaptic dopaminergic function between the two groups (Hedges' g=0.24, 95% CI: –0.40 to 0.88, p=0.46) (see Figure 2). The I^2 statistic was 77%, indicating substantial between-study inconsistency. Egger's test was significant (p=0.02), although a trim and fill analysis did not suggest any potentially missing studies.

The meta-analysis of variability did not show differences in variability for GHR individuals compared to controls (CVR= –0.04, 95% CI: –0.25 to 0.17, p=0.72) (see Figure 3).

Striatal D2/D3 receptor availability in clinical high-risk subjects

Five studies[43,46-48,53] examined striatal D2/D3 receptor availability in 83 CHR individuals and 79 controls (see Table 1). There were no significant differences between the two groups (Hedges' g=–0.08, 95% CI: –0.48 to 0.33, p=0.70) (see Figure 2). The I^2 value was 39%, indicating moderate between-study inconsistency. Neither Egger's test (p=0.9) nor trim and fill analysis suggested publication bias.

The meta-analysis of variability did not show differences in variability for CHR individuals compared to controls (CVR=0.11, 95% CI: –0.17 to 0.39, p=0.43) (see Figure 3).

Table 1 Studies investigating striatal dopamine in individuals at clinical or genetic high risk for psychosis

		Probands				Controls		
	Study	N	Age (yrs., mean)	At-risk group	Antipsychotic treatment	N	Age (yrs., mean)	PET tracer
Presynaptic dopaminergic function	Huttunen et al[49]	17	34.1	FDR	All naïve	17	33.0	^{18}F-DOPA
	Brunelin et al[28]	8	28.5	FDR	All naïve	10	27.7	^{11}C-raclopride + metabolic stress
	Shotbolt et al[27]	7	43.0	1 MZ, 6 DZ	All naïve	20	39.0	^{18}F-DOPA
	Kasanova et al[50]	16	42.4	FDR	All naïve	16	38.1	^{18}F-fallypride + reward task
	van Duin et al[51]	12	33.1	22q	All naïve	16	38.1	^{18}F-fallypride + reward task
	Rogdaki et al[52]	21	26.1	22q	All naïve	26	26.1	^{18}F-DOPA
	Abi-Dargham et al[43]	13	36.0	SPD	Free for ≥21 days	13	34.0	[^{123}I] IBZM + AMPH
	Howes et al[18]	30	24.2	CHR	All naïve	29	25.6	^{18}F-DOPA
	Egerton et al[44]	26	22.7	CHR	24 free/naïve, 2 medicated	20	24.5	^{18}F-DOPA
	Bloemen et al[45]	14	22.0	CHR	All free and less than 1 week lifetime use	15	22.2	[^{123}I]IBZM +AMPT
	Tseng et al[46]	24	23.6	CHR	All naïve	25	25.1	[^{11}C]-(+)-PHNO + MIST
	Howes et al[42]	51	23.0	CHR	All naïve	19	25.1	^{18}F-DOPA
	Girgis et al[47]	14	22.4	CHR	All free	14	22.7	[^{11}C]-(+)-PHNO + AMPH
	Thompson et al[48]	16	37.4	SPD	All naïve	16	37.0	^{11}C-raclopride + AMPH
D2/D3 receptor availability	Hirvonen et al[54]	11	50.2	6 MZ, 5 DZ	All naïve	13	51.5	^{11}C-raclopride
	Lee et al[55]	11	25.1	2 MZ, 9 FDR	All naïve	11	25.5	^{11}C-raclopride
	Brunelin et al[28]	8	27.7	FDR	All naïve	10	28.5	^{11}C-raclopride
	van Duin et al[51]	12	33.1	22q	All naïve	16	38.1	^{18}F-fallypride
	Vingerhoets et al[53]	15	28.2	22q	All naïve	11	26.6	[^{123}I]IBZM
	Abi-Dargham et al[43]	13	36.0	SPD	Free for ≥21 days	13	34.0	[^{123}I]IBZM
	Tseng et al[46]	24	23.6	CHR	All naïve	25	25.1	[^{11}C]-(+)-PHNO
	Vingerhoets et al[53]	16	23.1	CHR	All naïve	11	26.6	[^{123}I]IBZM
	Girgis et al[47]	14	22.4	CHR	All free	14	22.7	[^{11}C]-(+)-PHNO
	Thompson et al[48]	16	37.4	SPD	All naïve	16	37.0	^{11}C-raclopride

CHR – clinical high risk, FDR – first-degree relatives, MZ – monozygotic twins, DZ – dizygotic twins, 22q – 22q11 deletion syndrome, SPD – schizotypal disorder, PET – positron emission tomography, AMPH – dextroamphetamine, AMPT – alpha-methyl-paratyrosine depletion, MIST – Montreal Imaging Stress Test, IBZM – I-(S)-2-hydroxy-3-iodo-6-methoxy-N-[1-ethyl-2-pyrrodinyl)-methyl]benzamide

Striatal D2/D3 receptor availability in genetic high-risk subjects

Five studies[28,51,53-55] examined striatal D2/D3 receptor availability in 57 GHR individuals and 61 controls. There was no significant difference between the two groups (Hedges' g=–0.03, 95% CI: –0.39 to 0.34, p=0.88) (see Figure 2). The I^2 value was 0%, indicating low between-study inconsistency. Neither Egger's test (p=0.9) nor trim and fill analysis suggested publication bias.

The meta-analysis of variability showed significantly reduced variability for GHR individuals compared to controls (CVR=–0.24, 95% CI: –0.46 to –0.02, p=0.03) (see Figure 3).

Glutamate function in clinical high-risk subjects

Three studies[35,56,57] measured glutamate (215 CHR individuals, 133 controls), and ten studies[33,35,56-63] measured Glx (375 CHR individuals, 306 controls) in the prefrontal cortex (see Table 2). Neither set of studies found any significant differences between CHR individuals and controls (glutamate: g=0.01, 95% CI: –0.21 to 0.22, p=0.96; Glx: g=0.01, 95% CI: –0.15 to 0.16, p=0.92) (see Figure 2). Both glutamate and Glx studies showed low between-study inconsistency (I^2=0%). Neither set of studies showed evidence of publication bias as examined using Egger's test (glutamate: p=0.63; Glx: p=0.93) and trim and fill analysis.

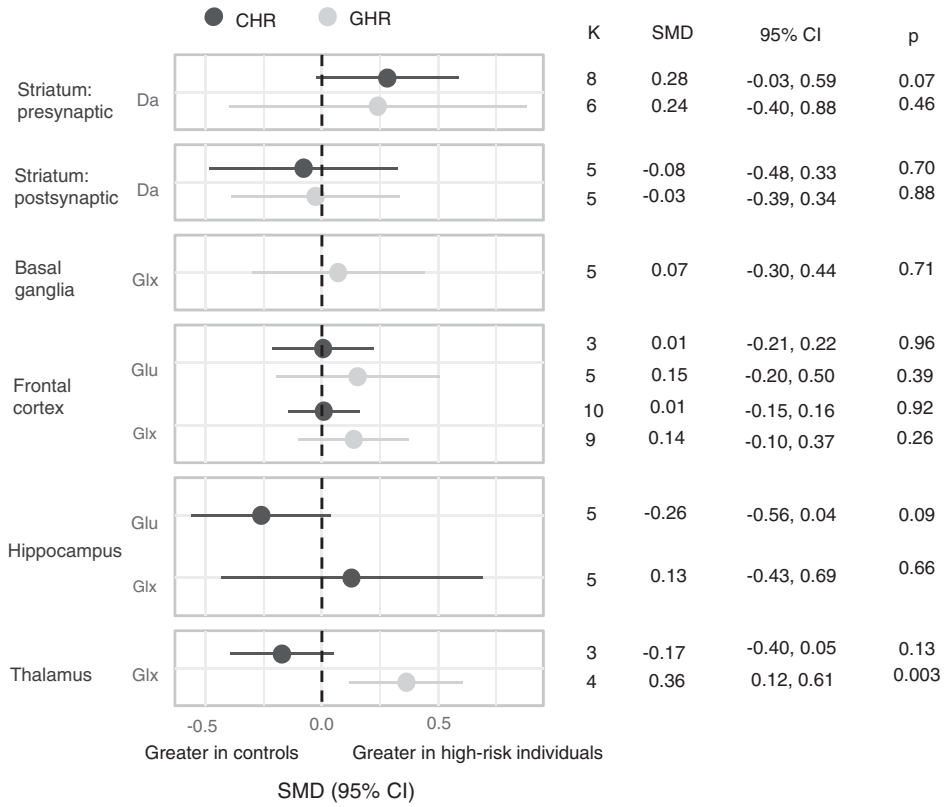

Figure 2 Forest plots of studies investigating standardized mean differences of measures of dopamine and glutamate in individuals at clinical or genetic high risk for psychosis. SMD – standardized mean difference (Hedges' g), CHR – clinical high risk, GHR – genetic high risk, Da – dopamine, Glu – glutamate, Glx – glutamate + glutamine; K – number of studies

There were no significant variability differences in either glutamate or Glx between CHR individuals and controls (glutamate: CVR=0.18, 95% CI: –0.12 to 0.48, p=0.24; Glx: CVR=0.08, 95% CI: –0.05 to 0.20, p=0.23) (see Figure 3).

Five studies[30,64-67] measured glutamate (177 CHR individuals, 141 controls), and five studies[30,34,64,67,68] measured Glx (240 CHR individuals, 126 controls) in the hippocampus (see Table 2). Neither set of studies found any significant differences between CHR individuals and controls (glutamate: g=–0.26, 95% CI: –0.56 to 0.04, p=0.09; Glx: g=0.13, 95% CI: –0.43 to 0.69, p=0.66) (see Figure 2). Between-study inconsistency was lower in the glutamate (I^2=36%) compared to the Glx studies (I^2=83%). Neither set of studies showed evidence of publication bias as examined using Egger's test (glutamate: p=0.10; Glx: p=0.78) or trim and fill analyses.

Neither set of studies showed significant variability differences between CHR individuals and controls (glutamate: CVR= –0.05, 95% CI: –0.29 to 0.18, p=0.66; Glx: CVR=0.03, 95% CI: –0.11 to 0.17, p=0.64) (see Figure 3).

Three studies[35,56,58] measured Glx (200 CHR individuals, 130 controls) in the thalamus. They found overall no significant differences between the two groups (Hedges' g = –0.17, 95% CI: –0.40 to 0.05, p=0.13) (see Figure 2). Between-study inconsistency was low (I^2=0%) and there was no evidence of publication bias (Egger's test: p=0.85).

There was no evidence of variability differences between CHR individuals and controls for the primary outcome measure (CVR=–0.21, 95% CI: –0.45 to 0.04, p=0.10) (see Figure 3). However, the VR was reduced in CHR individuals compared to controls (VR=–0.23, 95% CI: –0.45 to –0.01, p=0.04).

Glutamate function in genetic high-risk subjects

Five studies[32,70-73] measured glutamate (96 GHR individuals, 105 controls), and nine studies[31,32,70,71,74-78,] measured Glx (210 GHR individuals, 259 controls) in the prefrontal cortex (see Table 2). Neither set of studies found any significant differences between GHR individuals and controls (glutamate: g=0.15, 95% CI: –0.20 to 0.50, p=0.39; Glx: g=0.14, 95% CI: –0.10 to 0.37, p=0.26) (see Figure 2). Glutamate and Glx studies showed similar levels of between-study inconsistency (glutamate: I^2=43%; Glx: I^2=34%). Neither set of studies showed evidence of publication bias as examined using Egger's test (glutamate: p=0.40; Glx: p=0.71) and trim and fill analysis.

There were no significant variability differences in either glutamate or Glx between GHR individuals and controls (glutamate: CVR=0.04, 95% CI: –0.27 to –0.35, p=0.81; Glx: CVR= 0.05, 95% CI: –0.13 to 0.23, p=0.59) (see Figure 3).

Four studies[31,32,75,78] measured Glx in the thalamus in 113

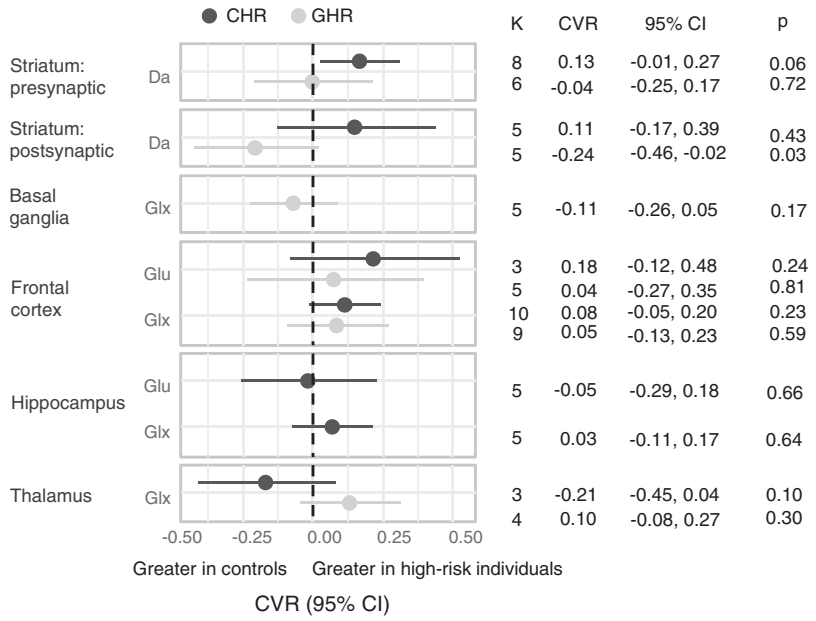

Figure 3 Forest plots of studies investigating variability differences of measures of dopamine and glutamate in individuals at clinical or genetic high risk for psychosis. CVR – coefficient of variation, CHR – clinical high risk, GHR – genetic high risk, Da – dopamine, Glu – glutamate, Glx – glutamate + glutamine, K – number of studies

GHR individuals and 163 controls (see Table 2). There were insufficient studies of glutamate alone to meta-analyze. Glx concentrations were significantly raised in GHR individuals compared to controls (Hedges' g=0.36, 95% CI: 0.12 to 0.61, p=0.003) (see Figure 2). The I^2 value was 0%, suggesting low between-study inconsistency. Both Egger's test (p=0.9) and trim and fill analysis did not indicate publication bias.

There was no evidence of variability differences (CVR=0.10, 95% CI: –0.08 to 0.27, p=0.30) (see Figure 3).

Five studies[31,74,78-80] measured Glx in the basal ganglia in 138 GHR individuals and 145 controls (see Table 2). There were insufficient studies of glutamate alone to meta-analyze. There was no significant difference in Glx concentrations between GHR individuals and controls (Hedges' g=0.07, 95% CI: –0.30 to 0.44, p=0.71) (see Figure 2). The I^2 value was 55%, indicating moderate between-study inconsistency. Neither Egger's test (p=0.93), nor trim and fill analysis suggested the possibility of publication bias.

There was no evidence of variability differences (CVR=–0.11, 95% CI: –0.26 to 0.05, p=0.17) (see Figure 3).

Meta-regressions

The magnitude of CHR-control differences in striatal presynaptic dopaminergic function and D2/D3 receptor availability was greater in studies published earlier (presynaptic dopaminergic function: estimate=–0.06, 95% CI: –0.11 to –0.007, p=0.025; D2/D3 receptor availability: estimate=–0.06, 95% CI: –0.12 to –0.007, p=0.028) (Figure 4). Publication year did not show a significant association with any measure of glutamate function.

The magnitude of CHR-control differences in hippocampal glutamate levels were greater in those studies containing a greater proportion of male patients (estimate=0.07, 95% CI: 0.006-0.13, p=0.030) (Figure 4). Gender was not associated with any other measure. Participant age did not show any significant relationship for any measure.

DISCUSSION

Our first main finding is that thalamic Glx is higher in people at genetic high risk for psychosis relative to controls, with a small to moderate effect size (g=0.36), while there are no marked differences in glutamate or dopamine measures in other brain regions so far examined. Our second main finding is that there are unlikely to be marked differences in dopamine or glutamate measures in people at clinical high risk for psychosis relative to controls.

Although we did not find significant differences in striatal presynaptic dopamine measures between people at clinical or genetic high risk for psychosis and controls, the confidence intervals include moderate to large effects and, in the case of people at clinical high risk for psychosis, these effects approach significance, indicating that it is premature to rule out the possibility of significant group differences.

We found evidence for lower variability of striatal D2/D3 receptor availability in people at genetic risk for schizophrenia relative to controls. In contrast, there was no evidence of significantly greater variability in high-risk individuals compared to controls for any measure.

Table 2 Studies investigating glutamate function in individuals at clinical or genetic high risk for psychosis

		Probands				Controls		
	Study	N	Age (yrs., mean)	At-risk group	Antipsychotic (AP) treatment	N	Age (yrs., mean)	Substance measured
Prefrontal cortex	Byun et al[58]	20	21.8	CHR	N=8 low-dose AP	20	22.0	Glx
	Natsubori et al[59]	24	21.7	CHR	N=10 taking AP	26	22.3	Glx
	Egerton et al[56]	75	23.3	CHR	N=3 taking AP	55	24.6	Glu, Glx
	de la Fuente-Sandoval et al[60]	23	21.4	CHR	All naïve	24	20.7	Glx
	Liemburg et al[61]	16	23.0	CHR	All naïve	36	27.1	Glx
	Wang et al[62]	21	21.1	CHR	All naïve	23	22.5	Glx
	Menschikov et al[33]	21	20.2	CHR	NS	26	20.2	Glx
	Modinos et al[57]	21	23.7	CHR	All naïve	20	22.2	Glu, Glx
	Da Silva et al[63]	35	21.3	CHR	All naïve	18	20.6	Glx
	Wenneberg et al[35]	119	23.9	CHR	N=57 naïve, N=44 free	58	25.3	Glu, Glx
	Block et al[74]	35	49.2	FDR, SDR	All naïve	19	40.2	Glx
	Tibbo et al[70]	20	16.4	FDR	All naïve	22	16.7	Glu, Glx
	Purdon et al[71]	15	46.3	FDR	All naïve	14	43.5	Glu, Glx
	Yoo et al[75]	22	22.6	FDR	All naïve	22	23.1	Glx
	Lutkenhoff et al[72]	12	49.5	FDR	All naïve	21	55.7	Glu
	Da Silva et al[76]	7	28.5	22q	All naïve	23	31.2	Glx
	Capizzano et al[77]	24	19.5	FDR, SDR	All naïve	20	20.2	Glx
	Tandon et al[78]	23	15.9	FDR	All naïve	24	15.6	Glx
	Rogdaki et al[31]	20	28.6	22q	N=2 taking AP	30	27.6	Glx
	Vingerhoets et al[73]	17	30.7	22q	All naïve	20	34.2	Glu
	Legind et al[32]	44	42.2	FDR	NS	85	41.2	Glu, Glx
Hippocampus	Stone et al[64]	24	25.0	CHR	N=6 taking AP	27	25.0	Glu, Glx
	Bloemen et al[65]	11	21.3	CHR	NS	11	22.2	Glu
	Nenadic et al[66]	31	23.7	CHR	All naïve	42	23.8	Glu
	Shakory et al[67]	25	22.2	CHR	N=6 low-dose AP	31	21.0	Glu, Glx
	Bossong et al[30]	86	24.7	CHR	N=10 taking AP, N=4 previous AP	30	22.4	Glu, Glx
	Wood et al[68]	61	19.2	CHR	All naïve	25	21.1	Glx
	Provenzano et al[34]	44	21.2	CHR	NS	13	23.3	Glx
	Lutkenhoff et al[72]	12	49.5	FDR	All naïve	21	57.3	Glu
	Da Silva et al[76]	7	28.5	22q	All naïve	16	31.2	Glu, Glx
	Capizzano et al[77]	35	19.4	FDR, SDR	All naïve	24	20.2	Glx
	Rogdaki et al[31]	23	28.6	22q	N=2 taking AP	17	27.6	Glx
Basal ganglia	de la Fuente-Sandoval et al[69]	18	19.6	CHR	All naïve	40	21.8	Glu, Glx
	de la Fuente-Sandoval et al[60]	23	21.4	CHR	All naïve	24	20.7	Glx
	Block et al[74]	35	49.2	FDR, SDR	All naïve	19	40.2	Glx
	Keshavan et al[79]	40	15.6	FDR	All naïve	48	15.6	Glx
	Tandon et al[78]	23	15.9	FDR	All naïve	24	15.6	Glx
	Thakkar et al[80]	23	31.2	FDR	All naïve	24	33.9	Glx
	Rogdaki et al[31]	17	28.6	22q	N=2 taking AP	30	27.6	Glx
	Vingerhoets et al[73]	20	30.7	22q	All naïve	16	34.2	Glu

Table 2 Studies investigating glutamate function in individuals at clinical or genetic high risk for psychosis *(continued)*

	Study	Probands N	Probands Age (yrs., mean)	Probands At-risk group	Probands Antipsychotic (AP) treatment	Controls N	Controls Age (yrs., mean)	Substance measured
Thalamus	Byun et al[58]	20	21.8	CHR	N=8 low-dose AP	20	22.0	Glx
	Egerton et al[56]	75	23.3	CHR	N=3 taking AP	55	24.6	Glu, Glx
	Wenneberg et al[35]	105	23.9	CHR	N=57 naïve, N=44 free	55	25.3	Glu, Glx
	Tandon et al[78]	23	15.9	FDR	All naïve	24	15.6	Glx
	Legind et al[32]	48	42.2	FDR	All naïve	88	41.2	Glu, Glx
	Yoo et al[75]	22	22.6	FDR	All naïve	22	23.1	Glx
	Rogdaki et al[31]	20	28.6	22q	N=2 taking AP	29	27.6	Glx

CHR – clinical high risk, FDR – first-degree relative, SDR – second-degree relative, 22q – 22q11 deletion syndrome, NS – not specified, Glu - glutamate, Glx – glutamate + glutamine

Dopamine function

Initial studies of striatal presynaptic dopaminergic function in CHR individuals provided evidence of striatal dopaminergic hyperactivity[25,43,44]. The lack of a significant difference between CHR subjects and controls in the current meta-analysis is therefore potentially surprising. It should, however, be considered in the light of four pieces of evidence: the wide confidence interval around the estimated average effect (g=0.28, 95% CI: –0.03 to 0.59); the negative correlation between effect size and publication year; the finding that transition to psychosis rates have diminished over time[15]; and the fact that striatal dopaminergic hyperactivity may be specific to individuals who go on to develop psychosis, rather than all CHR subjects[18].

Rates of transition to a psychotic disorder in clinical high-risk subjects have decreased from 30-40% to 15-20% in more recent studies[15]. This is reflected in the imaging studies included in our analyses, where studies in the last two years[42,47] report transition rates of 20% and 14% respectively, whereas a 2011 study reported a rate of 38%[18]. Thus, the lack of observed differences between CHR individuals and controls may result from more recent study cohorts containing a lower proportion of individuals who transition to psychosis, and therefore a lower proportion of individuals with striatal dopaminergic hyperactivity.

No significant dopaminergic abnormalities were found in individuals at increased genetic risk for schizophrenia. There was, however, again a wide confidence interval around the estimated effect for presynaptic dopaminergic function (g=0.24, 95% CI: –0.40 to 0.88). An important factor to consider is that many of these studies were conducted in relatives of individuals with schizophrenia, who may not carry risk genes for the disorder, and the studies did not actually confirm that subjects were carrying risk genes. Moreover, many of the subjects included were older than the age of peak risk for onset of schizophrenia (the mean age of subjects scanned was 33.7 years). Thus, it is quite possible that the individuals studied were not genetically enriched for schizophrenia risk.

In the case of the 22q deletion studies, the subjects were tested to directly confirm that they were at increased genetic risk. One of these studies demonstrated a large increase in dopamine synthesis capacity in 22q11.2 deletion carriers relative to controls[52]. Future research could benefit from exploring the relationship between measures of neurochemical function and other more direct measures of genetic risk such as polygenic risk scores.

We found no mean differences in striatal D2/D3 receptor availability in either risk group compared to controls. This is consistent with findings in schizophrenia[6]. PET studies of D2/D3 receptors are complicated by the fact that endogenous dopamine competes with the radioligand, which could mask a concurrent rise in receptor density[6,8], although findings to date do not indicate differences in synaptic dopamine levels[65]. We found significantly reduced variability in GHR individuals for measures of striatal D2/D3 receptor availability. This suggests that GHR individuals show greater neurobiological homogeneity, potentially due to increased within-group genetic similarity.

