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World Psychiatry

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Clozapine: past, present and future

Clozapine, synthetized over 65 years ago, remains the only antipsychotic approved for treatment-resistant schizophrenia. Despite its well-documented efficacy and effectiveness in randomized controlled trials (RCTs) and real-world studies[1], this drug's unclear mechanisms of action, complex side effect profile, and underutilization pose significant challenges for clinical practice. The recent approval of the first M1/M4 muscarinic agonist for schizophrenia has spurred hopes of added efficacy through this mechanism of action for people with insufficient treatment benefits from dopamine receptor antagonists/partial agonists. In this context, it is valuable to reflect on unresolved issues, including clozapine's pharmacologic mechanisms, unique clinical benefits, risks, and barriers to optimal use.

To date, the exact mechanisms underlying clozapine's superior efficacy in treatment-resistant schizophrenia remain incompletely understood. Unlike other dopamine receptor blocking antipsychotics, which have medium-strong affinity to dopamine D2 receptors, clozapine has weak D2 receptor affinity, binding more tightly to serotonergic, alpha-adrenergic, metabotropic glutamatergic, and muscarinic receptors. It also has neuroprotective, antiproliferative and anti-inflammatory activity.

Clozapine's metabolite, N-desmethylclozapine, acts as a positive allosteric modulator at muscarinic M1 receptors and as an M4 receptor agonist, raising the possibility that this mechanism of action could contribute to the unique efficacy of the drug. This aspect is particularly relevant, given the above-mentioned recent approval by the US Food and Drug Administration (FDA) of the M1/M4 receptor agonist xanomeline, paired with the peripherally restricted anticholinergic trospium, for the treatment of schizophrenia[2].

Clozapine offers distinct advantages in managing treatment-resistant schizophrenia, with demonstrated superiority over other dopamine receptor blocking antipsychotics for positive symptom reduction; reduced relapse/hospitalization risk, suicidal behaviors, substance use and aggressive behavior; increasing functionality, including employment; and reducing mortality risk. However, clozapine's use is limited by significant adverse effects, including agranulocytosis, myocarditis, pneumonia, ileus, weight gain, diabetes, dyslipidemia, and metabolic syndrome, as well as sedation and hypersalivation[3]. The seeming paradox of clozapine's lower risk for all-cause as well as cardiovascular disease-related mortality, despite higher risk of cardiometabolic adverse effects versus other antipsychotics, has been addressed by a nationwide within-subject study[4], indicating that patients taking clozapine also showed greater adherence to statins, antidiabetic medications and antihypertensives. Better psychiatric outcomes could also promote healthy lifestyle behaviors.

There is ongoing debate about when clozapine should be introduced in the treatment algorithm for people with schizophrenia. Current guidelines recommend its introduction after two antipsychotic efficacy failures. However, initiating clozapine after one failed treatment may improve outcomes and reduce delays in effective care, especially as delayed clozapine use has been associated with reduced efficacy. A recent nationwide database study – though presenting some methodological limitations – indicated that, after a first psychosis relapse, a switch to clozapine was associated with the lowest risk of a second psychosis relapse, while a switch to another oral antipsychotic monotherapy was almost as unhelpful in preventing a second relapse as stopping antipsychotics altogether[5]. These data, although preliminary, seem to challenge current clinical guidelines and practice of using yet another dopamine receptor blocking antipsychotic, either alone or in combination, after verified failure of treatment with a member of that same pharmacological class, elevating clozapine (or possibly other non-postsynaptic antidopaminergic agents) to a direct second treatment choice.

Additionally, to mitigate the risk of early (hyperthermia, tachycardia, orthostasis) and potentially severe (myocarditis, pneumonia, agranulocytosis, seizures, ileus) side effects, clozapine's initiation involves slow titration. Recently, ethnicity-specific differences in tolerability, and dosing as well as titration requirements, have been proposed[3], raising questions about whether standard protocols should be modified based on ethnic factors.

Obtaining clozapine blood levels can be helpful to inform titration for dose finding. Clozapine is one of the few psychotropic medications with an evidence base supporting measurement-based care, with an optimal threshold level of >350 (range: 250-550) ng/ml for efficacy. However, therapeutic blood monitoring is not always/widely available, and clozapine blood levels, when accessible, may take a long time to read out, further complicating clinician use.

Although up to 40% of patients fulfill criteria for treatment-resistant schizophrenia[6], clozapine – the only antipsychotic with regulatory approval for this condition – continues to be prescribed in less than 10% of patients with schizophrenia worldwide[7]. This discrepancy highlights significant barriers, including clinicians' insufficient training and hesitation, system-level constraints, and patient or caregiver concerns about side effects or ongoing hematologic monitoring. Educational initiatives aimed at clinicians and patients may help address misconceptions about clozapine. Contact to experienced prescribers can empower clinicians to use clozapine confidently.

The evidence-based justification for ongoing hematologic monitoring has been called into question, given data that the risk of agranulocytosis in people with normal white counts significantly declines after the first year[3]. Indeed, the FDA has recently decided to discontinue its previously mandated Risk Evaluation and Mitigation Strategy (REMS) program, which required patients to report an absolute neutrophil count blood test prior to pharmacies dispensing clozapine.