Glutamate function

A previous meta-analysis found that prefrontal Glx was significantly greater in high-risk individuals compared to healthy controls[1]. In our meta-analysis, we were able to include seven further studies for this region, and with these additional studies no difference between groups was found. This finding has the tightest confidence interval of all our results (g=0.01, 95% CI: –0.15 to 0.16), suggesting that, if any case-control differences do exist, they will at most be of a small magnitude.

Our findings for prefrontal glutamate, hippocampal glutamate and Glx, and basal ganglia Glx include more subjects than the previous meta-analysis, but are in keeping with its findings, in that no group differences were observed in these regions. However, confidence intervals tended to be wider for these regions and it is therefore not possible to conclusively rule out significant between-group differences.

The finding of increased thalamic Glx in GHR individuals adds to the evidence of raised thalamic glutamine in schizophrenia,

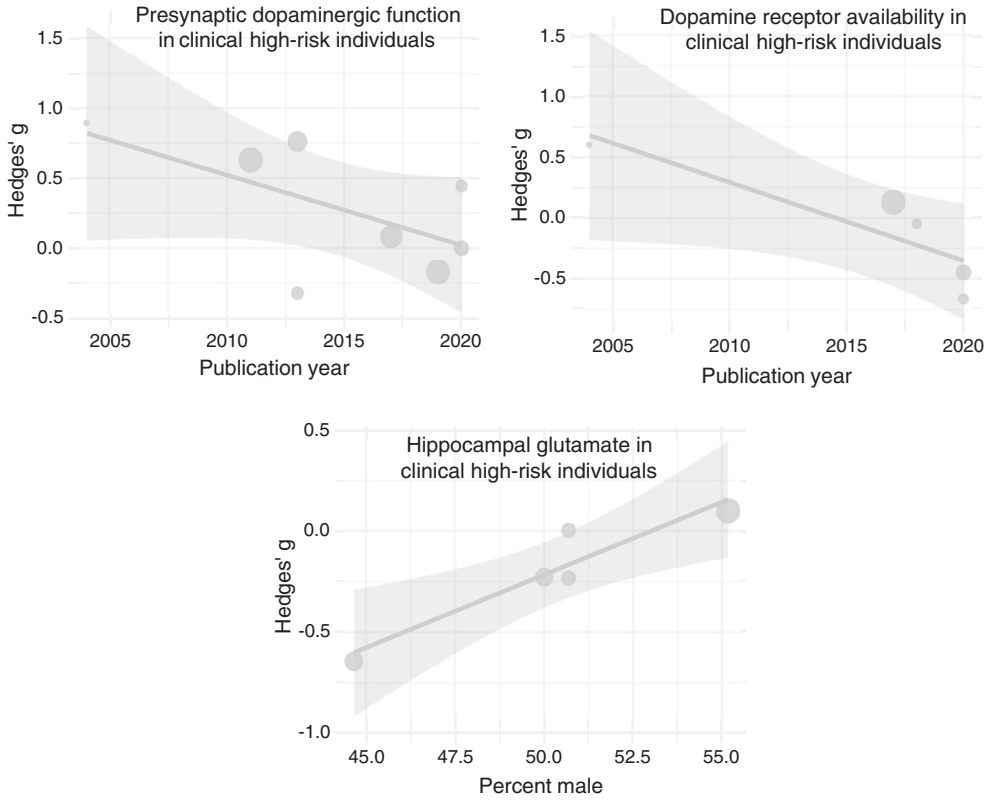

Figure 4 Meta-regressions of standardized mean differences against study level variables

although we did not detect significant Glx alterations in CHR subjects and there is no evidence of Glx differences from controls in schizophrenia[1].

Methodological considerations

Moderate between-study inconsistency was seen in most of the analyses undertaken. In addition to methodological factors such as differences in scanners, ligands used and voxel positioning, differences in the clinical characteristics of patients could contribute to between-study heterogeneity. Once again, increased dopaminergic activity in clinical high-risk groups may be restricted to those that experience clinical deterioration[81-83]. Similarly, for glutamate, elevations may only occur in high-risk individuals with poor outcomes. This is supported by reports that elevated hippocampal glutamate levels are specific to individuals who go on to transition[30], and that medial temporal glutamate levels are positively associated with symptom severity in schizophrenia[84].

The use of antipsychotics is unlikely to have had a significant impact on our findings, given that the vast majority of studies reported on antipsychotic-naïve cohorts. However, the use of other psychotropic drugs was not reported in many studies, and could contribute to inconsistencies. A recommendation for future studies is that all psychotropic drug use is reported to facilitate comparisons.

We combined studies of synthesis capacity, release capacity and synaptic dopamine levels, as in previous meta-analyses[5,6]. There is, however, evidence that these paradigms capture separate, although related, aspects of dopaminergic function[85-87].

Future directions

Our review has identified a number of sources of phenotypic heterogeneity that have not been fully addressed in currently available studies. In the case of GHR individuals, characterization of the genetic risk is needed to determine if subjects are indeed at risk. This in turn should allow for more precise estimates of any potential neurochemical abnormalities. In CHR subjects, key factors are the transition risk, age and specific symptoms[88]. In both groups, larger samples and clinical follow-up of subjects to determine transition are also key.

We focused on striatal presynaptic dopaminergic function and D2/D3 receptor availability, as these variables were measured in a sufficient number of studies to allow a meta-analysis. Recent studies have, however, looked at cortical and nigrostriatal dopaminergic function[46,89]. It would be useful for future studies to combine measures of cortical and nigrostriatal dopaminergic function to determine the regional specificity of findings. It would also be of interest to see if effect sizes are greater in studies where the patient population shows greater severity of symptoms,

which is currently precluded by the fact that many differing scales are used to assess symptoms.

CONCLUSIONS

Increased thalamic Glx concentrations are found in individuals at increased genetic risk for psychosis. There are no significant differences between high-risk individuals and controls in striatal presynaptic dopaminergic function, striatal D2/D3 receptor availability, prefrontal cortex glutamate or Glx, hippocampal glutamate or Glx, or basal ganglia Glx. There is also no evidence of increased variability of dopamine or glutamate measures in high-risk individuals compared to controls. Significant heterogeneity, however, exists between studies, which does not allow to rule out an increase in striatal dopamine synthesis and release capacity in subjects at increased clinical risk.

ACKNOWLEDGEMENTS

R.A. McCutcheon's work is funded by a Wellcome Trust grant (no. 200102/Z/15/Z) and UK National Institute for Health Research (NIHR) fellowships. K. Merritt is funded by a UK Medical Research Council grant (no. MR/S003436/1). O.D. Howes is funded by the UK Medical Research Council and the NIHR Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the funding bodies. R.A. McCutcheon and K. Merritt contributed equally to this paper. Supplementary information on the study is available at https://doi.org/10.5281/zenodo.4739435.

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DOI:10.1002/wps.20893

Risk and protective factors for mental disorders beyond genetics: an evidence-based atlas

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Decades of research have revealed numerous risk factors for mental disorders beyond genetics, but their consistency and magnitude remain uncertain. We conducted a "meta-umbrella" systematic synthesis of umbrella reviews, which are systematic reviews of meta-analyses of individual studies, by searching international databases from inception to January 1, 2021. We included umbrella reviews on non-purely genetic risk or protective factors for any ICD/DSM mental disorders, applying an established classification of the credibility of the evidence: class I (convincing), class II (highly suggestive), class III (suggestive), class IV (weak). Sensitivity analyses were conducted on prospective studies to test for temporality (reverse causation), TRANSD criteria were applied to test transdiagnosticity of factors, and A Measurement Tool to Assess Systematic Reviews (AMSTAR) was employed to address the quality of meta-analyses. Fourteen eligible umbrella reviews were retrieved, summarizing 390 meta-analyses and 1,180 associations between putative risk or protective factors and mental disorders. We included 176 class I to III evidence associations, relating to 142 risk/protective factors. The most robust risk factors (class I or II, from prospective designs) were 21. For dementia, they included type 2 diabetes mellitus (risk ratio, RR from 1.54 to 2.28), depression (RR from 1.65 to 1.99) and low frequency of social contacts (RR=1.57). For opioid use disorders, the most robust risk factor was tobacco smoking (odds ratio, OR=3.07). For non-organic psychotic disorders, the most robust risk factors were clinical high risk state for psychosis (OR=9.32), cannabis use (OR=3.90), and childhood adversities (OR=2.80). For depressive disorders, they were widowhood (RR=5.59), sexual dysfunction (OR=2.71), three (OR=1.99) or four-five (OR=2.06) metabolic factors, childhood physical (OR=1.98) and sexual (OR=2.42) abuse, job strain (OR=1.77), obesity (OR=1.35), and sleep disturbances (RR=1.92). For autism spectrum disorder, the most robust risk factor was maternal overweight pre/during pregnancy (RR=1.28). For attention-deficit/hyperactivity disorder (ADHD), they were maternal pre-pregnancy obesity (OR=1.63), maternal smoking during pregnancy (OR=1.60), and maternal overweight pre/during pregnancy (OR=1.28). Only one robust protective factor was detected: high physical activity (hazard ratio, HR=0.62) for Alzheimer's disease. In all, 32.9% of the associations were of high quality, 48.9% of medium quality, and 18.2% of low quality. Transdiagnostic class I-III risk/protective factors were mostly involved in the early neurodevelopmental period. The evidence-based atlas of key risk and protective factors identified in this study represents a benchmark for advancing clinical characterization and research, and for expanding early intervention and preventive strategies for mental disorders.

Key words: Risk factors, protective factors, mental disorders, dementia, psychotic disorders, mood disorders, autism spectrum disorder, attention-deficit/hyperactivity disorder, early intervention, preventive strategies

(World Psychiatry 2021;20:417–436)

Mental disorders are complex conditions of uncertain aetiopathology. Although a genetic predisposition is evident (e.g., for psychotic disorders[1-3], bipolar disorders[4,5], depressive and anxiety disorders[6,7]), even polyrisk genetic scores, on their own, explain only a small proportion of the phenotypic variance[8-10]. There is strong evidence that environmental factors underlie much of the variation in clinical and neurobiological phenotypes of mental disorders and their outcomes[11], and there are suggestions for dynamic three-dimensional gene-by-environment-by-time interactions.

Aetiopathological knowledge in psychiatry has often been plagued by scientific pessimism. However, there have been recent exponential developments in research, to the point that numerous non-purely genetic risk factors for mental disorders have been identified. The timing of their effect encompasses prenatal or perinatal, childhood, later (adolescent/young adult) or antecedent (shortly preceding the onset of a disorder) phases.

The number of individual studies exploring risk or protective factors for mental disorders has grown over the past decades,

and several meta-analyses have been published. More recently[12], umbrella review methods (i.e., systematic reviews of meta-analyses[13]) have allowed comparisons between different meta-analyses, by summarizing the findings with a uniform approach for all risk/protective factors, including expected variability in the quality, focus of interest, and several types of biases in the meta-analyses[14-16].

Umbrella reviews can also apply robust classification criteria[17] to rank the credibility of the evidence, controlling at the same time for several biases[18-21], which helps overcome conflicting meta-analytic findings on complex topics[13]. Accordingly, umbrella reviews with a classification of the credibility of evidence are employed to help synthesize the available literature in order to guide both clinical care and public health policies. Collectively, umbrella reviews are at the top of the hierarchy in the evaluation of evidence[16,22].

While several recent umbrella reviews have evaluated the consistency and magnitude of risk and protective factors for each specific mental disorder, no systematic synthesis has yet collectively appraised the evidence across all existing mental disorders. Therefore, the extent to which these factors may differently exert their influence within specific disorders or across different disorders is currently unknown.

We present here the first systematic synthesis of umbrella reviews of non-purely genetic risk and protective factors for mental disorders. This approach has been termed "meta-umbrella" and offers an overarching field-wide overview to comprehensively assess a certain topic[23]. Our aims were to provide an evidence-synthesis comparative atlas of the consistency and magnitude of risk and protective factors for mental disorders beyond genetics, and to formulate recommendations for the next generation of aetiopathological research and preventive psychiatry.

METHODS

Search strategy and selection criteria

We conducted a meta-umbrella systematic review of umbrella reviews[23]. The search strategy followed the PRISMA guidelines[24]. A multi-step systematic literature search was performed by independent researchers to explore Web of Science (Clarivate Analytics) databases (including the Web of Science Core Collection, BIOSIS Citation Index, MEDLINE, KCI-Korean Journal Database, SciELO Citation Index, and Russian Science Citation Index), PubMed, the Cochrane Central Register of Reviews, and Ovid/PsycINFO databases, from inception to January 1, 2021.

The following broad search terms were applied: "umbrella review" and ("risk" OR "protect*"). Papers identified were initially screened based on title and abstract reading. After the exclusion of those which were not relevant based on the topic investigated, full texts of the remaining papers were further assessed for inclusion. The references of umbrella reviews included in the final dataset were also reviewed to identify additional eligible papers.

Studies included were: a) umbrella reviews, defined as systematic collections and assessments of multiple systematic reviews and/or meta-analyses published on a specific research topic[14,15], b) reporting quantitative data from observational individual studies (i.e., case-control, cohort, cross-sectional or ecological studies) on non-purely genetic risk and/or protective factors for mental disorders based on established criteria for classifying the credibility of the evidence[18-21] (see below), and c) primarily investigating the association between these risk and/or protective factors and ICD (any version) or DSM (any version) mental disorders.

Mental disorders were stratified by using the corresponding ICD-10 diagnostic blocks: organic, including symptomatic, mental disorders; mental and behavioural disorders due to psychoactive substance use; schizophrenia, schizotypal and delusional disorders; mood (affective) disorders; neurotic, stress-related and somatoform disorders; behavioural syndromes associated with psychological disturbances and physical factors; disorders of adult personality and behaviour; mental retardation; disorders of psychological development; and behavioural and emotional disorders with onset usually occurring in childhood and adolescence.

Studies excluded were: a) systematic reviews or meta-analyses other than umbrella reviews, individual studies (including Mendelian randomization studies and randomized controlled trials), clinical cases, conference proceedings, and study protocols; b) umbrella reviews not reporting quantitative data; c) umbrella reviews addressing outcomes other than the onset of an established mental disorder (e.g., those related to clinical outcomes such as relapse, remission or treatment response[15,23], or biomarkers); d) umbrella reviews employing other classification approaches, such as GRADE[25], because these mostly apply to interventional effects, not aetiology[26].

We did not include pure genetic factors or biomarkers, because genetic/biomarker causality is tested with other analytical approaches (such as genome-wide association studies and meta/mega-analyses). When there were two or more umbrella reviews from the same centre, authors were contacted to clarify overlaps. When two papers presented overlapping datasets on the same risk/protective factor for the same disorder, only the paper with the largest dataset was retained for the analysis. Disagreements in search and selection were resolved through discussion and consensus.

Measures and data extraction

At least two independent researchers extracted a predetermined set of variables characterizing each umbrella review, including the first author and year of publication, the corresponding ICD-10 diagnostic block(s), the number of meta-analyses included, the median number of individual studies and of cases (with interquartile range) per association, the overall number of risk/protective factors investigated, and the range of years for which the evidence was reviewed.

Further variables were extracted to characterize the associa-

tion between each specific risk/protective factor and each mental disorder. We recorded each risk/protective factor (if the timing of effect was specified, this was additionally reported, e.g., childhood, midlife, elderhood). Following a pragmatic approach, each risk/protective factor was defined as originally operationalized by each individual study, without redefining it unless strictly necessary to improve the clarity of reporting. Since each factor (e.g., smoking) can be associated with multiple outcomes (e.g., lung and pancreatic cancer), the total number of associations tested in umbrella reviews typically exceeds that of factors[27].

We recorded the specific mental disorder which was the focus of each umbrella review and matched it with the corresponding ICD-10 diagnostic block. Furthermore, we recorded the number of individual studies and cases analyzed per each association, the strength of the association and its measurement – odds ratio (OR), risk ratio (RR), incidence rate ratio (IRR), hazard ratio (HR), Hedges' g, Cohen's d, and r – with the corresponding 95% confidence intervals (CI). A value of OR, RR, IRR or HR and its 95% CI higher than 1, or a value of Hedges' g, Cohen's d, or r higher than 0 indicates an association with an increased likelihood of a mental disorder (i.e., risk factor). A value of OR, RR, IRR or HR and its 95% CI lower than 1, or a value of Hedges' g, Cohen's d, or r lower than 0 indicates an association with a reduced likelihood of a mental disorder (i.e., protective factor). We also provided the equivalent OR (eOR) for all metrics: an eOR higher than 1 indicates an association with an increased likelihood of a mental disorder (i.e., risk factor), while an eOR lower than 1 indicates an association with a reduced likelihood of a mental disorder (i.e., protective factor)[15]. Finally, we extracted the overall class of evidence as reported for each association and the class of evidence reported in prospective studies of each association (see below).

Strategy for data synthesis

The results were systematically stratified across the corresponding ICD-10 diagnostic blocks and described across three sections: a) evidence for associations between risk/protective factors and individual mental disorders, b) evidence for transdiagnostic associations of risk/protective factors, c) evidence for factors that have both risk and protective associations with various mental disorders.

For the first analysis, we reported the classification of the credibility of the evidence in the included umbrella reviews according to established criteria[13,18-20]: class I, convincing (number of cases >1,000, $p<10^{-6}$, $I^2<50\%$, 95% prediction interval excluding the null, no small-study effects, and no excess significance bias); class II, highly suggestive (number of cases >1,000, $p<10^{-6}$, largest study with a statistically significant effect, and class I criteria not met); class III, suggestive (number of cases >1,000, $p<10^{-3}$, and class I-II criteria not met); class IV, weak ($p<0.05$ and class I-III criteria not met); and non-significant ($p>0.05$). We considered only factors with a class of evidence from I to III, and primarily focused on those with robust evidence (i.e., class I and II). We additionally reported the class of evidence for each association when the analyses were restricted to prospective studies (if provided by the umbrella reviews included). This sensitivity analysis deals with the problem of reverse causation that may affect, for example, case-control studies[20]. Furthermore, we indicated whether the associations involving medical treatments were likely confounded by underlying conditions which might themselves increase the risk of mental disorders (confounding by indication)[28]. We also reported the quality of the included meta-analyses measured by the AMSTAR (A Measurement Tool to Assess Systematic Reviews) tool[29].

The second analysis (transdiagnostic associations) was conducted only for those risk factors that were shared by at least two disorders. We applied the TRANSD criteria, which empirically evaluate the consistency and extent of putative transdiagnostic constructs across six domains[30,31]. In order to be validated, a transdiagnostic association had to adopt a transparent (criterion T) diagnostic definition according to the gold standard; clearly report (criterion R) the primary outcome of the study; be appraised (criterion A) as "across diagnoses and within spectrum" or "across diagnostic spectra"; numerate (criterion N) the corresponding ICD-10 diagnostic categories and spectra; and show (criterion S) a transdiagnostic class of evidence of at least III, and not inferior to the lowest class of evidence for the corresponding disorder-specific associations. The transdiagnostic class of evidence within prospective studies was additionally reported in order to demonstrate (criterion D) the generalizability of the transdiagnostic factor.

The third analysis was based on a systematic description of the findings.

RESULTS

Database

Overall, 1,361 records were retrieved, 800 suitable papers were screened, and 14 umbrella reviews were eligible[6,15,27,32-42] (see Figure 1). The eligible umbrella reviews were published between 2017 and 2021, and reviewed individual studies published from 1995 to 2020. The 14 eligible umbrella reviews (Table 1) included 390 meta-analyses. The median number of meta-analyses per umbrella review was 26 (interquartile range: 9-43).

Evidence for association between risk/protective factors and mental disorders

Altogether, 1,180 associations between putative risk or protective factors and mental disorders were analyzed. Among them, 497 were non-significant and 507 of class IV, leaving 176 risk/protective associations of class I-III, which were included in the current study. Twenty-one associations met class I or II from prospective designs (most robust associations). Table 2 summarizes the associations of risk/protective factors and mental disorders, stratified by ICD-10 diagnostic blocks.

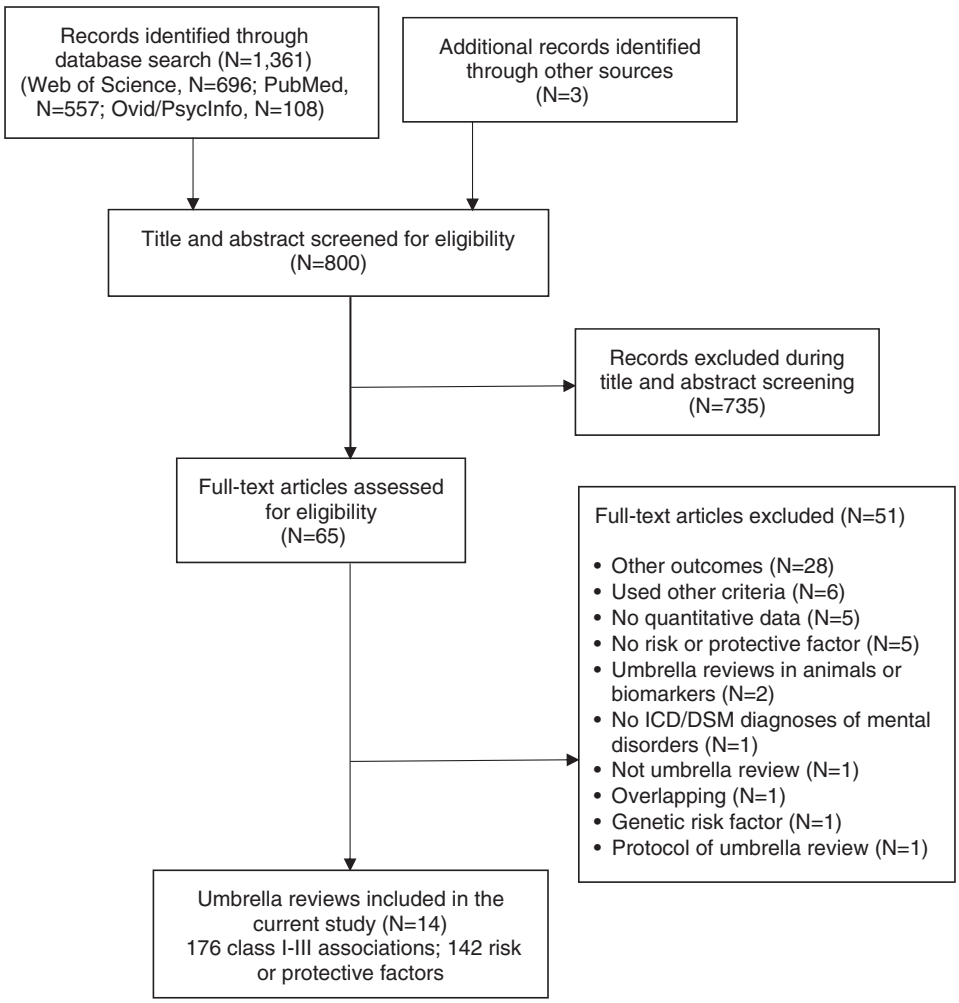

Figure 1 PRISMA flow chart outlining study selection process

Organic, including symptomatic, mental disorders

Twenty-one associations with any dementia, Alzheimer's disease, or vascular dementia were evaluated within this ICD-10 diagnostic block[27]. Seven associations were supported by class I evidence (Table 2). Four risk factors were involved in these associations: type 2 diabetes mellitus (with vascular dementia, RR=2.28, and with Alzheimer's disease, RR=1.54); depression (with any dementia, RR=1.99); depression in elderhood (with any dementia, RR=1.85, and with Alzheimer's disease, RR=1.65); low frequency of social contacts (with any dementia, RR=1.57); and benzodiazepine use (with any dementia, RR=1.49; likely confounding by indication such as difficulties with sleep and chronic anxiety with or without depression).

Four associations were supported by class II evidence (Table 2). These involved two risk factors, namely depression at any age (with Alzheimer's disease, RR=1.77) and type 2 diabetes mellitus (with any dementia, RR=1.60); and two protective factors, i.e. history of cancer (with Alzheimer's disease, HR=0.62, possibly due to survival bias) and high physical activity (with Alzheimer's disease, HR=0.62).

Ten associations were supported by class III evidence (Table 2), involving six risk factors (obesity in midlife, low education, low frequency electromagnetic fields, aluminium exposure, depression in childhood, and herpes viruses infection); and three protective factors (statin use, high physical activity, and non-steroidal anti-inflammatory drug use).

All factors with class I and II evidence remained at the same level of evidence in prospective analyses. For factors with class III evidence, no prospective analysis data were available (Table 2).

Mental and behavioural disorders due to psychoactive substance use

Twelve associations across tobacco related disorder, alcohol related disorder and opioid use disorder were evaluated within this ICD-10 diagnostic block[38,41]. None of the associations was supported by class I evidence. Only one association was supported by class II evidence, involving tobacco smoking as a risk factor for opioid use disorder (OR=3.07).

Table 1 Overall characteristics of the umbrella reviews included in the current study

	ICD-10 diagnostic block	Number of included meta-analyses	Median number of individual studies (IQR) per association	Median number of cases (IQR) per association	Number of risk or protective factors tested	Evidence reviewed (years range)
Bellou et al[27]	Organic, including symptomatic, mental disorders	43	7 (5-13)	1,139 (590-3,537)	53	2008-2016
Bortolato et al[32]	Mood (affective) disorders	7	8 (4-11)	1,163 (313-50,358)	7	2006-2016
Belbasis et al[33]	Schizophrenia, schizotypal and delusional disorders	41	7 (5-10)	384 (254-939)	41	1995-2016
Kohler et al[34]	Mood (affective) disorders	70	7.5 (5-11)	2,269 (621- 9,090)	134	2003-2017
Radua et al[15]	Schizophrenia, schizotypal and delusional disorders	55	5 (3-9)	424 (226-1,193)	170	1995-2017
Kim et al[35]	Disorders of psychological development	46	8 (2-24)	3,764(1,000-8,831)	67	2011-2019
Tortella-Feliu et al[6]	Neurotic, stress-related and somatoform disorders	33	1 (1-4)	46 (22-82)	130	2000-2018
Fullana et al[36]	Neurotic, stress-related and somatoform disorders	19	1 (1-1)	100 (54-224)	427	2000-2017
Kim et al[37]	Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	35	6 (4-8)	16,850 (1,490–37,086)	40	2012-2020
Solmi et al[39]	Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	10	6 (4-9)	485 (70-2,081)	12	2013-2018
Solmi et al[38]	Mental and behavioural disorders due to psychoactive substance use	12	8 (4-12)	1348 (842-2,064)	12	2003-2019
Solmi et al[40]	Behavioural syndromes associated with physiological disturbances and physical factors	9	32 (17-82)	514 (196-1,103)	49	2002-2019
Solmi et al[41]	Mental and behavioural disorders due to psychoactive substance use	5	10 (7-14)	634 (366-1,621)	12	2011-2019
Solmi et al[42]	Disorders of adult personality and behaviour; mental retardation	5	5 (3-14)	214 (98-2,420)	26	1999-2020

IQR – interquartile range

Eleven associations were supported by class III evidence (Table 2), involving eight risk factors and two protective factors. The three risk factors for tobacco related disorder were attention-deficit/hyperactivity disorder (ADHD), peer smoking behaviour, and smoking in movies; the five risk factors for alcohol related disorder were impulsivity-related personality traits in college or school or community adolescents, parental alcohol supply, and externalizing symptoms in adolescents. The two protective factors were surviving childhood cancer (for alcohol and tobacco related disorder) and parental stricter alcohol rules (for alcohol related disorder).

For class II evidence, the prospective analysis showed that tobacco smoking remained at the same level of evidence as a risk factor for opioid use disorder. For the remaining class III evidence factors, no prospective analysis data were available (Table 2).

Schizophrenia, schizotypal and delusional disorders

Twenty-two associations with any non-organic psychotic disorder and schizophrenia spectrum disorders were evaluated within this ICD-10 diagnostic block[15,33]. Only three associations were supported by class I evidence (Table 2). These all included risk factors: clinical high risk state for psychosis (with any non-organic psychotic disorder, OR=9.32), Black-Caribbean ethnicity in England (with any non-organic psychotic disorder, IRR=4.87), and obstetric complications (with schizophrenia spectrum disorders, OR=1.97).

Nine associations were supported by class II evidence (Table 2). Seven of these involved risk factors, namely minor physical anomalies (Hedges' g=0.92), trait anhedonia (Hedges' g=0.82), ethnic minority in low ethnic density area (IRR=3.71), and being a second generation immigrant (IRR=1.68), with any non-organic psychotic disorder; and cannabis use (OR=3.90), stressful events (OR=3.11), and adversities in childhood (OR=2.80), with schizophrenia spectrum disorders. Two associations involved protective factors: premorbid IQ (Hedges' g = –0.42) and olfactory identification ability (Hedges' g = –0.91) with any non-organic psychotic disorder.

Ten associations were supported by class III evidence (Table 2). These all involved risk factors: social withdrawal in childhood,

Table 2 Evidence for associations between non-purely genetic risk or protective factors and mental disorders

Risk or protective factor	Mental disorder	Number of individual studies (cases)	Strength of association, measure	95% CI	Class of evidence (prospective evidence class)	Quality (AMSTAR)	eOR
Organic, including symptomatic, mental disorders							
Type 2 diabetes mellitus	Vascular dementia	14 (1,396)	2.28, RR	1.94-2.66	I (I)	High	2.28
Depression	Any dementia	33 (25,106)	1.99, RR	1.84-2.16	I (I)	High	1.99
Depression in elderhood	Any dementia	25 (4,957)	1.85, RR	1.67-2.05	I (I)	Medium	1.85
Depression in elderhood	Alzheimer's disease	16 (3,358)	1.65, RR	1.42-1.92	I (I)	Medium	1.65
Low frequency of social contacts	Any dementia	8 (1,122)	1.57, RR	1.32-1.85	I (I)	Medium	1.57
Type 2 diabetes mellitus	Alzheimer's disease	21 (3,537)	1.54, RR	1.39-1.72	I (I)	High	1.54
Benzodiazepines use*	Any dementia	5 (11,741)	1.49, RR	1.30-1.72	I (I)	High	1.49
Depression	Alzheimer's disease	25 (5,101)	1.77, RR	1.48-2.13	II (II)	High	1.77
Type 2 diabetes mellitus	Any dementia	22 (15,707)	1.60, RR	1.43-1.79	II (II)	High	1.60
High physical activity	Alzheimer's disease	9 (1,358)	0.62, HR	0.52-0.72	II (II)	Medium	0.62
History of cancer	Alzheimer's disease	7 (4,635)	0.62, HR	0.53-0.74	II (II)	Medium	0.62
Obesity in midlife	Any dementia	5 (1,914)	1.91, RR	1.40-2.62	III (NA)	Medium	1.91
Low education	Any dementia	23 (8,739)	1.88, RR	1.51-2.33	III (NA)	High	1.88
Low education	Alzheimer's disease	16 (2,769)	1.82, RR	1.36-2.43	III (NA)	High	1.82
Low frequency electromagnetic fields	Alzheimer's disease	25 (3,238)	1.74, RR	1.37-2.21	III (NA)	High	1.74
Aluminium exposure	Alzheimer's disease	8 (1,383)	1.72, OR	1.33-2.21	III (NA)	Medium	1.72
Depression in childhood	Any dementia	9 (3,538)	1.63, RR	1.27-2.11	III (NA)	High	1.63
Herpes viruses infection	Alzheimer's disease	33 (1,330)	1.38, OR	1.14-1.65	III (NA)	Medium	1.38
Statins use	Any dementia	12 (37,798)	0.83, RR	0.76-0.91	III (NA)	High	0.83
High physical activity	Any dementia	21 (3,845)	0.76, RR	0.66-0.86	III (NA)	Medium	0.76
NSAID use	Alzheimer's disease	16 (53,372)	0.74, RR	0.64-0.86	III (NA)	High	0.74
Mental and behavioural disorders due to psychoactive substance use							
Tobacco smoking	Opioid use disorder	10 (2,447)	3.07, OR	2.27-4.14	II (II)	Low	3.07
Impulsivity-related personality traits in college adolescents	Alcohol related disorder	15 (NA)	0.53, d	0.43-0.64	III (NA)	Medium	2.63
ADHD	Tobacco related disorder	4 (NA)	2.36, OR	1.71-3.27	III (NA)	Medium	2.36
Impulsivity-related personality traits in community adolescents	Alcohol related disorder	9 (NA)	0.45, d	0.33-0.56	III (NA)	Medium	2.26
Impulsivity-related personality traits in school adolescents	Alcohol related disorder	12 (NA)	0.43, d	0.34-0.52	III (NA)	Medium	2.18
Parental alcohol supply	Alcohol related disorder	8 (NA)	2.00, OR	1.72-2.32	III (NA)	Medium	2.00
Peer smoking behaviour	Tobacco related disorder	71 (NA)	1.92, OR	1.76-2.09	III (NA)	Medium	1.92
Externalizing symptoms in adolescents	Alcohol related disorder	23 (NA)	1.63, OR	1.39-1.90	III (NA)	Medium	1.63
Smoking in movies	Tobacco related disorder	9 (4,398)	1.46, RR	1.23-1.73	III (NA)	Medium	1.46
Surviving childhood cancer	Alcohol related disorder	3 (1,348)	0.78, OR	0.68-0.88	III (NA)	Medium	0.78
Surviving childhood cancer	Tobacco related disorder	6 (2,064)	0.54, OR	0.42-0.70	III (NA)	Medium	0.54
Parental stricter alcohol rules	Alcohol related disorder	2 (NA)	0.41, OR	0.33-0.51	III (NA)	Medium	0.41
Schizophrenia, schizotypal and delusional disorders							
Clinical high-risk state for psychosis	Any non-organic psychotic disorder	9 (1,226)	9.32, OR	4.91-17.72	I (I)	High	9.32

Table 2 Evidence for associations between non-purely genetic risk or protective factors and mental disorders *(continued)*

Risk or protective factor	Mental disorder	Number of individual studies (cases)	Strength of association, measure	95% CI	Class of evidence (prospective evidence class)	Quality (AMSTAR)	eOR
Black-Caribbean ethnicity in England	Any non-organic psychotic disorder	9 (3,446)	4.87, IRR	3.96-6.00	I (IV)	High	4.87
Obstetric complications	Schizophrenia spectrum disorders	18 (1,000)	1.97, OR	1.55-2.50	I (NA)	Low	1.97
Minor physical anomalies	Any non-organic psychotic disorder	14 (1,212)	0.92, g	0.61-1.23	II (NA)	Medium	5.30
Trait anhedonia	Any non-organic psychotic disorder	44 (1,601)	0.82, g	0.72-0.92	II (NA)	Medium	4.41
Cannabis use	Schizophrenia spectrum disorders	10 (4,036)	3.90, OR	2.84-5.35	II (II)	High	3.90
Ethnic minority in low ethnic density area	Any non-organic psychotic disorder	5 (1,328)	3.71, IRR	2.47-5.58	II (IV)	High	3.71
Stressful events	Schizophrenia spectrum disorders	13 (2,218)	3.11, OR	2.31-4.18	II (NA)	Medium	3.11
Adversities in childhood	Schizophrenia spectrum disorders	34 (7,738)	2.80, OR	2.34-3.34	II (II)	Medium	2.80
Second generation immigrant	Any non-organic psychotic disorder	26 (28,753)	1.68, IRR	1.42-1.92	II (IV)	High	1.68
Premorbid IQ	Any non-organic psychotic disorder	16 (4,459)	–0.42, g	–0.52 to –0.33	II (IV)	Medium	0.47
Olfactory identification ability	Any non-organic psychotic disorder	55 (1,703)	–0.91, g	–1.05 to –0.78	II (NA)	High	0.19
Social withdrawal in childhood	Any non-organic psychotic disorder	15 (1,810)	0.59, g	0.33-0.85	III (IV)	High	2.91
Tobacco smoking	Schizophrenia spectrum disorder	17 (NA)	2.34, OR	1.65-3.33	III (NA)	High	2.34
North African immigrant in Europe	Any non-organic psychotic disorder	12 (2,577)	2.22, IRR	1.58-3.12	III (IV)	High	2.22
Urbanicity	Any non-organic psychotic disorder	8 (45,791)	2.19, OR	1.55-3.09	III (III)	Medium	2.19
Ethnic minority in high ethnic density area	Any non-organic psychotic disorder	5 (1,328)	2.11, IRR	1.39-3.20	III (IV)	High	2.11
First generation immigrant	Any non-organic psychotic disorder	42 (25,063)	2.10, IRR	1.72-2.56	III (IV)	High	2.10
Toxoplasma gondii IgG	Any non-organic psychotic disorder	42 (8,796)	1.82, OR	1.51-2.18	III (IV)	High	1.82
Non-right handedness	Any non-organic psychotic disorder	41 (2,652)	1.58, OR	1.35-1.86	III (NS)	Medium	1.58
Paternal age >35	Schizophrenia spectrum disorders	10 (NA)	1.28, OR	1.11-1.48	III (NA)	Medium	1.28
Winter/spring season of birth in the Northern hemisphere	Any non-organic psychotic disorder	27 (115,010)	1.04, OR	1.02-1.06	III (NA)	High	1.04
		Mood (affective) disorders					
Widowhood	Depressive disorders	5 (2,720)	5.59, RR	3.79-8.23	I (I)	Low	5.59
Sexual dysfunction	Depressive disorders	6 (5,488)	2.71, OR	1.93-3.79	I (I)	High	2.71
Irritable bowel syndrome	Bipolar disorders	6 (177,117)	2.48, OR	2.35-2.61	I (NA)	High	2.48
Four or five metabolic risk factors	Depressive disorders	8 (1,191)	2.06, OR	1.59-2.68	I (I)	Low	2.06
Physical abuse in childhood	Depressive disorders	10 (3,886)	1.98, OR	1.68-2.33	I (I)	Medium	1.98

Table 2 Evidence for associations between non-purely genetic risk or protective factors and mental disorders *(continued)*

Risk or protective factor	Mental disorder	Number of individual studies (cases)	Strength of association, measure	95% CI	Class of evidence (prospective evidence class)	Quality (AMSTAR)	eOR
Job strain	Depressive disorders	7 (1,909)	1.77, OR	1.46-2.13	I (I)	Medium	1.77
Obesity	Depressive disorders	8 (7,673)	1.35, OR	1.21-1.50	I (I)	Low	1.35
Dietary zinc	Depressive disorders	8 (3,708)	0.65, RR	0.57-0.75	I (NA)	Medium	0.65
Tea intake	Depressive disorders	13 (4,373)	0.68, RR	0.61-0.77	I (NA)	Medium	0.68
Dry eye disease with Sjögren's syndrome	Depressive disorders	7 (3,062)	4.25, OR	2.67-6.76	II (NA)	Low	4.25
Poor physical health	Depressive disorders in elderhood	11 (8,630)	4.08, OR	3.25-5.12	II (NA)	Low	4.08
Adversities in childhood	Bipolar disorders	13 (1,146)	2.86, OR	2.03-4.04	II (NA)	High	2.86
Emotional abuse in childhood	Depressive disorders	8 (4,112)	2.78, OR	1.89-4.09	II (III)	Medium	2.78
Chronic disease	Depressive disorders in elderhood	10 (9,090)	2.59, OR	1.78-3.76	II (III)	Low	2.59
Intimate partner violence against women	Depressive disorders	9 (3,003)	2.57, RR	2.25-2.94	II (NA)	Low	2.57
Sexual abuse in childhood	Depressive disorders	14 (4,586)	2.42, OR	1.94-3.02	II (II)	Medium	2.42
Gulf war veterans	Depressive disorders	11 (16,826)	2.37, OR	1.91-2.93	II (NA)	Low	2.37
Asthma	Depressive disorders in childhood	7 (2,828)	2.08, OR	1.56-2.77	II (NA)	Low	2.08
Three metabolic risk factors	Depressive disorders	8 (3,014)	1.99, OR	1.60-2.48	II (II)	Low	1.99
Poor vision	Depressive disorders in elderhood	12 (11,066)	1.94, OR	1.67-2.25	II (NA)	Medium	1.94
Sleep disturbances	Depressive disorders in elderhood	11 (2,610)	1.92, RR	1.59-2.33	II (II)	High	1.92
Psoriasis	Depressive disorders	9 (86,945)	1.64, OR	1.41-1.90	II (NA)	Medium	1.64
Low education	Depressive disorders in elderhood	24 (16,590)	1.58, OR	1.38-1.82	II (IV)	Low	1.58
Metabolic syndrome	Depressive disorders	27 (20,924)	1.42, OR	1.28-1.57	II (IV)	Medium	1.42
Sedentary behaviour	Depressive disorders	24 (60,526)	1.25, RR	1.16-1.35	II (NA)	Medium	1.25
Neglect in childhood	Depressive disorders	6 (1,668)	2.75, OR	1.59-4.74	III (NA)	Medium	2.75
Insomnia	Depressive disorders	21 (NA)	2.60, OR	1.98-3.42	III (NA)	Low	2.60
Chronic lung disease	Depressive disorders	4 (297,031)	2.38, RR	1.47-3.85	III (NA)	Medium	2.38
Dry eye disease without Sjögren's syndrome	Depressive disorders	6 (611,517)	2.24, OR	1.50-3.34	III (NA)	Low	2.24
Vitamin D deficiency	Depressive disorders	3 (NA)	2.22, HR	1.42-3.47	III (III)	High	2.22
Asthma	Bipolar disorders	4 (50,358)	2.12, OR	1.57-2.87	III (NA)	Medium	2.12
Maltreatment in childhood	Depressive disorders in childhood	5 (1,400)	2.03, OR	1.37–3.01	III (NA)	High	2.03
Terrorist act exposure	Depressive disorders	6 (NA)	2.02, OR	1.38-2.96	III (NA)	High	2.02
Diabetes	Depressive disorders in elderhood	9 (1,814)	1.88, OR	1.31-2.70	III (NA)	Medium	1.88
Heart disease	Depressive disorders in elderhood	6 (1,911)	1.81, OR	1.41-2.31	III (NA)	Medium	1.81
Obesity	Bipolar disorders	9 (12,259)	1.77, OR	1.40-2.23	III (NA)	Low	1.77
Hearing impairment	Depressive disorders in elderhood	7 (4,448)	1.71, OR	1.28-2.27	III (NA)	Medium	1.71

Table 2 Evidence for associations between non-purely genetic risk or protective factors and mental disorders *(continued)*

Risk or protective factor	Mental disorder	Number of individual studies (cases)	Strength of association, measure	95% CI	Class of evidence (prospective evidence class)	Quality (AMSTAR)	eOR
Age >65	Depressive disorders in elderhood	6 (15,017)	1.63, OR	1.24-2.16	III (NA)	Low	1.63
Living alone	Depressive disorders in elderhood	16 (10,478)	1.55, OR	1.23-1.95	III (NA)	Low	1.55
Age >85	Depressive disorders in elderhood	12 (4,559)	1.52, OR	1.20-1.93	III (NA)	Low	1.52
Two metabolic risk factors	Depressive disorders	8 (6,691)	1.45, OR	1.17-1.80	III (NA)	Low	1.45
Low birth weight (≤2,500 g)	Depressive disorders	21 (NA)	1.38, OR	1.16-1.65	III (NA)	Low	1.38
Age >75	Depressive disorders in elderhood	19 (11,219)	1.35, OR	1.17-1.56	III (NA)	Low	1.35
Type 2 diabetes mellitus	Depressive disorders	11 (37,964)	1.24, OR	1.09-1.40	III (NA)	Medium	1.24
Unemployment	Depressive disorders	13 (40,679)	1.16, OR	1.09-1.23	III (NA)	Medium	1.16
Fruit intake	Depressive disorders	8 (NA)	0.85, RR	0.77-0.93	III (NA)	Low	0.85
Traditional/healthy dietary patterns	Depressive disorders	17 (NA)	0.76, RR	0.68-0.86	III (NA)	Low	0.76
Iron intake	Depressive disorders	3 (1,045)	0.40, RR	0.24-0.65	III (NA)	Medium	0.40
Neurotic, stress-related and somatoform disorders							
Physical abuse in childhood	Social anxiety disorder	4 (1,191)	2.59, OR	2.17-3.10	I (IV)	High	2.59
Physical disease history	PTSD	4 (2,161)	2.29, OR	2.07-2.52	I (NA)	High	2.29
Family history of psychiatric disorder	PTSD	12 (1,765)	1.80, OR	1.48-2.19	I (NA)	Medium	1.80
Being an Indigenous American	PTSD	5 (3,214)	1.47, OR	1.28-1.69	I (NA)	High	1.47
Cumulative exposure to potentially traumatic experiences	PTSD	17 (3,094)	5.24, OR	3.54-7.76	II (NA)	High	5.24
Trauma severity	PTSD	25 (2,017)	0.66, g	0.44-0.88	II (IV)	Medium	3.32
Being trapped in an earthquake	PTSD	1 (2,028	2.86, OR	2.52-3.25	II (NA)	High	2.86
Female sex	PTSD	112 (9,137)	1.65, OR	1.45-1.87	II (NA)	Medium	1.65
Torture exposure	PTSD	10 (1,357)	4.46, OR	2.39-8.31	III (NA)	Low	4.46
Sexual abuse in childhood	Social anxiety disorder	5 (1,239)	3.18, OR	1.73-5.86	III (IV)	High	3.18
Personal psychiatric history	PTSD	27 (1,753)	2.45, OR	1.67-3.61	III (IV)	Medium	2.45
Overprotection from father	Obsessive-compulsive disorder	6 (716)	0.44, g	0.21-0.68	III (NA)	High	2.24
Behavioural syndromes associated with physiological disturbances and physical factors							
Appearance-related teasing victimization	Any eating disorder	10 (1,341)	2.91, OR	2.05-4.12	II (NA)	Medium	2.91
Sexual abuse in childhood	Bulimia nervosa	26 (1,103)	2.73, OR	1.96-3.79	II (NA)	Medium	2.73
ADHD	Any eating disorder	12 (3,618)	4.24, OR	2.62-6.87	III (NA)	Medium	4.24
Physical abuse in childhood	Binge eating disorder	4 (NA)	3.10, OR	2.48-3.88	III (NA)	Medium	3.10
Sexual abuse in childhood	Binge eating disorder	7 (NA)	2.31, OR	1.66-3.20	III (NA)	Medium	2.31
Self-reported dieting	Bulimia nervosa	7 (NA)	0.22, r	0.14-0.30	III (NA)	Medium	2.26
Body dissatisfaction	Any eating disorder	11 (NA)	0.14, r	0.11-0.17	III (NA)	Medium	1.67
Perceived pressure to be thin	Any eating disorder	4 (NA)	0.11, r	0.08-0.14	III (NA)	Medium	1.51
Negative affect	Any eating disorder	11 (NA)	0.09, r	0.06-0.12	III (NA)	Medium	1.38
5-min Apgar score <7	Anorexia nervosa	33 (2,701)	1.32, OR	1.17-1.49	III (NA)	Medium	1.32

Table 2 Evidence for associations between non-purely genetic risk or protective factors and mental disorders *(continued)*

Risk or protective factor	Mental disorder	Number of individual studies (cases)	Strength of association, measure	95% CI	Class of evidence (prospective evidence class)	Quality (AMSTAR)	eOR
Disorders of adult personality and behaviour							
Emotional abuse in childhood	Borderline personality disorder	27 (3,525)	28.15, OR	17.46-53.68	II (NA)	Medium	28.15
Emotional neglect in childhood	Borderline personality disorder	21 (3,225)	22.86, OR	11.55-45.22	II (NA)	Medium	22.86
Adversities in childhood	Borderline personality disorder	97 (16,098)	14.32, OR	10.80-18.98	II (NA)	Medium	14.32
Physical abuse in childhood	Borderline personality disorder	30 (2,869)	9.30, OR	6.57-13.17	II (NA)	Medium	9.30
Sexual abuse in childhood	Borderline personality disorder	31 (3,748)	7.95, OR	6.21-10.17	II (NA)	Medium	7.95
Physical neglect in childhood	Borderline personality disorder	20 (3,072)	5.73, OR	3.21-10.21	II (NA)	Medium	5.73
Mental retardation							
None of the factors was supported by class I, II or III evidence							
Disorders of psychological development							
Maternal SSRI use during pregnancy*	Autism spectrum disorder	7 (19,670)	1.84, OR	1.60-2.11	I (II)	Medium	1.84
Maternal pre-pregnancy antidepressant use*	Autism spectrum disorder	7 (22,877)	1.48, RR	1.29-1.71	I (NA)	Medium	1.48
Maternal chronic hypertension	Autism spectrum disorder	4 (22,864)	1.48, OR	1.29-1.70	I (NA)	Medium	1.48
Maternal gestational hypertension	Autism spectrum disorder	9 (4,334)	1.37, OR	1.21-1.54	I (NA)	Medium	1.37
Maternal pre-eclampsia	Autism spectrum disorder	10 (10,699)	1.32, RR	1.20-1.45	I (NA)	Medium	1.32
Maternal age ≥35 years	Autism spectrum disorder	11 (>1,000)	1.31, RR	1.18-1.45	I (NA)	Low	1.31
Maternal overweight pre/during pregnancy	Autism spectrum disorder	5 (7,872)	1.28, RR	1.19-1.36	I (II)	Low	1.28
Highest paternal age group vs. reference group	Autism spectrum disorder	20 (2,920)	1.55, OR	1.39-1.73	II (NA)	Medium	1.55
Paternal age >45 years	Autism spectrum disorder	18 (>1,000)	1.43, OR	1.33-1.53	II (III)	High	1.43
Highest maternal age group vs. reference group	Autism spectrum disorder	19 (2,254)	1.42, OR	1.29-1.55	II (IV)	Medium	1.42
Paternal age 40-45 years	Autism spectrum disorder	12 (>1,000)	1.37, OR	1.23-1.53	II (IV)	High	1.37
Maternal autoimmune disease	Autism spectrum disorder	10 (9,775)	1.37, OR	1.21-1.54	II (NA)	Medium	1.37
Higher paternal age (per 10-years increase)	Autism spectrum disorder	17 (47,373)	1.21, OR	1.18-1.24	II (NA)	Medium	1.21
Maternal paracetamol use during pregnancy*	Autism spectrum disorder	5 (>100)	1.20, RR	1.14-1.26	II (NA)	Medium	1.20
Maternal age 30-34	Autism spectrum disorder	8 (>1,000)	1.14, RR	1.09-1.18	II (NA)	Low	1.14
Hearing impairment	Autism spectrum disorder	7 (4,370)	14.16, RR	4.53-44.22	III (NA)	Medium	14.16
5-min Apgar score <7	Autism spectrum disorder	6 (3,676)	1.67, OR	1.34 -2.09	III (NA)	Medium	1.67
Family history of psoriasis	Autism spectrum disorder	8 (>1,000)	1.59, OR	1.28-1.97	III (NA)	Medium	1.59
Family history of rheumatoid arthritis	Autism spectrum disorder	8 (>1,000)	1.51, OR	1.19-1.91	III (NA)	Medium	1.51
Maternal diabetes	Autism spectrum disorder	16 (8,872)	1.49, RR	1.28-1.74	III (NA)	High	1.49
Family history of type 1 diabetes	Autism spectrum disorder	13 (>1,000)	1.49, OR	1.23-1.81	III (NA)	Medium	1.49
Maternal infection requiring hospitalization	Autism spectrum disorder	3 (34,547)	1.30, OR	1.14-1.50	III (NA)	Medium	1.30
Family history of any autoimmune disease	Autism spectrum disorder	17 (1,894)	1.28, OR	1.12-1.48	III (NA)	Medium	1.28
Reference group vs. lowest paternal age group	Autism spectrum disorder	15 (2,295)	1.24, OR	1.12-1.37	III (NA)	Medium	1.24

Table 2 Evidence for associations between non-purely genetic risk or protective factors and mental disorders *(continued)*

Risk or protective factor	Mental disorder	Number of individual studies (cases)	Strength of association, measure	95% CI	Class of evidence (prospective evidence class)	Quality (AMSTAR)	eOR
Higher maternal age (per 10-years increase)	Autism spectrum disorder	14 (46,025)	1.18, OR	1.10-1.26	III (NA)	Medium	1.18
Paternal age 35-40 years	Autism spectrum disorder	16 (>1,000)	1.14, OR	1.08-1.21	III (NA)	High	1.14
Behavioural and emotional disorders with onset usually occurring in childhood and adolescence							
Maternal pre-pregnancy obesity	ADHD	11 (40,880)	1.63, OR	1.49-1.77	I (I)	Low	1.63
Eczema in childhood	ADHD	6 (10,636)	1.31, OR	1.20-1.44	I (IV)	Low	1.31
Maternal hypertensive disorders during pregnancy	ADHD	8 (37,128)	1.29, OR	1.22-1.36	I (NA)	High	1.29
Maternal pre-eclampsia	ADHD	6 (>1,000)	1.28, OR	1.21-1.35	I (NA)	High	1.28
Maternal paracetamol use during pregnancy*	ADHD	8 (>1,000)	1.25, RR	1.17-1.34	I (I)	High	1.25
Maternal smoking during pregnancy	ADHD	20 (50,044)	1.60, OR	1.45-1.76	II (II)	High	1.60
Asthma in childhood	ADHD	11 (32,539)	1.51, OR	1.40-1.63	II (NA)	High	1.51
Maternal overweight pre/during pregnancy	ADHD	9 (23,525)	1.28, OR	1.21-1.35	II (I)	Low	1.28
Preterm birth	ADHD	11 (1,542)	1.84, OR	1.36-2.49	III (NA)	High	1.84
Maternal stress during pregnancy	ADHD	8 (25,547)	1.72, OR	1.27-2.34	III (NA)	High	1.72
Maternal SSRI use during pre-pregnancy period*	ADHD	3 (39,097)	1.59, RR	1.23-2.06	III (NA)	High	1.59
Maternal non-SSRI antidepressants use during pregnancy*	ADHD	6 (23,064)	1.50, RR	1.24-1.82	III (NA)	High	1.50
Maternal SSRI use during pregnancy*	ADHD	5 (56,502)	1.37, RR	1.16-1.63	III (NA)	High	1.37
Child 4 months younger than school classmates	ADHD	30 (>1,000)	1.36, RR	1.25-1.47	III (NA)	High	1.36
Maternal diabetes	ADHD	2 (>1,000)	1.36, HR	1.19-1.55	III (NA)	High	1.36
5-min Apgar score <7	ADHD	7 (37,414)	1.30, OR	1.11-1.52	III (NA)	High	1.30
High frequency of maternal cell phone use during pregnancy	ADHD	5 (6,922)	1.29, OR	1.12-1.48	III (NA)	Low	1.29
Caesarean delivery	ADHD	14 (92,426)	1.17, OR	1.08-1.26	III (NA)	High	1.17
Breech/transverse presentation	ADHD	5 (29,051)	1.14, OR	1.06-1.22	III (NA)	High	1.14

AMSTAR – A Measurement Tool to Assess Systematic Reviews, OR – odds ratio, RR – risk ratio, IRR – incidence rate ratio, HR – hazard ratio, eOR – equivalent OR, NA – not available, ADHD – attention-deficit/hyperactivity disorder, PTSD – post-traumatic stress disorder, NSAID – nonsteroidal anti-inflammatory drug, SSRI – selective serotonin-reuptake inhibitor, * documented or likely confounding by indication

tobacco smoking, being a North African immigrant in Europe, urbanicity, ethnic minority in high ethnic density area, being a first generation immigrant, Toxoplasma gondii IgG, non-right handedness, paternal age >35, and winter/spring season of birth in the Northern hemisphere.

For class I evidence, the prospective analysis of risk factors showed that only clinical high risk state for psychosis remained at the same level of evidence, while Black-Caribbean ethnicity in England was downgraded to class IV evidence, and for obstetric complications the level of evidence was not available. For class II evidence, the prospective analysis of risk factors showed that cannabis use and adversities in childhood remained at the same level of evidence, while ethnic minority in low ethnic density area and being a second generation immigrant were downgraded to class IV evidence. One class II evidence protective factor, premorbid IQ, was also downgraded to class IV evidence. For the remaining class II factors, the level of evidence in prospective studies was not available.

For class III evidence risk factors, the prospective analysis showed that only urbanicity remained at the same level of evidence, while social withdrawal in childhood, being a North African immigrant in Europe, ethnic minority in high ethnic density area, being a first generation immigrant and Toxoplasma gondii IgG were downgraded to class IV evidence. The remaining factors

were either downgraded to the non-significant level or the level of evidence was not available (Table 2).

Mood (affective) disorders

Forty-eight associations with depressive or bipolar disorders were evaluated within this ICD-10 diagnostic block[32,34]. Nine associations were supported by class I evidence (Table 2). Of these, six were risk factors for depressive disorders: widowhood (RR=5.59), sexual dysfunction (OR=2.71), four or five metabolic risk factors (OR=2.06), physical abuse in childhood (OR=1.98), job strain (OR=1.77), and obesity (OR=1.35). One was a risk factor for bipolar disorders: irritable bowel syndrome (OR=2.48). Two were protective factors for depressive disorders: dietary zinc (RR=0.65) and tea intake (RR=0.68).

Sixteen associations were supported by class II evidence (Table 2). These included nine risk factors for depressive disorders: dry eye disease with Sjögren's syndrome (OR=4.25), emotional abuse in childhood (OR=2.78), intimate partner violence against women (RR=2.57), sexual abuse in childhood (OR=2.42), being a Gulf War veteran (OR=2.37), three metabolic risk factors (OR=1.99), psoriasis (OR=1.64), metabolic syndrome (OR=1.42), and sedentary behaviour (RR=1.25). There were five risk factors for depressive disorders in elderhood: poor physical health (OR=4.08), chronic disease (OR=2.59), poor vision (OR=1.94), sleep disturbances (RR=1.92), and low education (OR=1.58). There was one risk factor for depressive disorders in childhood: asthma (OR=2.08). There was one risk factor for bipolar disorders: adversities in childhood (OR=2.86).

Twenty-three associations were supported by class III evidence (Table 2). These included ten risk factors for depressive disorders: neglect in childhood, insomnia, chronic lung disease, dry eye disease without Sjögren's syndrome, vitamin D deficiency, terrorist act exposure, two metabolic risk factors, low birth weight (≤2,500 g), type 2 diabetes mellitus, and unemployment. There was one risk factor for depressive disorders in childhood (maltreatment), and seven risk factors for depressive disorders in elderhood (diabetes, heart disease, hearing impairment, age >65, living alone, age >85, and age >75). There were two risk factors for bipolar disorders: asthma and obesity. There were also three protective factors for depressive disorders: fruit intake, traditional/healthy dietary patterns, and iron intake.

For class I evidence, the prospective analysis showed that six risk factors for depressive disorders – widowhood, sexual dysfunction, four or five metabolic risk factors, physical abuse in childhood, job strain, and obesity – remained at the same level of evidence, while dietary zinc and tea intake, as well as irritable bowel syndrome, which was associated with bipolar disorders, were either downgraded to the non-significant level, or the level of evidence was not available. For class II evidence, the prospective analysis showed that two risk factors for depressive disorders (sexual abuse in childhood, and three metabolic risk factors), and one risk factor for depressive disorders in elderhood (sleep disturbances) remained at the same level of evidence. Two class II risk factors for depressive disorders (emotional abuse in childhood, and metabolic syndrome), and two risk factors for depressive disorders in elderhood (chronic disease and low education) were downgraded to class III or IV evidence. For the remaining class II factors, the level of evidence in prospective studies was not available. For class III evidence, the prospective analysis showed that one risk factor for depressive disorders (vitamin D deficiency) remained at the same level of evidence, while all the other factors were either downgraded to the non-significant level or the level of evidence was not available (Table 2).

Neurotic, stress-related and somatoform disorders

Twelve associations across three mental disorders – social anxiety disorder, obsessive-compulsive disorder, and post-traumatic stress disorders (PTSD) – were evaluated within this ICD-10 diagnostic block[6,36]. Four associations were supported by class I evidence (Table 2). These involved one risk factor for social anxiety disorder, namely physical abuse in childhood (OR=2.59); and three risk factors for PTSD: physical disease history (OR=2.29), family history of psychiatric disorder (OR=1.80), and being an indigenous American (OR=1.47).

Four associations were supported by class II evidence (Table 2). These all involved risk factors for PTSD: cumulative exposure to potentially traumatic experiences (OR=5.24), trauma severity (Hedges' g = 0.66), being trapped in an earthquake (OR=2.86), and female sex (OR=1.65).

Four associations were supported by class III evidence (Table 2), involving two risk factors for PTSD (torture exposure and personal psychiatric history); one risk factor for social anxiety disorder (sexual abuse in childhood); and one risk factor for obsessive-compulsive disorder (overprotection from father).

For class I evidence, the prospective analysis showed that no factor retained its class of evidence. Physical abuse in childhood as a risk factor for social anxiety disorder was downgraded to class IV evidence, while the other factors were downgraded to the non-significant level or were not computable or available. For class II evidence, the prospective analysis showed that trauma severity as a risk factor for PTSD was downgraded to class IV evidence. For class III evidence, the prospective analysis showed that personal psychiatric history as a risk factor for PTSD, and sexual abuse in childhood as a risk factor for social anxiety disorder, were downgraded to class IV evidence. For the remaining class II and III evidence factors, no prospective analysis data were available (Table 2).

Behavioural syndromes associated with physiological disturbances and physical factors

Ten associations with eating disorders (any eating disorder, bulimia nervosa, anorexia nervosa, binge eating disorder) were evaluated within this ICD-10 diagnostic block[40]. None of the associations was supported by class I evidence. Two associations

were supported by class II evidence (Table 2), involving two risk factors: appearance-related teasing victimization (with any eating disorder, OR=2.91) and sexual abuse in childhood (with bulimia nervosa, OR=2.73).

Eight associations were supported by class III evidence (Table 2), involving ADHD, physical and sexual abuse in childhood, self-reported dieting, body dissatisfaction, perceived pressure to be thin, negative affect, and 5-min Apgar score <7.

No prospective analysis data were available for any of the factors (Table 2).

Disorders of adult personality and behaviour

Six associations with borderline personality disorder were evaluated within this ICD-10 diagnostic block[42]. The associations were all supported by class II evidence, involving emotional (OR=28.15), physical (OR=9.30) and sexual (OR=7.95) abuse; emotional (OR=22.86) and physical (OR=5.73) neglect; and adversities in childhood (OR=14.32) (Table 2).

The level of evidence in prospective studies was not available.

Mental retardation

No class I-III risk factor for mental retardation was identified.

Disorders of psychological development

Within this ICD-10 diagnostic block, 26 associations with autism spectrum disorder were evaluated[35]. Seven associations were supported by class I evidence (Table 2). These involved seven risk factors: maternal selective serotonin reuptake inhibitor (SSRI) use during pregnancy (OR=1.84, confounding by indication such as underlying maternal mental disorders), maternal pre-pregnancy antidepressant use (RR=1.48, confounding by indication as above), maternal chronic hypertension (OR=1.48), maternal gestational hypertension (OR=1.37), maternal pre-eclampsia (RR=1.32), maternal age ≥35 years (RR=1.31), and maternal overweight pre/during pregnancy (RR=1.28).

Eight associations were supported by class II evidence (Table 2), all involving risk factors. These were: highest paternal age group vs. reference group (OR=1.55), paternal age >45 years (OR=1.43), highest maternal age group vs. reference group (OR=1.42), paternal age 40-45 years (OR=1.37), maternal autoimmune disease (OR=1.37), higher paternal age per 10-years increase (OR=1.21), maternal paracetamol use during pregnancy (RR=1.20, likely confounding by indication such as maternal comorbidities involving inflammation or infection), and maternal age 30-34 (RR=1.14).

Eleven associations were supported by class III evidence (Table 2), all involving risk factors: hearing impairment, 5-min Apgar score <7, family history of psoriasis, family history of rheumatoid arthritis, maternal diabetes, family history of type 1 diabetes, maternal infection requiring hospitalization, family history of any autoimmune disease, reference group vs. lowest paternal age group, higher maternal age per 10-years increase, and paternal age 35-40 years.

For class I evidence, the prospective analysis showed that none of the risk factors remained at the same level. Maternal SSRI use during pregnancy (confounding by indication) and maternal overweight pre/during pregnancy were downgraded to class II evidence, while all other class I factors were downgraded to non-significant levels or prospective evidence was not available. For class II evidence, the prospective analysis showed that none of the factors retained the same level of evidence. Paternal age >45 years, highest maternal age group vs. reference group, and paternal age 40-45 years were downgraded to class III or IV evidence. For the remaining class II evidence factors and all class III evidence factors, no prospective analysis data were available (Table 2).

Behavioural and emotional disorders with onset usually occurring in childhood and adolescence

Nineteen associations with ADHD were evaluated within this ICD-10 diagnostic block[37]. Five associations were supported by class I evidence (Table 2), all including risk factors: maternal pre-pregnancy obesity (OR=1.63), eczema in childhood (OR=1.31), maternal hypertensive disorders during pregnancy (OR=1.29), maternal pre-eclampsia (OR=1.28), and maternal paracetamol use during pregnancy (OR=1.25, likely confounding by indication).

Three associations were supported by class II evidence (Table 2), involving three risk factors: maternal smoking during pregnancy (OR=1.60), asthma in childhood (OR=1.51), and maternal overweight pre/during pregnancy (OR=1.28).

Eleven associations, all involving risk factors, were supported by class III evidence (Table 2). They were: preterm birth, maternal stress during pregnancy, maternal SSRI use during pre-pregnancy period, maternal non-SSRI antidepressant use during pregnancy, maternal SSRI use during pregnancy (confounding by indication for all antidepressant exposures), child 4 months younger than school classmates, maternal diabetes, 5-min Apgar score <7, high frequency of maternal cell phone use during pregnancy, caesarean delivery, and breech/transverse presentation.

For class I evidence, the prospective analysis showed that maternal obesity pre-pregnancy and maternal paracetamol use during pregnancy (likely confounding by indication) remained at the same level of evidence, while eczema in childhood was downgraded to class IV evidence, and there were no prospective data for the remaining factors. For class II evidence, the prospective analysis showed that maternal smoking during pregnancy remained at the same level of evidence, while maternal overweight pre/during pregnancy was upgraded to class I level factor (there were no more small-study effects). For the remaining class II and all class III evidence factors, no prospective analysis data were available (Table 2).

Quality assessment

Based on the AMSTAR evaluation, 58 associations (32.9%) met the high-quality level, 86 (48.9%) were of medium quality, and 32 (18.2%) were of low quality (Table 2).

Evidence for transdiagnostic risk/protective factors

Eighteen risk factors had a consistent definition across umbrella reviews and were associated with different mental disorders, enabling us to pool them and test their transdiagnosticity against TRANSD criteria (Table 3).

Sexual abuse in childhood met TRANSD transdiagnostic criteria across at least five mental disorders: borderline personality disorder[42], bulimia nervosa[40], binge eating disorder[40], depressive disorders[34], and social anxiety disorder[36] (class II evidence; OR=3.92).

Physical abuse in childhood met TRANSD transdiagnostic criteria across at least four mental disorders: depressive disorders[34], social anxiety disorder[36], borderline personality disorder[42], and binge eating disorder[40] (class II evidence; OR=4.82).

Adversities in childhood were associated with at least three mental disorders: borderline personality disorder[42], bipolar disorders[32], and schizophrenia spectrum disorders[33] (class II evidence; OR=13.83). However, bipolar disorders did not meet the criterion T of the TRANSD framework, because the ICD/DSM gold standard was not acknowledged[32].

Five-min Apgar score <7 met TRANSD transdiagnostic criteria across three mental disorders: autism spectrum disorder[35], anorexia nervosa[40], and ADHD[37] (class III evidence; OR=1.27).

Type 2 diabetes mellitus was associated with Alzheimer's disease[27], vascular dementia[27], and depressive disorders[34] (class II evidence; OR=1.53); and obesity was associated with depressive disorders[34], bipolar disorders[32], and any dementia[27] (class II evidence; OR=1.58). However, they did not meet the TRANSD criterion T[27,32,34].

Asthma was associated with depressive disorders in childhood[34], bipolar disorders[32], and ADHD[37] (class II evidence; OR=1.79). However, bipolar disorders did not met the criterion T of the TRANSD framework[32]. Several other risk factors were associated with at least two mental disorders, as shown in Table 3.

When the transdiagnostic class of evidence was restricted to prospective analyses, 5-min Apgar score <7 remained in class III, while type 2 diabetes mellitus was downgraded from class II to class III. Prospective data were not available for the remaining transdiagnostic factors associated with at least three mental disorders.

Evidence for factors having both risk and protective associations with various mental disorders

No factors were found to have both risk and protective associations with various mental disorders. There were only reciprocal operationalizations of the same factor showing risk-increasing or protective effects (e.g., high physical activity vs. sedentary behaviour, or parental alcohol supply vs. parental stricter alcohol rules).

DISCUSSION

This is the largest available systematic evidence-based risk atlas of mental disorders. Its main strength is the rigorous assessment of the credibility of the evidence, which is essential to overcome several types of biases in aetiopathological research. Furthermore, we have adopted a lifespan approach spanning from the pre/perinatal period to childhood, adulthood and elderhood.

A first overarching finding is that 176 associations between risk/protective factors and mental disorders met the criteria for class I-III evidence. These associations reflected large-scale observational studies conducted worldwide, thus representing consolidated risk signatures for mental disorders and countering replication crisis[43] and scientific pessimism in psychiatry.

At the same time, it is essential to acknowledge that association is not necessarily causation. In particular, reverse causation can confound aetiopathological research[44]. Accordingly, assessing temporality between exposures and outcome is one of the core Bradford Hill criteria that may be considered when navigating the difficult question of causation vs. plain association[45,46]. This potential bias was controlled in sensitivity analyses. Some factors were additionally excluded because of survival biases (i.e., history of cancer[27]). Others were excluded because of confounding by indication, as documented in previous umbrella reviews and meta-analyses[21,47] (i.e., maternal SSRI use before and during pregnancy[35,37], maternal antidepressant use before pregnancy[35], maternal non-SSRI antidepressant use during pregnancy[37]) or acknowledged as likely (benzodiazepine use[27], maternal paracetamol use during pregnancy[35,37]). We found that 26 associations, relating to 20 risk factors and one protective factor, retained convincing or highly suggestive credibility of evidence (i.e., class I or II) in prospective analyses. The provision of such robust knowledge is essential to allow a more detailed characterization of mental disorders which overcomes the current diagnostic limitations[48-50], and a prerequisite for evidence-based preventive and early intervention approaches[51,52], because most of the identified risk factors are, at least theoretically, modifiable.

Specifically, we have found that type 2 diabetes mellitus, depression and low frequency of social contacts are consistently associated with dementia. These exposures should be systematically screened in the elderly and could be considered part of refined management strategies in the early phases of dementia. At the same time, our finding of the protective role of high-intensity exercise is consistent with meta-analytic evidence that this exercise improves some outcomes of dementia, such as motor performance and daily functioning[53].

Beyond dementia, impaired physical health emerged as an overarching core cluster, with three or four-five metabolic risk

Table 3 Evidence for transdiagnostic risk factors

Factor	Mental disorders	Transdiagnostic class of evidence (prospective evidence class)	Transdiagnostic odds ratio (95% CI)	Number of individual studies (cases)	TRANSD criteria met or not
Sexual abuse in childhood	Borderline personality disorder	II (NA)	3.92 (3.33-4.61)	83 (>10,676)	Yes
	Bulimia nervosa				
	Binge eating disorder				
	Depressive disorders				
	Social anxiety disorder				
Physical abuse in childhood	Depressive disorders	II (NA)	4.82 (3.92-5.91)	48 (>7,946)	Yes
	Social anxiety disorder				
	Borderline personality disorder				
	Binge eating disorder				
Adversities in childhood	Borderline personality disorder	II (NA)	13.83 (10.49-18.23)	144 (24,982)	Yes (for two disorders only)
	Bipolar disorders				
	Schizophrenia spectrum disorders				
5-min Apgar score <7	Autism spectrum disorder	III (III)	1.27 (1.11-1.46)	46 (43,791)	Yes
	Anorexia nervosa				
	ADHD				
Type 2 diabetes mellitus	Alzheimer's disease	II (III)	1.53 (1.39-1.69)	46 (42,897)	No
	Vascular dementia				
	Depressive disorders				
Obesity	Depressive disorders	II (NA)	1.58 (1.40- 1.79)	22 (21,846)	No
	Bipolar disorders				
	Any dementia				
Asthma	Depressive disorders in childhood	II (NA)	1.79 (1.62- 1.97)	22 (85,725)	Yes (for two disorders only)
	Bipolar disorders				
	ADHD				
Low education	Depressive disorders in elderhood	II (NA)	1.68 (1.46-1.93)	40 (19,359)	No
	Alzheimer's disease				
ADHD	Any eating disorder	III (NA)	3.58 (2.50-5.14)	16 (>3,618)	Yes
	Tobacco related disorder				
Tobacco smoking	Opioid use disorder	II (II)	2.61 (2.04-3.33)	27 (>2,447)	No
	Schizophrenia spectrum disorders				
Emotional abuse in childhood	Borderline personality disorder	II (NA)	15.22 (10.02-23.10)	35 (7,637)	Yes
	Depressive disorders				
Hearing impairment	Autism spectrum disorder	III (NA)	4.98 (2.17- 11.45)	14 (8,818)	No
	Depressive disorders in elderhood				
Maternal pre-eclampsia	Autism spectrum disorder	I (II)	1.29 (1.22-1.36)	16 (>11,699)	Yes
	ADHD				
Maternal paracetamol use during pregnancy*	Autism spectrum disorder	II (II)	1.23 (1.17-1.28)	13 (>2,000)	Yes
	ADHD				
Maternal SSRI use during pregnancy*	Autism spectrum disorder	I (II)	1.62 (1.44- 1.82)	12 (76,112)	Yes
	ADHD				

Table 3 Evidence for transdiagnostic risk factors *(continued)*

Factor	Mental disorders	Transdiagnostic class of evidence (prospective evidence class)	Transdiagnostic odds ratio (95% CI)	Number of individual studies (cases)	TRANSD criteria met or not
Maternal overweight pre/during pregnancy	Autism spectrum disorder	I (I)	1.26 (1.22- 1.30)	14 (31,397)	No
	ADHD				
Maternal diabetes	Autism spectrum disorder	III (III)	1.44 (1.27-1.65)	18 (>9,872)	No
	ADHD				
Surviving childhood cancer	Tobacco related disorder	III (NA)	0.61 (0.50-0.75)	9 (3,412)	No
	Alcohol related disorder				

ADHD – attention-deficit/hyperactivity disorder, SSRI – selective serotonin-reuptake inhibitor, NA – not available, * documented or likely confounding by indication

factors and obesity being associated with depressive disorders; maternal overweight before/during pregnancy with autism spectrum disorder; and maternal overweight or obesity before/during pregnancy with ADHD. These findings reflect the close interplay between environmental factors and early brain development, as well as the close interconnection of mental and physical domains[54]. The latter has the potential to offset the numerator of efforts and costs for preventive and early intervention by a denominator of multiple mental and physical disease endpoints. Physical activity is recommended[55] for improving outcomes across several mental disorders, including substance related disorders[56], and is also indicated to protect physical health of people with mental disorders[57]. The emerging field of lifestyle psychiatry recommends physical activity together with other "lifestyle factors", even beyond clinical populations, as a universal tool for public health strategies[58].

A related risk domain points to the potential impact of reducing tobacco smoking[41] or maternal smoking during pregnancy[37] in order to prevent opioid use disorder and ADHD, respectively; similarly, reducing cannabis use[33] emerges as an accessible mainstream approach to prevent psychosis[59]. Effective public health (e.g., community pharmacy-delivered interventions[60]), psychoeducation[61] and pharmacological interventions (e.g., varenicline[62-64]) are available to reduce tobacco smoking, but no interventions have yet been consolidated to reduce maternal smoking[65] or cannabis use[66,67].

A further cluster includes risk factors related to environmental stressors, with childhood adversities being associated with psychosis, and widowhood, childhood physical or sexual abuse, and job strain with depressive disorders. Early traumatic experiences have been suggested to be associated with a pro-inflammatory state in adulthood, with specific inflammatory profiles depending on the type of trauma[68]. Unfortunately, the current evidence is insufficient to recommend specific interventions to prevent early traumatic experiences[69]. Future research should prioritize population-level actions on social determinants of mental health (demographic, economic, neighbourhood, environmental events, social and cultural domains) to replace negative cycles of poverty, abuse, violence, environmental degradation and high personal stress with virtuous cycles of mental health, well-being, and sustainable development[52,70].

Another important finding is that the strongest level I risk factor surviving prospective analyses was the clinical high risk state for psychosis[15,71], with an eOR of about 9. However, this state may be better conceptualized as a risk marker, because it represents the result of different interacting risk factors[72,73] that accumulate during the recruitment phase[74] of these individuals. The clinical high risk state for psychosis is also the prototypical example of antecedent conditions[75], for which the boundaries with the onset of the disorder itself may become blurred[76-79].

According to methodological guidelines, ORs greater than 4.72 are to be considered large (assuming a prevalence rate of mental disorders in the non-exposed ranging from 1% to 5%)[80]. The vast majority of identified class I-III factors (independently of prospective sensitivity analyses) had only a small to medium effect size, with a few exceptions mostly relating to childhood trauma. This finding indicates that future aetiopathological studies need to move away from univariable analyses to rather augment polygenic risk prediction by multivariable measurements of environmental exposures in the same individuals.

In fact, mental disorders exhibit both equifinality (multiple factors can lead to the same disorder) and multifinality (the same aetiological factor can result in different mental disorders). For example, recent genome-wide association, copy number variant and exome sequencing studies have detected shared genetic risk loci among schizophrenia, bipolar disorder and autism, indicating a broad genetic vulnerability to mental disorders (i.e., genetic pleiotropy)[81,82]. On the other hand, recent transdiagnostic approaches in psychiatry have explored multifinality of environmental exposures. However, to date, transdiagnostic approaches have been limited by several methodological caveats, mostly involving reporting inaccuracies[83].

Our approach of combining robust classification of evidence with the TRANSD recommendations[30] has addressed these biases to deliver robust transdiagnostic evidence inasmuch as data were available. As shown in Table 3, we failed to identify a universal transdiagnostic factor that could account for most mental disorders (such as the "p" factor marker for general psychopa-

thology[83]). This finding is supported by the lack of convincing evidence supporting the existence of a truly transdiagnostic biomarker[84]. However, it is important to acknowledge that transdiagnostic aetiopathological research is still an emerging field and that only a few observational studies have conducted multivariable measurements that both lump (transdiagnostic) and split (specific) risk/protective factors across diagnostic dimensions[85]. The factors identified in Table 3 could represent the starting set of exposures to be tested across different mental disorders or intermediate phenotypes (e.g., those proposed by the Research Domain Criteria[86]).

Notably, about one-third of any class I-II factors listed in Table 2 and the vast majority of transdiagnostic factors listed in Table 3 impact the early neurodevelopment. This finding confirms that the maximal window of opportunity for discovering and therapeutically addressing transdiagnostic risk or protective factors is during the very early phases of neurodevelopment, where the chances of impacting the course of multiple disorders are the highest. Conceptually, these results corroborate the essential neurodevelopmental nature of many mental disorders and suggest that pre/perinatal psychiatry should become a mainstream focus of future applied clinical research and prevention psychiatry.

Genetic factors can be measured *en masse* with high precision, building on variation in specific single nucleotides in exact positions in the genome, and thus are unambiguously defined at all ages for all individuals and across all studies. In contrast, massive measurements of multiple environmental (or epigenetic) factors are challenging.

First, environmental factors pose logistic barriers, because their assessment may be particularly time consuming and lead to missing data. Recent developments in digital technologies (e.g., electronic medical records, mobile apps)[87,88] and sequential testing frameworks[89], as well as the recent availability of poly-environmental risk scores (e.g., psychosis poly-risk score[87,90] or exposome[91]), may make it possible to record multiple exposures in the same individuals in a deep phenotyping approach and over time.

Second, the distinction between clear-cut genetic and environmental factors in several circumstances may be spurious. For example, family history of mental disorders and socioeconomic status comprise both a genetic and an environmental component[90], genetic disposition for ADHD increases the risk of exposure to adverse environments[92], and polygenic risk scores for psychosis impact certain behavioural traits and risk exposures[93]. Epigenetic factors at the crossroads between genes and the environment[94] add another level of complexity. A pragmatic approach could be to define environmental factors as non-purely genetic factors, in line with the current study.

Third, while some risk factors are clearly operationalized (e.g., 5-min Apgar score <7 and low birth weight ≤2,500 g), numerous others (e.g., stressful events, childhood adversities) are not. Specifically, some of them are imprecisely defined, assessed through different instruments, or include contextual specifiers. For example, stressful events can be ascertained through multiple psychometric instruments, generally falling into two categories: checklists (e.g., the Life Events Checklist) and semi-structured interviews (e.g., the Life Events and Difficulties Schedule)[95]. While pooling these different instruments is legitimate within meta-analytical approaches, their empirical interchangeability for future use in research or clinical settings remains questionable. Similarly, while we found that advanced paternal age has been associated with autism, some associations have defined this factor by comparing the highest paternal age group vs. a reference group[96]. Interestingly, the authors themselves acknowledged that, as the reference groups were heterogeneous, it was "impossible to define a specific age range as the reference group"[96]. Because an unclear reference group is used for this factor, it is not truly measurable.

The associated caveat is that using loose operationalizations of factors will inevitably inflate their non-specificity of association across mental disorders, and therefore lead to an observed artificial transdiagnosticity across different dimensions. For example, psychotic experiences[97] measured through self-administered questionnaires[98] are relatively frequent at the population level (prevalence about 8% in young adults[99]) but poorly predictive of psychosis onset (risk of psychosis: 0.5-1% per year[99]). These manifestations cannot be conflated with the clinical high risk state for psychosis, which requires detection by an experienced and trained clinician[100], is not common in the general population (only 0.3% of individuals[101]), and is highly predictive of psychosis onset (risk of psychosis: 20% at 2 years[71,102]). The trivialization of the contextual significance of complex phenomena and their operationalization may result in non-specificity, triggering illusions of continuity and transdiagnostic phenomena[103].

In a similar vein, other factors may require temporal (e.g., childhood, midlife, elderhood) or contextual specifiers (e.g., Black-Caribbean ethnicity in England or indigenous Americans), since their validity may depend on their timing of action or different cultural scenarios. We also found that some factors may be influenced by changes in the contextual environment (e.g., cumulative exposure to potentially traumatic experiences), which may impact their durability over time. A further important methodological limitation is that there are several spurious risk markers (beyond the clinical high risk state for psychosis). For example, some experiences included among "childhood adversities", such as bullying, may be a marker of early vulnerability in social contexts[104].

The lack of standardized assessment measures to reliably record environmental exposures may prevent their usability in research and clinical settings. Accordingly, a significant advancement of knowledge would likely be reached by a global collaborative harmonization effort to standardize the multimodal (e.g., psychopathological, neurobiological, neurocognitive) measurement of these exposures, as well as a specific support from funders to achieve these goals. The set of exposures provided in Table 2 may represent the starting point for emerging international efforts promoted by research funders, such as the Common Measures in Mental Health Science Governance Board[105], which aims to drive the adoption of harmonized data collection instruments that are transferable to a variety of locations and ar-

eas of mental health research, considering aspects of diversity, inclusivity, cultural and geographical appropriateness.

The main limitation of the current study is that, because confounding (e.g., by indication, as highlighted above[21,47]) cannot be ruled out in findings of observational studies, it is not possible to establish causation from the associations. More robust epidemiological methods are needed to control for confounders and better identify causal risk factors for major mental disorders that would enhance the precision and generalizability of the current evidence[106]. Nevertheless, our findings represent an important agenda for experimental research that can do this, including intervention trials for treatments and prevention. Second, the observed risk factors have been mostly measured in univariable analyses that cannot control for their intercorrelation. Third, gene-by-environment correlations and interactions have been inadequately reported. Fourth, we could only identify a small number of protective factors (only 9% of the 176 analyzed factors), likely because current research has been disease-centred, with resilience factors and good mental health outcomes being investigated only more recently[107,108].

Finally, the umbrella review approach favours the selection of more commonly and readily studied factors, which are more likely to be meta-analyzed. However, although some emerging risk or protective factors may not have a corresponding eligible meta-analysis to be included in an umbrella review, this possibility is unlikely, since meta-analyses are now being performed frequently. In any case, for most of these emerging factors, the current grade of evidence is unlikely to be remarkable, given the limited data. Furthermore, the primary aim of the current study was to provide an evidence-based classification of the existing knowledge, as opposed to appraising emerging factors that may be consolidated by future research. The rapid progress in aetiopathological meta-research in this field will nevertheless require periodic updates of knowledge via umbrella reviews, which could leverage the methodological framework validated in the current study.

In conclusion, the evidence-based atlas of key risk and protective factors identified in the current study equips clinicians and researchers with a solid benchmark for advancing aetiopathological research and for expanding early intervention and preventive strategies for mental disorders.

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DOI:10.1002/wps.20894

Victimization in people with severe mental health problems: the need to improve research quality, risk stratification and preventive measures

Research over the last few decades has reported high rates of victimization in people with severe mental health problems[1], and this is increasingly viewed as a key adverse outcome to prevent. Consequences can arise directly: more commonly, worsening of psychiatric conditions through the effects of trauma, but also physical health morbidities and even death. Indirect consequences may be disruptions to care, breakdowns in social support and networks, and the harmful use of drugs and alcohol to manage the physical and psychological effects of victimization.

However, despite the importance of the issue, research designs have had until now significant limitations. Many studies have used cross-sectional designs, asking people with vs. without psychiatric conditions to report on their victimization histories. This approach can be informative, but is likely to overestimate the association with psychiatric conditions, as people who are unwell are more likely to attribute their current problems to external causes. More importantly, these studies cannot deal with reverse causality – that the victimization has led to severe mental health problems rather than the reverse. This information remains useful to estimate needs, but not in terms of understanding causal links, which is necessary for prevention.

These designs are particularly problematic when rates of victimization are compared with other adverse outcomes, such as violence perpetration, as thresholds and time scales for these outcomes may be different. The commonly repeated statement that psychiatric patients are ten times more likely to be victims of crime than the general population, and that this rate is higher than the perpetration rate, is based on research with these suboptimal designs.

More informative are cohort studies, which can account for the timing of victimization and mental health conditions. Birth cohorts in the UK[2] and New Zealand[3] have reported that the following factors increase victimization risk: male gender, self-reported financial difficulties (but not other more objective markers of socioeconomic status), and comorbid alcohol and cannabis dependence. Confounds can be accounted for, but only those that are measured, and measured accurately. Residual confounding is, therefore, a threat to the validity of these studies.

One way of addressing such residual confounds is to use genetically informed controls, such as siblings. With biological full-sibling controls, half the co-segregating genes and much of the early environment are accounted for, which most observational studies do not capture. Siblings with and without mental health conditions can be followed up for victimization outcomes and, after adjusting for age and using same-sex sibling controls, studies can rule out several alternative hypotheses and provide stronger evidence for the associations to be consistent with a causal inference.

One such study using Swedish registers examined more than 250,000 patients diagnosed with psychiatric disorders and compared them with nearly 195,000 of their full siblings without psychiatric disorders[4]. Those with psychiatric diagnoses were found to be about three times as likely as their siblings to be violently victimized, and there was a four-fold increase in perpetration of violence in psychiatric patients.

Another genetically informative cohort is the E-Risk twin study, which found that measures of victimization up to age 18 were at least moderately heritable (>30%) and correlated with other heritable traits, including lower self-control and cognitive abilities, childhood conduct disorder, substance misuse, and family history of mental illness and antisocial behaviours[5]. These findings underline the importance of accounting for unmeasured genetic confounding in studies of victimization risk.

In the above-mentioned Swedish study[4], the risk of victimization was increased three-fold in siblings with bipolar disorder and doubled in those with depression compared to siblings without mental health problems. Unexpectedly, the risk was not increased in siblings with schizophrenia-spectrum disorders compared to their unaffected siblings, which may be explained by the fact that people with such disorders are more socially isolated, with less opportunities to be victimized than others.

Another national investigation that used a novel design, in which individuals acted as their own controls ("within individual"), found that violent victimization was the strongest trigger for violent perpetration in psychotic disorders[6]. Consideration, therefore, should be given to providing psychosocial support for at least one week following any victimization, to minimize the risk of a cycle of violence.

What do these findings mean for psychiatrists, other mental health professionals, and services? First, there is a considerable overlap between violence perpetration and victimization. Any improvements are likely to lead to reductions across these outcomes, and may also reduce suicide and premature mortality. Second, research design is critically important in this area, since small study effects have been magnified by poor measurement in previous work. Third, prevention will require two components: better risk stratification and effective interventions.

Risk stratification is required to determine who can benefit from additional interventions aimed at prevention, which will likely be resource intensive and complex. Criticisms of risk assessment rarely consider real world implications: psychiatric services need to stratify in order to allocate resources effectively, transparently and consistently, and cannot provide gold standard interventions to all people with mental health problems.

Most clinicians are unable to weigh up more than a few risk factors simultaneously, and very unlikely to make sense of their interactions. Once you reach more than five or so risk factors, assessment will benefit from simple algorithms to support, rather than replace, clinical decision-making. Simple scalable online

tools with high negative predictive values can usefully screen out low-risk persons to preserve resources[7].

But evidence-based risk assessment will only improve outcomes if linked to interventions, and effective ones. A key uncertainty is whether treating symptoms of mental illness will prevent victimization outcomes. There is some evidence suggesting that depressive symptoms may be predictive of victimization[8], but this work needs replication.

Research on specific interventions aiming to reduce victimization risk in persons with mental disorders remains rare, because victimization has traditionally been viewed as a risk factor rather than a consequence of mental illness. One significant change would be to consider including victimization as an outcome in mental health treatment trials, particularly those that follow up people beyond a few weeks. Improving access to treatment for comorbid substance misuse is an important policy consideration, as research has clearly demonstrated that this comorbidity explains a large share of the elevated victimization risk in persons with mental illness[4].

More contact with friends and family members may act as a protective factor against victimization risk, and supporting measures to promote this can be enhanced across all mental health services. However, it is important to make sure that such interactions do not actually lead to increased exposure to criminogenic environments[9]. Finally, large-scale clinical and genetically informed studies, preferably linked with registry data and electronic health records, may clarify specific etiological mechanisms involved, leading to trials of interventions targeting these mechanisms.

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DOI:10.1002/wps.20908

Malpractice claims in psychiatry: approaches to reducing risk

Medical malpractice claims offer patients who have experienced harm as the result of negligence by physicians, hospitals and other health care providers the opportunity to obtain financial compensation. Negligence in malpractice cases is defined as the failure to conform to an accepted standard of care, i.e., in one common formulation, to fail to behave as a reasonable physician would in a similar circumstance[1].

In the US and many other countries, allegations of malpractice are litigated in civil courts, with patient-plaintiffs carrying the burden of proving that their caregivers acted in a negligent fashion. Recent years have seen growing interest in identifying alternatives to this expensive, stress-inducing, and time-consuming process, with New Zealand's no-fault compensation system for medical errors offering a very different model of compensating patients for harms they experience[2].

Although just over 7% of physicians in the US have a malpractice claim filed against them every year, this ranges from nearly 20% in high-risk specialties (e.g., neurosurgery, thoracic-cardiovascular surgery) to approximately 2.6% in psychiatry[3]. Even though psychiatrists are among the medical specialists in the US least likely to be sued, like other physicians they have experienced a substantial increase in malpractice claims in recent years[3].

A small proportion of physicians have recurrent claims, with 1% of physicians accounting for one-third of paid malpractice claims. The risk of recurrent claims is lower among psychiatrists[4]. Psychiatrists, like other physicians, are generally required by state law to carry a minimum amount of malpractice insurance, which covers the cost of defending a claim and, if necessary, of compensating an injured patient.

Data about the bases for malpractice claims in psychiatry are not compiled systematically, but most successful claims appear to involve physical injury resulting from patients' behavior (e.g., suicidal or assaultive behavior that results in harm to the patient or to a third party) or the actions or inactions of the psychiatrist that result in physical harm (e.g., failure to monitor medication side effects leading to persistent organ-system damage). Claims based on alleged negligence in psychotherapy are much more difficult to prove and, unless they involve boundary violations by the psychiatrist – such as sexual activity with the patient – are unlikely to be successful.

Malpractice costs in the US, including the costs of settlements, judgments, legal defense, and defensive medical practices aimed at reducing the risk of malpractice claims, have been estimated at over $55.6 billion dollars annually[5]. Although this cost accounts for only a small fraction of health care spending, it is significantly higher than in other countries. Physicians win the majority of the roughly 10% of cases that proceed to trial[4]. However, since a trial is not without cost, and given the risk of losing even a strong case, malpractice insurers often choose to settle claims prior to trial, reasoning that the cost of a modest settlement may be less than the financial costs of defending the case. The cost of malpractice cases and the associated burden of defensive medical practices have led to a number of efforts to reduce the frequency of claims.

State legislators in the US have pursued a variety of approaches to reducing malpractice claims, including eliminating punitive damages, reducing the period after an injury during which

claims can be brought ("statutes of limitations"), and capping the fees that attorneys can receive from such cases. The most effective laws set limits on non-economic damages that injured patients can recover, e.g., compensation for pain and suffering[6]. The variable impact of these changes in the law have stimulated medical associations and health systems to experiment with approaches outside the legal system that might reduce liability risk.

Medical associations, such as the American Psychiatric Association, have produced practice guidelines, in part as a means of reducing clinicians' liability exposure. Practice guidelines attempt to define the parameters within which appropriate clinical care may take place, based on evidence in the relevant medical literature. They are often written so as to provide flexibility to clinicians, typically noting a variety of acceptable approaches to any clinical situation. Conformance to a generally accepted practice guideline will generally constitute a defense to malpractice claims by offering proof that the defendant-physician has complied with a professional standard of care. On the other hand, failure to comply with a practice guideline does not necessarily prove negligence; the physician can challenge the guidelines themselves or otherwise attempt to demonstrate that his/her behavior fell within the parameters of reasonable physician choice. As with many attempts to reduce malpractice claims, it has been difficult to demonstrate that practice guidelines have been effective for this purpose, even when systematic efforts have been made to encourage their use[7].

A second innovative effort to reduce malpractice claims is exemplified by the approach adopted by the University of Michigan Health System[8]. When medical errors result in harm to a patient, the system encourages prompt apology by the physicians involved and an offer of payment that is usually well below what might be awarded by a court. Evaluation of the program demonstrated that it led to a reduction in the number of lawsuits, lower liability costs, and shorter time to resolution of cases. Its success may be based, at least in part, on many injured patients' desire for an explanation of what went wrong and an apology for mistakes that were made. However, apology laws may have paradoxical effects. One recent study found that they increased the risk of malpractice suits being filed against physicians who do not perform surgery, while having no effect on surgeons' liability risk[9]. The effect may derive from patients' greater knowledge that an error was made, which increases motivation to seek compensation.

Given the uncertain effectiveness of legal and systemic efforts to reduce the likelihood that a physician will be subject to a claim of malpractice, the best preventive measures may rest in the hands of individual clinicians. That psychiatrists are among the least frequently sued physicians is probably due, at least in part, to the deeper and more empathic relationships they tend to have with patients. Patients who believe that their psychiatrists truly care about their well-being are less likely to sue, even if something goes wrong. In addition to maintaining a caring doctor-patient relationship, other pillars of prevention include seeking consultation when facing a challenging clinical situation and documenting the rationale for treatment decisions in the patient's record, including explanations of potential management options that were not selected[1]. As a general matter, doing what is best for the patient remains the surest path to reduce risk of malpractice claims.

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DOI:10.1002/wps.20907

The critical distinction between suicidal ideation and suicide attempts

Suicide remains a leading cause of death worldwide[1]. A key reason for limited progress is inadequate understanding about the transition from suicidal ideation to suicide attempts. This knowledge is important because the majority of instances of suicidal ideation do not lead to suicide attempts. A World Health Organization study found that approximately two-thirds of individuals with suicidal ideation never make a suicide attempt[2], and a population-based study found that only 7% of individuals with suicidal ideation attempted suicide during the subsequent two years[3].

Unfortunately, little is known about when or for whom ideation leads to attempts. For example, psychiatric disorders that predict suicidal ideation only weakly or negligibly predict progression from ideation to attempts[2]. Similarly, in meta-analytic data, variables such as depression and hopelessness are strong correlates of suicidal ideation, but are weakly or negligibly associated with attempts among ideators[4]. Currently, not even a single strong predictor of suicide attempts among ideators has been identified.

To advance suicide knowledge and prevention we must better understand the transition from suicidal ideation to suicide attempts. A response to this need may be provided by the ideation-to-action framework, which suggests that the development of suicidal ideation and the transition from suicide ideation to attempts are distinct processes with distinct predictors and explanations[5]. This framework has implications for suicide research, risk assessment, intervention, and theory.

Regarding research, the framework underscores the need for

studies to identify variables that help predict and explain transition from ideation to attempts. Many studies on suicide attempts examine differences between attempters and non-attempters; however, because all (or virtually all) attempters have suicidal ideation, this common research design confounds attempts and ideation, making it impossible to tell what the differences are attributable to. Studies seeking to identify predictors of suicide attempts must in some way control for suicidal ideation; one option is to conduct analyses that test what predicts suicide attempts among those with ideation.

The framework also has implications for risk assessment and prevention. One implication is that suicide risk factors should not comprise a single list, but be organized according to whether they raise risk for suicidal ideation, suicide attempts among ideators, or both. For example, research to date suggests that depression primarily is a risk factor for suicidal ideation, access to lethal means is a risk factor for suicide attempts among those with ideation, and nonsuicidal self-injury increases risk for both. The framework has similar implications for intervention. Specifically, any intervention for suicide risk should be clear about which aspects are meant to reduce suicidal ideation and which are meant to stop transition from ideation to attempts.

The ideation-to-action framework also applies to suicide theory. Historically, different theories of suicide emphasized different factors, such as social isolation, psychological pain, and hopelessness; these theories have been extremely beneficial for guiding research and providing a foundation that informs contemporary theories. At the same time, traditional theories share a common limitation: they tend to treat suicidality as a single phenomenon in need of a single explanation[1,6]. As a result, these theories did not provide separate explanations for suicidal ideation and suicide attempts.

In this context, the Interpersonal Theory of Suicide (IPTS)[7] represents an important theoretical advance. The IPTS provides separate explanations for the development of suicidal ideation and the progression from suicidal ideation to suicide attempts. Specifically, the IPTS suggests that suicidal desire is caused by thwarted belongingness and perceived burdensomeness, whereas progression from suicidal desire to suicide attempts occurs when one has acquired the capability to make a suicide attempt. Thus, the IPTS may be viewed as the first of a new generation of suicide theories that positioned themselves within an ideation-to-action framework[6].

The most recent ideation-to-action theory is the Three-Step Theory of Suicide (3ST)[8]. In brief, the 3ST suggests that: a) suicidal ideation is caused by the combination of unbearable pain (usually psychological) and hopelessness, b) suicidal ideation is strong when one's pain exceeds or overwhelms one's connectedness (to valued people, communities, or sources of purpose and meaning), and c) transition from strong suicidal ideation to potentially lethal suicide attempts is facilitated by dispositional, acquired and practical contributors to capability for suicide. Thus, the 3ST is a concise theory that explains suicide in terms of just four variables: pain, hopelessness, connectedness, and suicide capability.

A growing body of research – including studies on correlates of suicidal ideation and suicide attempts, predictors of suicidal ideation and suicide attempts, motivations for suicide, warning signs for suicide and suicide attempts, and means safety interventions – support the validity of the 3ST[8]. As a result, the 3ST has been incorporated into suicide education and prevention programs, including continuing education courses, campus-based suicide prevention programs, and self-help suicide prevention materials[8].

An advantage of the 3ST is that it provides a context for understanding the impacts of diverse biopsychosocial risk factors and interventions. Specifically, anything that impacts pain, hopelessness, connection, and/or suicide capability would be expected to impact suicide risk. For example, if an antidepressant were to reduce suicide risk, we might hypothesize that this occurs by reducing depression, and thus psychological pain. We might further hypothesize that an improvement in depression may increase one's sense of hope for the future, and/or enhance one's ability to engage with valued connections. Similarly, the 3ST can be applied to understand elevated risk in various populations. For example, increased suicide risk in transgender individuals is likely due to increased pain, hopelessness, and disconnection caused by widespread prejudice and discrimination, whereas elevated suicide risk in certain medical professionals may be best explained by elevated suicide capability (i.e., knowledge and access to lethal means). Thus, the 3ST can improve understanding of suicide risk across a variety of clinical, social and scientific contexts.

Despite recent theoretical advances, it remains critical for the field to continue to clarify the conditions under which ideation results in attempts. Perhaps the most promising variable to date explaining this progression is suicide capability. As noted above, this construct was first introduced in the IPTS[7] and subsequently elaborated by the 3ST[8]. In short, because suicide involves the potential for pain, injury and death, and because people are biologically (and arguably evolutionarily) disposed to fear and avoid pain, injury and death, making a suicide attempt requires the capability to overcome these barriers.

Different definitions and measures of suicide capability have been proposed, and much of the evidence is mixed. Perhaps the most robust finding is that risk of attempts among ideators is higher when practical capability is higher (practical capability refers to knowledge of, access to, and expertise with lethal means). This conclusion is supported not only by recent studies demonstrating a relationship of practical capability to suicide attempts[8], but also by a long history of research showing impacts of access to lethal means and means safety interventions on suicide rates [9].

Moving forward, it is imperative that research better illuminate when and for whom suicidal ideation leads to suicide attempts. This effort requires use of multiple measurements within longitudinal designs so that the ebb and flow of variables that contribute to suicidal ideation and attempts can be captured precisely and accurately. Understanding the phenomena of suicidal ideation and suicide attempts through the ideation-to-action lens will accelerate the development and refinement of essential suicide research, theory and clinical care.

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DOI:10.1002/wps.20909

Thinking too much: rumination and psychopathology

Patients suffering from mental health problems often complain about thinking too much. Their mind is frequently focused on negative thoughts about their symptoms, problems, or negative experiences.

Traditionally, researchers and clinicians have either regarded this type of rumination as an epiphenomenon or consequence of suffering from mental health problems, or – as in the case of cognitive therapy – have mostly been interested in the *content* of these thoughts. However, there is increasing evidence suggesting that rumination, defined as a *process* of repetitive negative thinking, is a causal mechanism involved in the development and maintenance of psychopathology[1].

The vast majority of research on rumination has been conducted in the context of depression. In her seminal response styles theory, S. Nolen-Hoeksema introduced rumination as a way of responding to depressed mood that is characterized by repetitively and passively focusing on the symptoms of depression, and their possible causes and consequences[2]. The tendency to engage in a ruminative response style appears to be a reasonably stable trait, and can be assessed with the Response Styles Questionnaire (RSQ)[2].

There is now extensive longitudinal research showing that rumination assessed in this way: a) predicts the onset of new episodes of depression; b) predicts the maintenance of already existing depressive symptoms; c) is a mediator between other known risk factors (e.g., negative cognitive styles, childhood adversity, psychosocial stress) and depression, and d) is related to reduced response to treatment[1-4].

Converging evidence comes from experimental research showing that induced rumination leads to negative thinking, poor problem solving, inhibition of instrumental behavior, biased information processing, and impaired interpersonal functioning[1,2,4].

Importantly, however, rumination is not only related to depression, but is involved in the development and/or maintenance of a broad range of disorders, including post-traumatic stress disorder (PTSD), anxiety disorders, insomnia, eating disorders, somatic symptom disorder, and substance use disorders[2,3].

It has been argued that repetitive negative thinking (RNT) is a transdiagnostic process, and that rumination can be subsumed under this overarching concept[3,5]. For example, our group has defined RNT as a style of thinking about one's problems (current, past or future) or negative experiences (past or anticipated) that is: a) repetitive, b) intrusive, c) difficult to disengage from, d) perceived as unproductive, and e) capturing mental capacity[6].

Importantly, RNT is characterized by its process features, not its content. Specifically, the transdiagnostic perspective states that RNT shares the same process across different disorders, but is applied to disorder-specific and/or idiosyncratic topics. Thus, phenomena that have traditionally been studied from a disorder-specific perspective (e.g., depressive rumination, excessive worry in generalized anxiety disorder, trauma-related rumination in PTSD, or post-event processing in social anxiety) are now regarded as different expressions of the same underlying construct.

Supporting evidence for this conceptualization comes from research showing that the common aspects of RNT (i.e., the transdiagnostic process) are more predictive of depression and anxiety disorders than unique features of disorder-specific worry or rumination[7]. Different questionnaire measures to assess the transdiagnostic properties of RNT have been developed, including the Perseverative Thinking Questionnaire (PTQ)[6].

Thus, current evidence is in line with the idea that RNT in general (as well as rumination as a specific subfacet) can be regarded as an important process, involved in the development and maintenance of psychopathology across different diagnostic categories.

Why do some individuals then frequently engage in RNT despite the proven negative consequences? A number of different theoretical perspectives have been put forward to explain this puzzling phenomenon[1,5]. An important basic tenet of many models is the assumption that RNT is essentially a normal process that usually serves the adaptive function to alert us to a current goal discrepancy and motivate us to engage in action to reduce this discrepancy. However, excessive RNT observed in the context of psychopathology has apparently lost this function.

According to Wells[8], excessive RNT is maintained by a combination of positive metacognitive beliefs (e.g., "RNT helps me to better cope with problems"), negative metacognitive beliefs (e.g., "RNT is dangerous") as well as dysfunctional control strategies (e.g., thought suppression) triggered by negative metacognitions. In addition, there is evidence that RNT in the context of psychopathology often serves the function to avoid both unpleasant experiences (e.g., negative emotions, arousal, aversive imagery or memories) as well as action, leading to negative reinforcement. Moreover, RNT can become a mental habit that can be triggered independent of goal pursuit simply by contextual cues.

From an information processing perspective, RNT can be regarded as the consequence of cognitive biases leading to the frequent involuntary activation of representations with negative content. In addition, deficits in cognitive control then lead to a lack

of top-down control of these representations, resulting in attention remaining allocated to negative content in the form of RNT.

In his influential theoretical model, Watkins highlights that adaptive and maladaptive forms of RNT can additionally be distinguished by their processing mode[1,4]. There is now extensive evidence showing that dysfunctional RNT is characterized by an *abstract* processing mode (focus on general and decontextualized mental representations), whereas a more *concrete* processing mode (focus on the direct, specific and contextualized experience of concrete events and actions) is related to functional outcomes.

The important transdiagnostic role of RNT makes this process a promising target for prevention and treatment. Based on the theoretical models described, researchers have developed a number of interventions focused on modifying RNT, including mindfulness-based treatments, metacognitive interventions, cognitive control training, and rumination-focused cognitive-behavioral therapy[4]. In addition, there is promising evidence showing that targeting RNT in a high-risk group of adolescents has strong preventive effects by significantly reducing the incidence of depression[9].

In sum, whereas RNT had originally mainly been studied from a disorder-specific perspective, with a strong focus on the content of thinking (e.g., rumination in depression, worry in generalized anxiety disorder), there is now an emerging consensus that it is best studied from a transdiagnostic perspective focused on the characteristic process.

An important future direction for research into RNT includes clarifying links to current meta-models of transdiagnostic processes and mechanisms, such as the Research Domain Criteria framework. In addition, although there is promising evidence for the efficacy of interventions directly targeting RNT, more systematic research is needed to compare these novel interventions to traditional evidence-based treatments, and investigate the proposed mechanisms of change.

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DOI:10.1002/wps.20910

Lack of robust meta-analytic evidence to favour cognitive behavioural therapy for prevention of psychosis

While achievements in detection and prognostic assessment of young people at clinical high risk for psychosis (CHR-P) have been recently consolidated, the efficacy of preventive interventions remains unclear[1].

Cognitive behavioural therapy (CBT) is the currently recommended preventive intervention, but the most updated network meta-analysis[2] found no robust evidence to favour it (and any of the other indicated interventions) compared to the control condition (i.e., needs-based interventions). A subsequent independent pairwise meta-analysis by the Cochrane group[3] confirmed these findings, concluding that there was "no convincing unbiased, high-quality evidence" that any type of intervention is more effective than needs-based interventions (another pairwise meta-analysis was subsequently published[4], but used older data). A further umbrella review showed no evidence that CBT impacts other clinical outcomes such as acceptability of treatments, severity of attenuated positive/negative psychotic symptoms, depression, symptom-related distress, social functioning, general functioning, and quality of life[5]. These studies highlighted that uncertainty of evidence is high and that caution is required in recommending CBT for the prevention of psychosis in CHR-P individuals.

In contrast with these cautionary warnings, a recent pairwise meta-analysis[6] concluded that "robust and sound evidence supports cognitive behavioural therapy in reducing transition" to psychosis and in decreasing the severity of attenuated psychotic symptoms.

First, no new large-scale randomized controlled trials of CBT have been published since the previous network/Cochrane meta-analyses[2,3], which could justify different conclusions. Only a small, single-site trial (N=58) of CBT has been published meanwhile[7]. This trial has several weaknesses relating to the measurement of outcomes, incorrect interpretation of Kaplan-Meier outputs, selective reporting, and failure to adhere to CONSORT guidance (e.g., failure to report trial registration)[8]. Using the Clinical Trials Assessment Measure, the recent meta-analysis[6] assigned to this CBT trial the highest methodological quality (97/100) of all randomized controlled trials ever conducted in CHR-P individuals. It is difficult to understand how a trial that was never registered, with inaccuracies in psychometric classification and basic mistakes in statistical reporting rates so highly, casting doubts on the validity of the quality assessment conducted in the meta-analysis[6].

Second, while the protocol of this recent meta-analysis[6] stated that unpublished literature was considered for inclusion, the authors did exclude the large CBT PREVENT trial (N=216), although its preliminary findings – showing no statistical significant effect of CBT in preventing psychosis – were presented at a major international conference and included in the previous network meta-analysis[3]. The fact that a large CBT trial has been excluded means that the findings of the new meta-analysis[6] may be affected by publication bias.

Indeed, the authors of the meta-analysis acknowledged that only one missing trial would be needed to render their end-of-treatment results non-significant[6]. To empirically test this, we have updated that meta-analysis by removing the low-quality small trial[7] and adding the large PREVENT trial. The updated risk ratio for CBT vs. control interventions to prevent transition to psychosis at 12 months was 0.631 (95% CI: 0.388-1.028, p=0.064), which shows no significant meta-analytic evidence that CBT can robustly prevent transition to psychosis.

Third, the authors' conclusion that CBT can robustly improve attenuated psychotic symptoms conflicts with the very small effect size, approaching the non-significance level (standardized mean difference = –0.15; 95% CI: –0.28 to –0.01)[6], which is unlikely to be associated with clinically meaningful benefits in the real-world.

Finally, the meta-analysis in question may be affected by reporting biases, which increased the likelihood of the results being significant in favour of CBT. For example, additional transitions to psychosis beyond those originally reported were included as "the most accurate data on transition rates"[6]. These data have never been acknowledged as primary outcomes in the original publications, and operationalization of primary outcomes is not clearly specified *a priori* in the corresponding meta-analytic protocol.

Based on the considerations above, we conclude that the lack of robust meta-analytic evidence to favour CBT to prevent psychosis, as appraised by the most recent network meta-analysis[2] and the Cochrane meta-analysis[3], still stands. These meta-analyses, which emphasized methodological biases and the inconsistency of the current evidence, may have caused disappointment and frustration and the production of some over-optimistic literature favouring CBT.

It has been claimed that unfavourable meta-analytic evidence needs to be contextualized, because preventive benefits are a key message for patients, families and practitioners[9]. However, while the goal of preventing psychosis is certainly noble, transparent appraisal of limitations of knowledge is a prerequisite for any reliable scientific advancements. We believe that the lack of robust meta-analytic evidence to favour CBT should stimulate, rather than discourage, collegial efforts for developing novel preventive interventions for CHR-P subjects.

Several large-scale international studies of experimental therapeutics (e.g., cannabidiol), combined with strategies to control risk enrichment, innovative youth mental health services, adaptive trial designs, and stratification and precision medicine approaches, are underway[5]. It is hoped that these global initiatives will soon deliver the much-needed effective interventions to prevent psychosis in CHR-P individuals.

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DOI:10.1002/wps.20896

Selective outcome reporting and the effectiveness of psychotherapies for depression

Only 40% of trials of psychotherapies for depression published between 2015 and 2018 were prospectively registered, and discrepancies between publications and protocols were noted for 76% of registered trials[1]. It is often assumed that such divergences are the result of intentionally favoring statistically significant findings ("selective reporting"). However, discrepancies could be due to other reasons, such as justified protocol amendments, logistic difficulties or carelessness.

A survey of trials published in high-impact clinical psychology journals over four years[2] identified 27 prospectively registered trials, of which only 13 with a clearly specified primary outcome measure and time of assessment. Among these 13 trials, four contained protocol deviations favoring significant findings (for two others this was impossible to adjudicate). However, it is difficult to reliably estimate the prevalence and impact of selective reporting from investigations of such small cohorts of trials. Therefore, we examined differences in effectiveness associated with selective reporting across a complete cohort of prospectively registered trials of psychotherapies for depression.

We conducted a pre-registered survey (PROSPERO: CRD42019136130) of all randomized trials comparing psychological interventions to control conditions for adult depression which started enrollment after July 1, 2005, when journal registration mandates became widespread[3]. We selected trials from a regularly updated meta-analysis of psychotherapies for depression (https://osf.io/825c6/), using the most recent update (January 1, 2020). We identified matching registrations from the publication, key word searches in public registries, or, failing these, by contact with investigators.

Registration was considered prospective if it occurred within one month of enrollment start. For prospectively registered trials with a pre-specified outcome measure and assessment time point, we examined changes in primary depression outcomes between registries and publications. Potential discrepancies included[4]: a) omission of registered primary outcome (non-reporting); b) addition of new, not registered, primary outcome; c) downgrading of registered primary outcome to secondary; d) upgrading of secondary registered outcome to primary; e) assessment time point changes; f) analysis method changes. Selective reporting was adjudicated for a) or b), and, for other discrepancies, on the basis of the judgement of two independent researchers.

Effect sizes were computed as standardized mean differences (SMDs) between intervention and control for primary depression outcomes at post-treatment or the time point specified as primary, using data from publications. For event data (e.g., response, remission), we computed odds ratios and converted them into SMDs[5]. We pooled effect sizes separately for trials with and without selective reporting, using robust variance estimation with weights from a random effects model, small sample adjustment and an assumed correlation between all pairs of observed effects sizes of 0.8[6]. Analyses were run in Stata/SE 16.1.

We found that, out of 353 randomized controlled trials in the cohort, 185 commenced enrollment after July 2005. Of these, 142 (77%, 95% CI: 70%-83%) were registered. Seventy-five trials (40%, 95% CI: 33%-48%) were registered prospectively, 11 of which (15%, 95% CI: 8%-25%) without specifying outcome measures or assessment time points. Fifty-one trials (68%, 95% CI: 56%-78%) were rated as free from selective reporting. Discrepancies between registries and reports were identified for 19/75 (25%, 95% CI: 16%-37%) trials, of which 13 (17%, 95% CI: 10%-28%) were judged as involving selective reporting. For six trials with an omitted registered primary outcome, we queried primary investigators and received four replies, all explaining that the outcome measure had been dropped out before starting data collection.

The summary effect size was –0.81 (95% CI: –1.25 to –0.38, tau^2= 0.22) for trials with selective reporting, and –0.54 (95% CI: –0.65 to –0.43, tau^2=0.10) for trials without. When analyses were limited to outcomes registered as primary, the effect size in trials with selective reporting was slightly reduced to –0.75 (95% CI: –1.21 to –0.29). Conversely, excluding the six trials that omitted a registered primary outcome led to a considerably reduced effect size for trials with selective reporting (SMD=–0.51, 95% CI: –0.83 to –0.19), closely resembling that of trials without selective reporting. Similarly, excluding the four trials with an added non-registered primary outcome led to a reduced estimate (SMD=–0.62, 95% CI: –1.00 to –0.24) in trials with selective reporting. Finally, analyses restricted to self-report and unblinded measures showed a substantially increased effect size for trials with selective reporting (SMD=–1.02, 95% CI: –1.66 to –0.38), but minimal changes in the effect size for trials without selective reporting (SMD=–0.57, 95% CI: –0.69 to –0.44).

Our findings confirm prior smaller and more circumscribed surveys[1,2], by showing that, even after many journals condition-

ed submission on prior registration, prospective registration is implemented in only 40% of trials of psychotherapies for depression. Among prospectively registered trials, 25% displayed discrepancies between registration and publications, and for 17% we judged these discrepancies as favoring statistical significance. Though relatively few, trials with selective reporting were associated with considerably larger effectiveness, when combined in a meta-analysis. Effect sizes diverged by a SMD of 0.27 between trials with and without selective reporting. For reference, selective publication of trials of psychotherapies for depression has been associated with differences in effectiveness of 0.32[7]. Trials with non-reporting of registered outcomes or addition of non-registered ones emerged as the main drivers of effect size inflation.

These data suggest that lack of prior registration and discrepancies between registration and publications remain common in trials of psychotherapies for depression, and are associated with an inflation of effect sizes in those trials, contributing to the current uncertainties in assessing the outcomes of psychological interventions[8,9].

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Supplementary information on the study is available at https://doi.org/10.17605/OSF.IO/NBYW8.

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DOI:10.1002/wps.20900

Estimating the reproducibility of psychotherapy effects in mood and anxiety disorders: the possible utility of multicenter trials

Estimating the reproducibility of psychotherapy effects is essential. This is particularly crucial for trials with large effects, as the inclusion of false-positive trials can lead to erroneous conclusions about treatment efficacy in research syntheses[1].

Multicenter studies allow researchers to estimate the reproducibility of effects directly across centers under comparable study conditions (e.g., comparable enrollment procedures, inclusion/exclusion criteria, assessment plans). In an important sense, implementation of trials at various centers is close to a direct replication of findings. Accordingly, recent standards recognize the benefit of describing individual center effects in multicenter studies[2].

We aimed to review what we know about center effects in multicenter trials with psychotherapy components for the treatment of mood and anxiety disorders. We examined the extent to which such multicenter trials: a) reported the variability of treatment outcomes for individual centers (i.e., random center effects) and/or b) provided an estimate of the strengths of treatment by center interactions (i.e., fixed center effects)[3].

To obtain a representative sample of recent multicenter studies, we conducted on July 18, 2020 a systematic search of studies indexed between 2010 and 2020 in Medline, PsycINFO and Educational Resources Information Center (ERIC). We used the key words "multicenter or multi-center" combined with "psychotherapy or therapy or counseling" and "depression or anxiety" and publication type "clinical trial" and "adult population". We identified 184 papers, of which 30 referred to treatment outcomes in a multicenter randomized clinical trial (overall 6,638 patients, range 22-1025). Descriptive characteristics of the 30 identified multicenter studies can be obtained from the authors upon request.

In all 30 reports, "multicenter" was mentioned in the title or abstract and in the Methods section. The number of centers ranged from 2 to 30, but in four reports this number was not reported. The majority of the trials investigated treatment efficacy (e.g., changes in symptoms) and four studies investigated economic outcomes (e.g., cost-effectiveness analyses). In 20 studies, at least one significant treatment effect was reported (max. Cohen's d ranged from 0.23 to 3.44).

Only one (3%) out of the 30 studies[4] considered sites a random factor, thereby permitting conclusions about variability in outcomes due to sites in general. Only three (10%) studies[5-7] reported an estimate of the treatment by center interactions. Furthermore, seven studies reported that center effects were "not significant", without further specification of the effect. Among the seven studies with large significant treatment contrasts (max. Cohen's d >0.80), only one[4] reported a statistical estimate of a center effect.

One of the strengths of multicenter studies is the opportunity to estimate the reproducibility of effects. The results of our systematic review indicate that, although studies state clearly that they involve multiple sites and often indicate that this adds to the importance of the trial, they typically do not use the full potential of this design to estimate center effects (either random or fixed), thereby obscuring evidence about reproducibility of effects.

To properly assess the degree to which results are reproducible, we recommend that the authors of multicenter studies report the outcomes for all centers and estimate center effects (i.e., differences in effects amongst centers)[8].

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Further information on the multicenter studies included in the systematic review can be obtained from the authors (christoph.flueckiger@uzh.ch).

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DOI:10.1002/wps.20901

New resources for understanding patients' values in the context of shared clinical decision-making

The importance of shared decision-making between clinician and patient as the basis of personalized care is increasingly widely recognized. In the UK, for example, a recent Supreme Court decision, developed in part from precedents in international human rights law, made shared decision-making the basis of consent to treatment[1], and there have since been corresponding updates in regulatory guidance.

Shared decision-making, so understood, means clinician and patient coming through dialogue to a shared understanding of the relevant evidence (of the risks and benefits of the evidence-based interventions available) and how this connects with the patient's values (i.e., what matters or is important to the individual patient concerned). Both the evidence side and the values side of this model of shared decision-making present particular challenges for psychiatry[2]. The result, as a recent paper published in this journal pointed out[3], is a gap between principle and practice: the principle of shared decision-making is widely endorsed by psychiatrists, but in practice decisions continue to be largely clinician-led.

It is here – in bridging the gap between principle and practice – that new resources from values-based practice have a role to play. It is widely assumed that it is the evidence side of shared decision-making that is the more problematic (and, certainly, it may be). But, in many contexts, the values side – understanding what matters or is important to the patient in question – may be at least equally problematic[4]. This is why values-based practice has from the start aimed to provide training and other resources to support improved understanding of values[5]. Recent developments in values-based practice have extended these resources in two respects, from individual to cultural values, and from overt to hidden values. Both are relevant to the challenges of shared decision-making in psychiatry.

That understanding cultural values is increasingly important in psychiatry needs hardly be said. The expansion of transcultural psychiatry in recent years is a direct response to the growing impact of factors such as globalization, multiculturalism and migration. Illustrative of the resources from transcultural psychiatry for shared decision-making is the "cultural formulation", introduced first in DSM-IV and upgraded in DSM-5 with an explicit focus on personalized care.

Among new resources from values-based practice for understanding cultural values is a recently published open access collection of some fifty case studies and commentaries illustrating the diversity of mental health policy and practice from around the world[6]. Like the cultural formulation, this collection is comprehensive in scope, covering not only different geographical regions (Western as well as non-Western) but also psychiatry's different stakeholder groups (e.g., it includes a number of autobiographical accounts by service users). The collection complements and extends the resources of the cultural formulation in two key respects: in its focus on values (implicit in, but not highlighted by, the cultural formulation), and in a shift of focus from negative to positive. The latter shift is of particular relevance for recovery in psychiatry: as the paper cited above reminds us[3], recovery in psychiatry depends critically on an individual's protective factors and resilience.

A similar shift from negative to positive is evident in new resources from values-based practice for meeting the challenges presented by hidden values. Like cultural values, hidden values are not, as such, new to psychiatry. Much of psychoanalytic practice after all involves making unconscious (hence hidden) wishes, values and beliefs accessible to consciousness. Contemporary values-based practice offers a range of new resources for accessing hidden (including unconscious) values. Phenomenology, for example, the foundation of traditional descriptive psychopathology, has been applied to the challenge of understanding hidden values in anorexia nervosa[7], and in alcohol and addictive disorders[8]. Other resources for understanding hidden values are available from hermeneutics, from aesthetics and related areas of the humanities, from analytic moral philosophy, from the history of ideas, and from models used in cognitive sciences. As with cultural values, each of these, consistently with the approach of values-based practice as a whole, encompasses not only the negatives of a patient's needs and difficulties, but also the positives of his/her protective factors and resilience as assets for recovery.

There is, of course, more that is required to bridge the gap between principle and practice in shared decision-making than just understanding patients' values (important as this is). Other relevant areas of values-based practice currently being developed include a number of policy and service development initiatives: for example, a guidance for employers on the needs of people who hear voices (https://valuesbasedpractice.org/more-about-vbp); a shared learning initiative on race equality in mental health (https://valuesbasedpractice.org/what-do-we-do/webinars); and a recently funded co-produced national programme exploring new models of public mental health (https://valuesbasedpractice.org/what-do-we-do/webinars).

A further key area of development of values-based practice

is training. Again, training has from the start been foundational to values-based practice. Among new training initiatives is an international web-based masters-level programme in Phenomenology and Values-based Clinical Care (PVbCC). Jointly sponsored by the Collaborating Centre for Values-based Practice in Oxford and the Santa Casa de São Paulo School of Medical Sciences in Brazil, with international partners (including the WPA Section on Philosophy and Humanities), the programme offers a series of master classes delivered by experts from different parts of the world (see https://metamastersonline.com). Participating students will thereby gain an additional international level of experience over and above their respective national home study programmes. As such, the PVbCC programme will help to build what, many years ago, and anticipating contemporary developments, a former President of the Royal College of Psychiatrists, J. Birley[9], called an international "open society" of mental health stakeholders underpinning best practice in personalized mental health care.

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DOI:10.1002/wps.20902

Use of DSM-5 diagnoses vs. other clinical information by US academic-affiliated psychiatrists in assessing and treating psychotic disorders

The DSM is based on extensive observations of patients, with suggestions on categories going back over 100 years. The originators commented that the models were not entirely adequate and needed further modifications[1]. Current models, too, have been called "a first approximation" needing additional features to achieve better utility and validity[2]. Specific issues identified as needing improvement include reliability, validity, completeness and utility[3,4].

While standard clinical practice does employ DSM diagnoses in making treatment decisions, it often emphasizes additional information from patient assessment. That is, physicians often use a broad problem solving rather than a diagnosis specific approach[5].

Explicitly targeting utility and completeness, we asked a sample of clinicians, by an online RedCap survey, how they use DSM diagnoses in the context of other clinical information in assessing and treating psychotic disorders (i.e, schizophrenia spectrum and bipolar and major depressive disorder with psychotic features). Psychiatrists surveyed were at 27 academic centers in the US, as they are the greatest users of DSM and are most engaged in ongoing consideration of how to choose and use DSM criteria. Answers were anonymous and physicians did not receive any compensation for completing the survey. The study was approved and classified as exempt by the Partners Healthcare institutional review board.

Respondents ranked the importance in their practice of nine clinical assessment considerations (DSM-5 diagnosis, specific presenting signs and symptoms, severity of signs and symptoms, history of signs and symptoms, comorbidities, treatment history, social assessment, family history, and medication history), rated for each of four clinical decision and intervention domains (prognosis, recommended level of care, recommended medications, and recommended psychosocial therapies), using a five-choice Likert-type scale ranging from not important (assigned a value of 1) to extremely important (assigned a value of 5).

Of 566 psychiatrists who were invited to participate in the survey, 129 (22.8%) responded. They represented both sexes, and many ages, regions, sites and types of practice. Results indicated that all of the nine assessment considerations were considered at least moderately important for at least one clinical purpose. Primary hypothesis testing found highly significant evidence of a greater mean rating for current signs and symptoms than other clinical assessment considerations (X^2=667, p<0.001). Using a secondary intersection-union approach, we found strong evidence that psychiatrists rate current signs and symptoms as more important than every other assessment consideration included in the survey (mean importance rating=4.46, t=5.86, p<0.001). DSM-5 diagnosis had the lowest observed mean importance rating (mean=2.77).

Post-hoc t-tests found evidence that the mean for DSM-5 diagnosis was significantly lower than the mean for every other assessment consideration (mean>3.58, $t_{121\text{-}123}$<–9.65, p<0.001) except family history (mean=2.84, t_{123}=–0.77, p=0.44). Post-hoc tests using linear regression found no association of the difference in mean importance ratings between current signs and symptoms and DSM-5 diagnosis with age (t_{122}=–0.43, p=0.67); sex (t_{120}=1.04, p=0.30); US region ($X_{(4)}^2$=1.21, p=0.88); site (categorized as hospital only, hospital and other, private practice only, and clinic only, $X_{(3)}^2$=2.37, p=0.50); and number of patients seen ($X_{(4)}^2$=0.97, p=0.91).

We did not sample all possible elements that clinicians use in

assessments, but had an open question where psychiatrists could note factors not surveyed. Factors suggested included: previous diagnoses, age, cognitive function, risk or history of suicide or violence, forensic history, legal status, cultural background, social networks, work history, family involvement, insight, acceptance of illness and treatment, preferences among treatments, rapport between doctor and patient, and financial resources.

While our survey was being completed, a worldwide screen of expert opinion from mental health clinicians, assessing the value of ICD-11, which is similar to DSM in its categorical approach and content, was published[6]. This global survey addressed all the categories in the ICD and DSM, exploring the relative use of ICD/DSM for administrative purposes, managing treatment, communicating with other treaters, and teaching. Our survey targeted only US psychiatrists, focused on psychotic disorders, and obtained relative rankings of the use of DSM diagnoses versus other clinical findings in choosing and guiding treatment. Thus, the two studies were partially overlapping. Consistent with our project, the authors of the global survey concluded that the ICD and DSM categories are most useful for administrative and billing purposes and for communicating with other clinicians. They are least used and substantially less useful for choosing individual treatments or advising on prognosis.

Our results suggest that, among patients with psychotic disorders, the DSM-5 diagnosis is less important than identifying other individual features of illness, especially type and severity of symptoms, but also comorbidities and some aspects of personal history. Relevant factors noted by other investigators include suicidality, recreational drug use, obstetric complications, early or recent adverse events, social cognition and neurocognition[5]. The use of these factors allows more flexibility in description than categories alone. Course can be included as well.

Notable for interpreting the responses, we only contacted clinicians at well-known academic centers. The majority (70.5%) of respondents had hospital-based practices, but this might be expected for those who treat many patients with psychotic disorders. The results represent opinions of clinicians who teach and perform research, in addition to their clinical practices. Most psychiatrists did not respond. Nonetheless, the response rate (22.8%) was typical of online surveys[7]. Possibly, those who did respond were interested in the subject and might have thought about the matters raised. We are not suggesting that responders were representative of US psychiatrists, but it might be noted that the suggestions, made a century ago, on which ICD and DSM are based, were also from clinical observations, largely from clinicians in select sites. They were not made or since have been confirmed on the basis of other validators[1].

Lastly, an argument has been made that changes in DSM and ICD should strive to improve utility and accuracy[8]. Accuracy in choosing treatments and predicting outcome might be enhanced by incorporating factors that clinicians cite as most important into formal diagnostic systems. That these factors are already in use for making clinical decisions shows that they are practical and suggests that they may be valid. An improved system might incorporate both categorical entities and additional features, such as those provided by recognizing individual symptoms and severity of those symptoms, in new models[9]. Such models can be tried and tested, then implemented if they show advantages compared to existing systems.

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D. Öngür receives support from US National Institutes of Health/National Institute of Mental Health (grant no. K24MH104449). Further information on the study is available at https://www.mcleanhospital.org/figures-tables.

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DOI:10.1002/wps.20903

Anorexia nervosa and the long-term risk of mortality in women

Anorexia nervosa affects up to 3% of young women and has the highest mortality rate of any psychiatric disorder[1,2], with approximately 5% of patients dying within four years of the diagnosis[1]. Severe weight loss and malnutrition can cause widespread damage to organs that may persist over time, even if anorexia nervosa is ultimately well-managed[1,2]. However, the factors involved in the high mortality associated with anorexia nervosa remain unclear[3].

Among a longitudinal cohort of 1,298,890 women from the Maintenance and Use of Data for the Study of Hospital Clientele registry[4] in the province of Quebec, Canada, we identified women admitted to hospital for anorexia nervosa between 1989 and 2016. A comparison group of women of similar age who presented for either delivery or pregnancy termination and were representative of the large majority of women in Quebec was also identified. We measured anorexia nervosa as a binary variable (yes, no), and included a categorical variable for the total number of anorexia admissions (0, 1, 2, ≥3 admissions) to capture disease severity.

We followed the women over time to identify in-hospital deaths up to March 31, 2018. We categorized the cause of death as anorexia nervosa, suicide, cardiovascular, pulmonary (including pneumonia), cancer, liver and other digestive disease, infectious (other than pneumonia), kidney, nervous system, diabetes and other endocrine disease, shock and organ failure, obstetric, other, or unknown causes.

We used Cox regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for each cause of death, adjusted for baseline age, pre-existing morbidity (depression, anxiety,

and alcohol, tobacco or other substance use at or before cohort entry), socioeconomic deprivation, rurality, and the time period of index hospitalization. We included quadratic time interaction terms to determine associations by year of follow-up.

There were 5,169 women with anorexia nervosa in the cohort, including 227 who died during follow-up. Mortality was higher for women with anorexia than no anorexia (3.24 vs. 0.38 per 1,000 person-years). In adjusted models, anorexia was associated with 2.47 times the risk of death compared with no anorexia (95% CI: 2.01-3.04). Women with three or more anorexia admissions had 4.05 times the risk of death over time (95% CI: 2.85-5.75). Anorexia nervosa was associated with 9.01 times the risk of death at 5 years (95% CI: 7.28-11.16), 7.18 times the risk at 10 years (95% CI: 6.07-8.51), and 2.90 times the risk at 20 years (95% CI: 2.16-3.89), but was not significantly associated with mortality at 25 years of follow-up (HR=1.47, 95% CI: 0.88-2.45).

Anorexia nervosa was associated with death from suicide (HR=4.90, 95% CI: 1.93-12.46), pulmonary disease (HR=3.49, 95% CI: 1.77-6.89), diabetes and other endocrine disease (HR=7.58, 95% CI: 1.89-30.42), liver and other digestive disease (HR=3.27, 95% CI: 1.33-8.06), and shock and organ failure (HR=3.59, 95% CI: 1.23-10.49). Among pulmonary causes, anorexia was most strongly associated with death due to pneumonia (HR=8.19, 95% CI: 2.78-24.14). The cause of death was specified as anorexia nervosa for five patients (2.2%). There was no long-term association with death from cardiovascular or other causes.

Risk of death was particularly elevated for diabetes and pneumonia, disorders that may be underappreciated conditions associated with anorexia nervosa. While it is plausible that severe calorie restriction has effects on pancreatic and lung function, it is also known that women with type 1 diabetes are at greater risk of developing eating disorders[5]. Diabetic women with anorexia nervosa sometimes manipulate their insulin injections to control weight, increasing the risk of hyperglycemic episodes, diabetic ketoacidosis, and life-threatening complications such as diabetic coma[5]. Women with anorexia nervosa may be at risk of pneumonia due to food aspiration. The elevated risk of pneumonia mortality may also be due to a reduced immune response to bacterial infections, leading to delayed diagnosis or treatment and more severe pulmonary infections[6,7].

Suicide was also a leading cause of death. Anorexia nervosa frequently clusters with depression, anxiety, and personality disorders, as well as substance use[2]. Alcohol use in particular is associated with a high risk of suicide attempt in patients with anorexia nervosa[8,9]. However, some data suggest that mortality rates are elevated even in women with anorexia nervosa who do not have psychiatric comorbidities[9]. In the present study, anorexia nervosa was associated with greater mortality even after adjusting for depression and anxiety, suggesting that at least some of the pathways linking anorexia nervosa with mortality are independent of comorbid mental disorders.

In contrast to the frequent involvement of the cardiovascular system in acute anorexia nervosa[3], cardiovascular disease was not a leading cause of death in this analysis. In a prior study of 6,009 Swedish women, anorexia nervosa was similarly more strongly associated with suicide, respiratory and endocrine-related causes than cardiovascular death[6]. It may be that low weight due to decreased calorie intake mitigates damage to the cardiovascular system[6].

This study has limitations. We assessed severe anorexia nervosa requiring hospitalization, not milder anorexia adequately managed in outpatient settings. We did not have information on anorexia relapse or recovery status, body mass index, physical activity, or nutrition. Cause of death data were partially missing before 2006. We used a comparison group comprised of fertile women. Our results may therefore differ from studies using the general population as a reference group.

The long-term role of anorexia nervosa in mortality has yet to be fully appreciated. In this study with 29 years of follow-up, anorexia nervosa hospitalization was associated with an increased risk of death up to 20 years later and was strongly associated with mortality due to diabetes, pneumonia and suicide. As the risk of death was most pronounced in the first two decades, earlier interventions to treat anorexia nervosa may have greatest potential for reducing harm. To improve survival and reduce morbidity, better documentation of the impact of anorexia nervosa over the life course is needed.

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DOI:10.1002/wps.20904

The WHO EQUIP Foundational Helping Skills Trainer's Curriculum

Foundational helping skills are the provider's competencies needed to build a warm and trustworthy relationship with a client. Examples include effective verbal and non-verbal communication, demonstrating empathy, rapport building, and promoting hope and expectancy of change[1].

These skills have been widely established as an essential and

universal prerequisite for the delivery of any effective psychosocial or psychological care[1], and identified as core competencies required for all health workers in the forthcoming World Health Organization (WHO)'s Global Competency Framework for Universal Health Coverage[2].

Competent use of these skills by providers improves treatment outcomes for people accessing the whole range of health services, from surgery to mental health services[1,3], and use of these skills has been shown to support greater treatment compliance also outside the mental health field – for example, HIV treatment adherence[4].

The recent global experience of the COVID-19 pandemic has demonstrated that mental health and psychosocial support skills cannot be limited to mental health specialists only. Health systems will be able to better respond to public health emergencies as well as provide superior routine care if all health care providers are competent in foundational helping skills. Yet, in many health training programs, the attention to these skills and their evaluation is limited[5].

The WHO developed the Ensuring Quality in Psychological Support (EQUIP) project, which aims to strengthen quality in the delivery of psychosocial support and psychological training within the Universal Health Coverage agenda. The EQUIP platform will offer materials for trainers, supervisors, and program managers on competency-based training and assessment[6]. One such resource for trainers is the competency-based Foundational Helping Skills Trainer's Curriculum.

The formative process to develop this training package included a narrative review, identification of empirically supported common factors used across effective interventions[7], human centered design inputs, and extensive expert consultation, including experts from field sites, programme managers, and academics. Based on these contributions, a range of skills were identified. Examples include verbal and non-verbal communication skills, using culturally and age-appropriate terminology and concepts for distress, confidentiality, normalization of feelings, expression of empathy, promoting hope, and suicide risk assessment. In addition, based on the importance of attitudes in motivating caring behaviours[8], a module on attitudes toward helping others was included.

The training curriculum is in a modular format, to allow trainers to fit it to the trainees' needs based on brief competency assessments conducted throughout the training programme. The curriculum includes didactics, participatory group activities, and skill remediation techniques, which can be delivered online, face-to-face, or in a combined approach. Role-play based competency assessments[9] are conducted throughout the training to monitor progress, to determine minimum competency, and to ensure that the trainee does not engage in harmful behaviours (e.g., being dismissive or judgmental, ignoring or minimizing suicide warning signs)[9].

The EQUIP Foundational Helping Skills Trainer's Curriculum is intended to be a brief course: approximately 20 content hours, with flexibility based on the prior skill level of trainees. It is designed for implementation across a wide variety of government and non-government organization sectors, such as public health, family and community services, education, and law enforcement, with trainees such as professionals and para-professionals without prior training in mental health and psychosocial support skills.

Pilot testing of the training package is currently underway in Uganda, Nepal and Peru, assessing its feasibility, acceptability, and perceived benefit for remote and in-person delivery.

The EQUIP Foundational Helping Skills Trainer's Curriculum aims to meet an indispensable need by ensuring that the growing workforce of health care professionals and non-specialist providers are competent in foundational helping skills. This, alongside other activities, will hopefully lead to improved quality of care and will be one step closer to achieving the goal of a competent health workforce for Universal Health Coverage.

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This work is funded by the World Health Organization through a grant from the US Agency for International Development (USAID). The authors alone are responsible for the views expressed here, and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

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DOI:10.1002/wps.20880

Implementation of the WPA Action Plan 2020-2023

The COVID-19 pandemic has put tremendous burden on health care systems all over the world. Unfortunately, mental health services have also been severely affected. This is evident in reduced resource allocation and downsizing of many mental health services or even closing of services worldwide[1-4].

The WPA has been reviewing its Action Plan 2020-2023[5] in the light of the pandemic. The plan is already underway, and the Executive Committee has met several times to finalize any changes needed. The success of the implementation of the Action Plan is largely dependent on the well-coordinated interaction of all components of the WPA structure. We have, unfortunately, faced several difficulties for the functioning at our Secretariat due to lockdown and other COVID-19-related problems. However, we are confident that the Association will successfully overcome the difficulties associated with this critical period.

The WPA General Assembly adopted the Association's Code of Ethics for Psychiatry in October 2020[6]. The Code was developed by the Standing Committee on Ethics and Review with contributions from psychiatric societies worldwide. The Code now stands as the WPA's official statement on the ethics of psychiatry. It is not meant to replace national codes of ethics, which can better address local circumstances of each country and incorporate local sociocultural values. The WPA is asking its Member Societies to endorse the Code's principles and to confirm that their codes are not in conflict with the Association's general principles.

The WPA has established 16 working groups to address the six priorities of its Action Plan 2020-2023: capacity building; public mental health; child, adolescent and youth mental health; addressing comorbidity in mental health; partnerships with other professional and non-governmental organizations; and continuation and completion of the previous Action Plan's work. Each of these groups has developed terms of reference and identified projects for the future[7].

Among the current priorities, public mental health continues getting particular attention. The WPA aims to promote an increasing understanding of public mental health among professionals and the public, including collaboration with patient and family organizations[8,9].

Our program of scientific meetings is now in full swing. In December 2020, we held the first virtual Thematic Congress on Intersectional Collaboration under the theme "Psychological trauma: global burden on mental and physical health". Presentations from the meeting are now available on our website (www.wpanet.org). The WPA's first-ever virtual World Congress of Psychiatry was held in March 2021, with a wonderful program of interactive sessions and world-class speakers. It was an engaging and fulfilling experience. We also held recently a virtual Regional Congress organized by the Russian Society of Psychiatrists. The 21st World Congress of Psychiatry is taking place virtually from 18 to 21 October 2021.

The WPA membership is familiar with the courses we usually run during World Congresses. A key part of our educational program appears now as a learning management system and educational portal on our website[10]. The portal was launched at the beginning of 2021. It now houses many educational resources, including our COVID-19 Resource Library. To celebrate the launch of the education portal, our membership is eligible to register free for any of the online education courses taking place over the coming year.

Just like in our in-person courses, there will be activities, discussion, and opportunities for interaction, and those who successfully complete the course will receive a certificate of participation. This opportunity is a valuable addition to an already outstanding scientific agenda, and we are grateful to our colleagues who are contributing their time and expertise to this new program. All courses from the online education program will eventually be available on the WPA education portal.

This year, a selection of new and updated resources has been added to the portal, including courses on tele-psychiatry and evidence-based psychotherapies. Also available on the portal is our exceedingly popular Intimate Partner and Sexual Violence Against Women curriculum. The portal has now been updated to be more interactive, with presentations, reading lists, teaching points and quizzes. We will be working over the next months to update the other language versions as well. It is our hope that this new portal will not only facilitate further education in psychiatry, but will encourage and inspire learning among colleagues and trainees around the world.

The WPA keeps on helping its membership to develop an effective and rapid response to requests for support for policy issues. The recent response to the Ukraine crisis exemplifies the collaboration between the Association and Member Societies in this regard[11]. This serves as a model for future work of a similar nature, and of how organizations with a different profile can work successfully to help improve treatment and care for people living with mental disorders.

The WPA's Scientific Sections continue to be at the forefront of bringing diversity to the work of the Association. Furthermore, members from Sections are actively involved in teaching, training and research programmes focused on the objectives of WPA's Action Plan[12-14]. Some examples from this work include the activities of the Early Career Psychiatrists Section, collecting the views of early career psychiatrists on their role in clinical practice, and supporting them in utilizing current and future psychiatric classification systems across the world[15,16].

The COVID-19 pandemic has changed the world as we knew it. The WPA is mindful that the continuous global spread of the infection is increasing risk of developing mental disorders, relapse of existing mental disorders and poor mental health, in addition to impacting the work of mental health services. We are hopeful that the WPA will continue generating interest among all its components to develop strategies for future work. We are optimistic that we will receive support, active input, and advice from our

membership in addressing our targeted priorities and making a real difference in mental health.

Afzal Javed
WPA President

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DOI:10.1002/wps.20895

Psychiatric care in oncology and palliative medicine: new challenges and future perspectives

The World Health Organization (WHO) reports forecast an increase of cancer incidence of 40% in high-income countries and more than 80% in low-income countries by 2030, and a rise of both mortality and long survivorship. Consequently, the agenda of psychiatry in oncology and palliative medicine needs to be reviewed and updated.

The mental health implications of oncologic diseases have been in fact repeatedly stressed in the last 40 years as needing attention in clinical practice, as part of person-centered interdisciplinary care. At least 30% of patients with cancer are reported to receive a psychiatric diagnosis (e.g., major depression, depressive spectrum, stress-related and anxiety disorders), while a higher percentage show other clinically relevant psychosocial conditions (e.g., demoralization, health anxiety, irritable mood)[1].

Mental health problems amongst patients and their families are associated with reduction of quality of life, impairment in social relationships, longer rehabilitation time, poorer adherence to treatment, abnormal illness behaviour, and possibly shorter survival[2]. In advanced cancer patients, these problems are even more evident, with a series of significant psychiatric and psychosocial conditions that should be a target of end-of-life care.

For these reasons, it has been stated that "it is not possible to deliver good-quality cancer care without addressing patient's psychosocial health needs"[3]. Today, it is part of the oncology agenda worldwide that psychosocial cancer care should be recognized as a universal human right; that the psychosocial domain should be integrated into routine cancer care; and that distress should be measured as the 6th vital sign after temperature, blood pressure, pulse, respiratory rate and pain in patients with cancer[4].

The significant advances of research in the area of psycho-oncology have favored the development, implementation and dissemination of evidence-based treatments, both in terms of psychotherapy (e.g., supportive-expressive psychotherapy, cognitive-behavioural and cognitive-existential therapy, meaning centered psychotherapy) and integrated pharmacotherapy for psychiatric disorders and cancer-related symptoms (e.g., pain, hot flashes). However, inequalities exist in the development of psychosocial oncology worldwide. Significant economic constraints within health systems may undermine both the monitoring of distress and the process of referral to mental health services and psychiatric treatment[5].

A new challenge is represented by the debate on euthanasia and physician-assisted death, in which psychiatry and psycho-oncology have a specific role. Also, the implications of cancer screening and treatment among people with severe mental illness are an extremely important part of the psycho-oncology and palliative care agenda.

The WPA Section on Psycho-Oncology and Palliative Care was founded in the late 1980s with the specific aim of fostering psychiatry and behavioural sciences within all fields of oncology and palliative care. The main goal is to provide optimal psychosocial care to patients at all stages of disease and survivorship, as well as support to families.

The Section is committed to collect and disseminate scientific information on the most common psychopathological and psychosocial problems of patients with cancer and their families; and to establish working relations with other organizations in the field of psycho-oncology and palliative care at the international level.

Collaboration with other WPA Sections, especially that on Psychiatry, Medicine and Primary Care, has been established over time, with presentations at WPA meetings worldwide and production of books[6-8], scientific papers and book chapters. A number of other WPA Sections have the potential to be involved in this collaboration.

Today, psycho-oncology and psychiatry in palliative care are recognized as disciplines in themselves, within the wider field of consultation-liaison psychiatry. Many medical student and psychiatry residency programs as well as fellowships in consultation-liaison psychiatry include clinical rotations in psycho-oncology and palliative care. Screening for distress is now an accepted part of protocols in cancer centers and there is a growth of research aimed to better understand how to screen and provide psychiatric care using evidence-based guidelines and protocols[9].

Our Section has had a leading role in addressing the multiple issues related to patients with co-occurring oncologic and psy-

chiatric conditions. It will continue to work in order to improve the quality of training as well as of clinical care and research in this interdisciplinary area worldwide. Scholarly activities will continue to include opportunities for scientific presentations and training at WPA meetings, as well as collaborative research and clinical projects.

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DOI:10.1002/wps.20836

Advancing psychotherapy in psychiatry: the contribution of the WPA Section on Psychotherapy

Psychotherapy has been an essential component of psychiatric theory and practice for over a century. There is sufficient evidence to consider it a treatment which may produce enduring epigenetic, neuroendocrine and structural changes in the brain[1].

Many psychotherapy modalities have been manualized over the last three decades and proven helpful for most mental disorders. Randomized controlled trials show that all psychotherapies are equally efficacious for anxiety and mood disorders, with a robust effect size for supportive psychotherapy, interpersonal therapy (IPT), cognitive behavioral therapy (CBT) and psychodynamic psychotherapy[2].

Clinicians often combine psychotherapy modalities in daily practice[3], and common factors such as empathy, validation, support, affirmation, the therapeutic alliance, reflective functioning/mentalization, and expression of affect promote symptom reduction and improvement in functional domains. Effectiveness studies have shown that common factors may be at the core of positive outcomes[3,4]. The WPA Section on Psychotherapy supports efforts to delineate the role that these factors play in patient care even when formal psychotherapy is unavailable or deliberately not used, and to develop educational approaches to foster their implementation.

Individual participant data meta-analyses are now being used to examine the differential treatment efficacy among empirically supported treatments, to help identify if subgroups of patients may respond better to particular forms of psychotherapy[5]. Preliminary findings are encouraging and could help clinicians triage patients to one or more forms of therapy, based on the presence of comorbid conditions or the duration and severity of symptoms. For example, there is pooled data showing that psychodynamic psychotherapy may be more efficacious than CBT, when combined with antidepressant medication, for depressive episodes of longer duration. On the other hand, CBT may be superior for patients with shorter duration of depressive symptoms and with comorbid anxiety[5]. These research developments, expanding the availability of data sets to significantly increase statistical power, may advance the field to create guidelines to select psychotherapy modalities based on specifiers and subgroups of patients with anxiety and depressive disorders[2,4-8].

The WPA Section on Psychotherapy provides a forum to advance the practice, training and research on evidence-based psychotherapies within psychiatry. The Section currently has over 200 active members, representing 32 countries. Given the eagerness to develop expertise in evidence-based psychotherapies, we created eleven special interest groups to promote targeted formal academic and educational activities. These groups are further subdivided into two categories: "Psychotherapy for Special Populations" and "Cultural Adaptations of Evidence-Based Psychotherapies".

The "Psychotherapy for Special Populations" groups seek to explore the delivery of psychotherapies in an economically responsible way to disenfranchised and underserved groups or populations. They include "Psychotherapy with Refugees, Displaced Persons and Survivors of Trauma", "Psychotherapy with Lesbian, Gay, Bisexual, Transgender, Queer and Others (LGBTQ+)", "Psychotherapy in Late Life", "Psychotherapy in Consultation and Liaison Psychiatry", and "Psychotherapy with Adolescents and Young Adults". During the last triennium, these groups contributed presentations at the WPA Co-Sponsored Meeting on Psychotraumatology held in Duhok, Iraq in June 2019, and the WPA Intersectional Congress on Psychological Trauma held virtually in December 2020.

The "Cultural Adaptations of Evidence-Based Psychotherapies" groups seek to develop culturally consonant and sensible psychosocial treatments. They include "Cultural Adaptations of CBT", "Cultural Adaptations of IPT", "Cultural Adaptations of Third-Wave Psychotherapies", "Cultural Adaptations of Psychodynamic Psychotherapies", "Cultural Adaptations of Supportive Psychotherapy", and "Cultural Adaptations of Motivational Interviewing". The leaders of these groups were instrumental in developing the WPA Supportive Psychotherapy Course in April 2021, which had close to 1,000 registrants and was offered free of charge on a virtual platform. Additionally, they designed eight comprehensive teaching modules on Evidence-Based Psychotherapies now available on the WPA

website (www.wpanet.org). Each module is composed of a variety of educational materials, such as journal and chapter reprints, slide presentations, self-assessment multiple-choice questions, informative theoretical and clinical video links, and a comprehensive bibliography.

Another educational activity coordinated by the Section at the beginning of the COVID-19 pandemic was a lecture series for health care workers in China, delivered in Chinese and English, dealing with psychotherapeutic interventions for COVID-19-related stress, anxiety and mood disorders, burnout prevention and physician well-being. These lectures were given virtually over a period of three months in early 2020.

All leaders and many members of the Section's special interest groups presented at the First WPA Psychotherapy Conference held in Kuala Lumpur, Malaysia in July 2019. This conference, hosted by the Malaysian Psychiatric Association and co-sponsored by the World Association of Dynamic Psychiatry and the American Academy of Psychodynamic Psychiatry and Psychoanalysis, had almost 500 registrants from 20 countries. Given the success of this collaborative conference model, we are planning to hold a second and a third conference during this triennium, hosted respectively by the Egyptian Association of Cognitive Behavioral Therapy and the Philippine Psychiatric Association. We are also developing ways to interface and liaise with the International Federation for Psychotherapy.

Cultural adaptation of psychotherapies takes into consideration values and belief systems, idioms of distress, health-seeking behaviors, and culture-specific understanding of disease processes and illness experiences[9]. Although some academics debate the merits of developing manualized cultural adaptations of evidence-based psychotherapies[2,9,10], the leadership of our Section agrees that, in clinical practice, all psychotherapists intuitively perform a cultural adaptation. Our Section contributed in 2021 a special issue of the journal *Asia-Pacific Psychiatry*[9] addressing transcultural aspects of the delivery of psychotherapy services, with authors from 19 countries.

Further research areas are now emerging that are likely to enhance our field, such as exploring the biological underpinnings of the curative factors of psychotherapy, streamlining the delivery of Internet-assisted psychotherapies, and studying the effectiveness of tele-therapy. The WPA Section on Psychotherapy welcomes all psychiatrists worldwide interested in developing their psychotherapeutic skills and affirming the place of psychotherapy in psychiatry.

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DOI:10.1002/wps.20897

The Lifestyle Psychiatry project of the WPA Section on Medicine, Psychiatry and Primary Care

The importance of psychiatry and behavioral health in the delivery of overall health care and optimization of health is widely acknowledged. However, the stigma related to mental illness in society and the separation of psychiatric care from traditional medical settings has resulted in significant challenges in integrating all aspects of care necessary in maintaining optimal health and well-being.

The sub-specialty of consultation/liaison psychiatry has attempted to address this issue in the inpatient medical setting by providing psychiatric consultation to medical patients experiencing psychiatric symptoms and syndromes. Unfortunately, we have been less effective in creating integrated models of care, especially in the outpatient setting. Compounding this problem is the lack of psychiatrists internationally, with very few formally trained in integrated care models.

The COVID-19 pandemic has produced unprecedented challenges, while generating unique opportunities for education and novel clinical care models. The need for interdisciplinary collaborative models of care, integrating public health, public policy and public education, in concert with mental health and primary care provision, has never been so significant.

The WPA Section on Medicine, Psychiatry and Primary Care has restructured to address these issues, with a focus on expanding collaboration with other WPA Scientific Sections and by reaching out to interprofessional colleagues and health care professional organizations. The Section leadership has created projects to focus on various aspects of this new strategy. One of these is the Lifestyle Psychiatry project. We see this as a true opportunity for collaboration between many WPA Scientific Sections with related interests, along with non-psychiatric stakeholders. The WPA leadership has endorsed the concept and is supporting the growth of this model. Any WPA member or Section Chair is warmly invited to contact our Section to discuss additional collaborations.

Lifestyle psychiatry refers to the application of lifestyle medicine principles to support individuals in managing psychiatric disorders and cultivating brain health[1]. It

includes studies on the impact of lifestyle behaviors on the prevalence of psychiatric symptoms or disorders in general populations, the impact of lifestyle behaviors on symptoms among people at risk for psychiatric disorders, the impact of lifestyle interventions on severity of symptoms among people with a psychiatric disorder, the neuroscience of brain response to lifestyle behaviors, and the science of lifestyle behavior change[2]. The domains of lifestyle behaviors include physical exercise, diet and nutrition, meditation, mind-body practices, sleep, and social relationships[1,2].

There is now an impressive body of literature on the neuroscience of physical exercise suggesting an upregulation of neurotransmitters associated with positive mood and neurotrophic factors that support neuronal vitality. Neurotrophins promote neoneurogenesis and synaptic proliferation associated with increases in regional brain volume and connectivity and enhanced cognitive function[3]. Sustained exercise leads to epigenetic upregulation of brain-derived neurotrophic factor (BDNF) synthesis, promoting brain health over a lifetime[4]. These regulatory interactions have been correlated with the evolutionary steps allowing early hominids to thrive in a hunter-gather lifestyle[5]. There is a similarly impressive literature demonstrating robust brain functional and volumetric responses to meditation and sleep[6].

We also know that lifestyle factors are powerfully correlated with the prevalence, onset and perpetuation of psychiatric symptoms and syndromes. Sedentary behavior has been correlated with risk for suicidal behavior, depression, cognitive decline of aging, and psychosis, while physical exercise has been correlated with improvements in mood, motivation and cognition[7]. Sleeping less than 6 hours nightly is correlated with risk for major neurocognitive disorders. Mindfulness practices have been associated with improvements in anxiety and treatment-resistant depression. A Mediterranean style diet has been correlated with improvements in depression, and omega-3 fatty acids and N-acetylcysteine appear to have neuroprotective effects[8].

However, our societies continue to shape human behavior in unhealthy directions. Sedentary time continues to rise in parallel to increases in substance abuse, suicide and emergency room visits for mental health care. Traditional diets are being progressively displaced by processed foods. Twenty-four hour virtual experiences constrain sleep opportunity, and social interaction is increasingly impersonal[9]. Global health care systems are stressed by escalating rates of lifestyle-related disorders such as diabetes mellitus type 2, cardiovascular disease, cancer and psychiatric disorders.

Lifestyle Psychiatry offers a unique opportunity for psychiatrists to join and lead other medical disciplines in promoting attention to the impact of lifestyle on health and disease. When clearly identified, the potential dual benefit for mental and physical health may enhance motivation to adhere to positive lifestyle changes. Psychiatrists also bring expertise in effective behavior change strategies. Lifestyle interventions may be useful for primary prevention, first-line therapy, multimodal therapy, augmentation, precision therapy and relapse prevention.

There is an urgent need for psychiatry to step forward to assist governments, employers, corporations and health care systems to effectively position health-promoting lifestyle practices to address the rising tide of distress, disability and loss of life flowing from modern cultural trends in a global society.

We must articulate the strength of the current evidence on the impact of lifestyle behaviors on mental and physical health outcomes, while identifying areas where further evidence is needed to offset the influences of globalization and corporate interest on human and societal health.

The WPA Section on Medicine, Psychiatry and Primary Care aims to develop awareness and expand consideration of Lifestyle Psychiatry as a vital component in improving the health and well-being of people around the world.

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DOI:10.1002/wps.20898

Loneliness and abuse as risk factors for suicide in older adults: new developments and the contribution of the WPA Section on Old Age Psychiatry

Suicide is a major public health problem, with 817,000 cases worldwide in 2016. The incidence is highest in those aged 70 years or older, among both men and women, in almost all regions of the world[1].

Effective interventions that mitigate identified risk factors and sustain protective factors are relevant across all age groups, but research specifically focused on suicide prevention in older adults is still in its early stages. The evidence on the effectiveness of suicide prevention interventions for older adults remains limited. The International Association for Suicide Prevention Interest Group on Suicide in Old Age[2] recommend-

ed multi-component approaches, based on the available scientific evidence, with an organized system of distribution of resources and the monitoring of the effectiveness of each intervention.

Loneliness occurs when a person feels disconnected from his/her closest social circle: partners, family members, peers, friends and significant others. It often affects older adults, particularly men when single, widowed or divorced[3]. It may result from the loss of an important intimate relationship or a social role that previously used to give a person his/her sense of self-esteem and dignity. In case of negative life events or other psychological stressful situations, when the person has nobody to share his/her feelings with, loneliness can have particularly negative consequences. This, in combination with other risk factors, can lead to an increase of the risk for suicidal behaviour. A particular expression of loneliness among older adults is the fact that suicides more often occur when the person is alone at home[4].

The consequences of the COVID-19 pandemic have resulted in new challenges for older adults, and we are just beginning to see the effects on morbidity, mortality and suicide rates worldwide[5]. Many government policies to tackle the pandemic that include social isolation, lockdown and social distancing have resulted in increased distress in older adults. We therefore need to develop strong primary care and community assets to support older adults. A rise in suicide deaths in older adults as a result of the pandemic is not inevitable[6]. The traditional approaches to suicide prevention need to be re-considered[7], so that we can develop innovative ways to address this issue in older adults in the new context. The voices of people with lived experience should be heard to inform developments in strategies.

Previous traumatic experiences (e.g., history of abuse during childhood, loss of a parent) can have consequences in later life and be associated with increased likelihood of suicidal behaviour. But present traumatic experiences may also increase the risk for suicide. According to the World Health Organization, around 1 in 6 older people experienced some form of abuse in the past year[8]. However, the prevalence rates reported in existing population-based elder abuse studies likely underestimate the true population prevalence. Not only this field of research suffers from methodological and comparability challenges, but elder abuse prevalence surveys also carry substantial participation bias, in that they exclude individuals with cognitive impairment, who could potentially be most vulnerable to abuse, especially in institutions.

Older adults with mental health problems are at high risk for abuse. There are many forms of elder abuse, including psychological, physical, sexual, financial and social abuse, as well as neglect and abandonment. Abuse should never be condoned, whatever the mitigating circumstances. What may not be considered abusive towards a healthy, competent person may be so in a vulnerable older adult. This is mainly explained by the high risk of older adults to be dependent (financially, emotionally, physically) from the persons who perpetrate acts of violence, abuse or neglect against them.

Each form of elder abuse represents a risk factor for suicide. Several psychosocial risk factors found in severely abused older adults are also frequently present in older adults who attempted or completed suicide. Abused older adults have been paid inadequate attention in suicide prevention efforts. This omission must be remedied, as the aged global population will dramatically increase in coming decades, which, in the absence of meaningful preventive efforts, may drive a sharp rise in the incidence of older adults' abuse and suicide[9].

Help to establish strong social relationships and an effective legal frame to protect the individual against any form of violence are common protective factors against suicide. However, in the case of older adults, we should recognize that efforts to sustain these protective factors have been weaker than for the younger population.

Considering the high potential of loneliness as a risk factor for suicide, the WPA Section on Old Age Psychiatry has supported the establishment of an End Loneliness Day. The Section is also going to become partner of the Campaign to End Loneliness. Having the friendship and support we need is a fundamental part of our well-being. When loneliness becomes entrenched in later life, it can be hardest to overcome. The campaign aims to involve academics, front-line practitioners, decision-makers and businesses (see https://www.campaigntoendloneliness.org).

Considering that all forms of elder abuse are a violation of basic human rights, the WPA Section on Old Age Psychiatry is contributing to the effort to develop a new United Nations Convention on the Rights of Older Persons. A first action was a webinar organized in collaboration with the International Psychogeriatric Association on December 10, 2020, on the occasion of the Human Rights Day. The Section also organized an intersectional symposium on Threats to the Dignity of Older Adults with Mental Disorders during COVID-19 Pandemic within the 2020 WPA Thematic Meeting on Intersectional Collaboration. A Position Statement on Human Rights and Mental Health of Older Adults is now in preparation.

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DOI:10.1002/wps.20899

The 2021-2024 Work Plan of WPA Collaborating Centres

The network of WPA Collaborating Centres was established in 2016 with the aim to provide practical advice on teaching, policy, research and clinical activities in psychiatry worldwide[1]. In 2021, the network has been renewed for three years in order to support the implementation of the WPA Presidential Strategic Plan[2] and to build a global alliance for better mental health.

The network now includes eight sites: the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India; the Department of Psychiatry of the Chinese University of Hong Kong; the Africa Mental Health Research and Training Foundation (AMHRTF) in Nairobi, Kenya; the Department of Psychiatry and Mental Health, University of Cape Town, South Africa; the Okasha Institute of Psychiatry, Faculty of Medicine, Ain Shams University, Cairo, Egypt; the Department of Psychiatry and Nuffield Department of Primary Care Health Sciences, University of Oxford, UK; the Department of Psychiatry, University of Campania "L. Vanvitelli", Naples, Italy; and the Department of Psychiatry at Sidra Medicine in Doha, Qatar. This last site has been included among the Collaborating Centres in 2021 with a special focus on women and children's mental health.

The WPA Collaborating Centres have developed a Work Plan for the period 2021-2024 focusing on the following topics: a) multi-morbidities in patients with severe mental disorders, in collaboration with the WPA Working Group on Physical Comorbidities led by N. Sartorius; b) implementation of the ICD-11, with the dissemination of training materials, bearing in mind local contexts; c) policy, legislation and protection of human rights, in order to develop a WPA policy position paper and a campaign on protecting human rights of patients with mental disorders worldwide; d) adolescent mental health, focusing on the development and dissemination of innovative prevention and intervention programmes in youth; e) community mental health in low- and middle-income countries; f) COVID-19 and mental health response; g) development of high-quality WPA Global Seminars, which will be made available to the WPA Member Societies and posted on the WPA website; and h) development and/or update of WPA Position Statements, with the active involvement of trainees and early career researchers.

Given the current pandemic situation, the network has included in its Work Plan a special focus on COVID-19, in particular on challenges and difficulties to manage the psychosocial consequences of the pandemic, and the responses from the mental health sector worldwide[3-6]. Moreover, the Centres will share and disseminate policy papers, clinical guidelines and research documents in order to improve patient care and public mental health.

The network actively collaborates with many WPA Scientific Sections[7-9], including the Section on Education in Psychiatry[10] and the Section of Early Career Psychiatrists[11,12], in order to identify the unmet educational needs for early career psychiatrists and to provide scholarship opportunities for medical students and psychiatric trainees across the different WPA Member Societies.

The work of the Collaborating Centres will be presented at major WPA Conferences and through policy papers and educational materials[13], which will be made available to the entire WPA community.

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DOI:10.1002/wps.20917

ICD-11-related educational activities

The chapter on mental, behavioural and neurodevelopmental disorders of the 11th revision of the International Classification of Diseases (ICD-11), developed by the Department of Mental Health and Substance Use of the World Health Organization (WHO), has been formally adopted by the 72nd World Health Assembly in Geneva on May 25, 2019.

The most significant innovations and changes in this chapter with respect to the ICD-10, and the most important differences from the DSM-5, have been presented in detail in a paper published in this journal[1], while more specific differences concerning individual diagnostic groupings have been recently discussed elsewhere[2,3]. The involvement of the WPA in the development of the chapter has been also described in previous reports[4-6]. Several issues debated in the process of the development of the chapter – including the role of a dimensional approach as complementary to the categorical one, and the need for a further clinical characterization of the individual

patient in addition to diagnosis in order to personalize management – have been addressed in this journal as well[7-15].

Educational courses focusing on various sections of the ICD-11 chapter on mental, behavioural and neurodevelopmental disorders have been held in connection with several WPA meetings, including the 18th, 19th and 20th World Congresses of Psychiatry (Mexico City, Mexico, September 27-30, 2018; Lisbon, Portugal, August 21-24, 2019; Bangkok, Thailand, March 10-13, 2021), and the Regional Congresses on "Interdisciplinary Understanding of Co-morbidity in Psychiatry: from Science to Integrated Care" (St. Petersburg, Russia, May 16-18, 2021) and "Psychopathology in Periods of Transition" (Kyiv, Ukraine, July 7-9, 2021).

A more comprehensive online 20-hr training course has been organized by the Naples WHO Collaborating Centre on Research and Training in Mental Health and the European Psychiatric Association from 9 to 30 April, 2021. The course has been coordinated by G.M. Reed and M. Maj, and has covered all the main sections of the ICD-11 chapter on mental disorders. W. Gaebel, M. Cloitre, M. Maj, C.S. Kogan, P. Monteleone, M. Swales, J.B. Saunders and N.A. Fineberg composed the Faculty. The live course has been attended by 120 psychiatrists, selected from almost 500 applicants, representing 78 different countries. A further group of 250 psychiatrists have had access to the course on demand.

A training course with exclusive access to the members of the WHO Global Clinical Practice Network (https://gcp.network) has been recently set up by the WHO Collaborating Centre at Columbia University, in collaboration with the WHO Department of Mental Health and Substance Use. The course consists of 15 online training units, each focusing on a different disorder grouping and taking from one to one and a half hours. Each unit provides a description of the relevant diagnostic grouping and the main innovations with respect to the ICD-10. Knowledge check questions are provided to ensure comprehension. Participants have the opportunity to practice by applying diagnostic guidelines to clinical case examples. This training course is going to be available also in Spanish, and additional translations are planned.

A WHO International Advisory Group on Training and Implementation for ICD-11 Mental, Behavioural and Neurodevelopmental Disorders has been established to develop and evaluate educational, training and implementation processes related to the ICD-11 in various countries. WPA former officers who contributed to the development of the ICD-11 chapter on mental disorders, such as M. Maj and W. Gaebel, are members of this Advisory Group.

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DOI:10.1002/wps.20920

Acknowledgement
This publication has been partially supported by
an unrestricted educational grant from Janssen-Cilag SpA,
which is hereby gratefully acknowledged.