Unfortunately, even with clozapine, about 50-60% of patients respond insufficiently[8]. Although electroconvulsive treatment added to clozapine is currently the most evidence-based treatment option, this is used even less than clozapine. Instead, other psychotropic medications, especially other antipsychotics, are frequently added to clozapine. A meta-analysis of two nationwide cohorts (Finland

and Sweden), which appears in this issue of the journal[9], found in within-subject analyses that medium-dose aripiprazole augmentation of clozapine treatment was associated with a 20-30% risk reduction of hospitalization versus clozapine monotherapy. On the other hand, augmentation with higher doses of aripiprazole, as with high doses of all other antipsychotics, was associated with an increased hospitalization risk.

Improving clozapine utilization will require multifaceted strategies, increasing clinician education on proper initiation, titration, and management of adverse effects, and achieving system-based reduction of non-evidence-based hematological monitoring schedules. Ethnicity-based dosing and titration schedules[3] require prospective validation.

Since clozapine treatment inevitably increases contact with health care providers due to hematologic exams and, sometimes, therapeutic blood level monitoring, RCTs should compare clozapine with long-acting injectable antipsychotics, including after antipsychotic treatment failure in patients with a first episode of schizophrenia. Ensuring adherence in the long-acting antipsychotic arm would help disentangle non-specific, adherence-increasing effects of clozapine related to patients' increased contact with health care providers from potentially specific effects of the drug responsible for its increased effectiveness in real-world studies.

Moreover, the finding that medium-dose aripiprazole augmentation of clozapine decreases hospitalization risk in real-world settings should be followed up by RCTs also investigating symptom reduction and improved functioning.

In patients with treatment-resistant schizophrenia, head-to-head RCTs are needed that compare muscarinic receptor agonists/positive allosteric modulators as monotherapy or augmentation treatment versus continuation of a failed dopamine receptor blocking antipsychotic or switch to another member of this class, or even versus clozapine or augmenting clozapine, as long as excessive cumulative anticholinergic burden can be avoided. Finally, clozapine also has unique efficacy for treatment-resistant bipolar disorder and other psychiatric conditions, indicating that improving clinicians' acceptability and confidence in its use could potentially improve outcomes of patients with other severe mental disorders.

Clozapine's unparalleled efficacy in treatment-resistant schizophrenia, anti-suicidal and mortality-reducing effects underscore its importance in psychiatric care. However, its unclear mechanisms of action, underutilization, delayed initiation, and complex safety profile highlight the need for improved education, research and systemic changes. Efforts should focus on expanding access to clozapine for appropriate patients, while increasing exploration of novel pharmacological strategies that could potentially offer similar efficacy with improved tolerability.

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What makes Internet-based interventions work?

Numerous studies, including controlled trials and ordinary clinical investigations, document that clinician-supported psychological treatments can be delivered online in a course format, not requiring scheduled real-time therapy sessions[1]. In fact, available research suggests that guided Internet-based psychological treatments can be as effective as face-to-face psychotherapies[2]. Not only Internet-delivered cognitive behavior therapy has been found to work, but also other psychotherapies, such as psychodynamic interventions[3].

Different technologies have been used and are currently being developed – as reviewed by Torous et al in this issue of the journal[4] – but their added value against text and video content is still uncertain. In fact, it is even not obvious how much technology adds in relation to providing treatment via text in a book format, as old-school therapist-supported bibliotherapy often has about the same effects as digital treatments, although with much smaller studies and less implementation[1]. Where more recent advancements will lead us, when artificial intelligence (AI) and digital phenotyping become increasingly used in research[4], remains an open question.

The way digital treatments should be presented is far from certain. First, it is tempting to shorten treatments, sometimes even presenting them in a single session format[5]. While such condensing of information may be useful for preventive purposes, it needs to be acknowledged that very brief treatments may lead to short processing time. From cognitive psychology we know that deep learning is less likely to occur if material is just briefly processed at a surface level.

Second, much effort has been placed on making treatments more attractive and persuasive. This can pay off, if it does not come at the expense of missing useful change strategies and intervention components. Game features can be added, but should not distract. Instead, educational aspects can make a difference: by focusing on strengthening learning of treatment content, both interactive features and gamification can be helpful[6].

Third, a long-standing discussion in the field of digital treat-

ments concerns the role of clinicians. This discussion involves not only guided treatments often being superior to purely self-guided interventions, but also patient preferences. Now we have the possibility of AI-therapists[4]: this is currently being investigated, as it is over and beyond what has previously been done with automated conversational agents, but challenges remain[4]. The question of patient preferences is relevant again in this respect, as it may be that at least a proportion of users prefer a "real person" and are sensitive to any cues suggesting that the AI-therapist is fake. On the other hand, with informed consent and well-trained models, it is also likely that, at least for some patients and conditions (for example insomnia), this will be a useful addition to our clinical services.

But what works for whom? This is the eternal question in all clinical and research settings, also from the user perspective, as patients make decisions informed by what they hear from their networks and also by research (albeit often indirectly through the press). Numerous studies on digital treatments have explored predictors of outcome. As with psychotherapies in general, there is limited evidence for most candidates (including also moderators and mediators of outcome). Biological markers have also been studied, but the relevant state of knowledge is far from being sufficiently robust[1]. A systematic review focusing on Internet interventions included 80 studies and a total of 88 predictors[7]. The authors reported that better adherence, credibility of the treatment, and patient-rated therapeutic working alliance did predict the outcome, which is pretty much in line with research on face-to-face psychotherapies. They also reported the fairly obvious correlation between high pre-treatment scores and more change, which is a natural consequence of data structure and not much informative for treatment planning.

Having been involved in many controlled trials, it is pretty obvious for me why we fail to find predictors. The reason is that we remove them from the studies by using inclusion and exclusion criteria. While the situation is somewhat better in regular clinical settings, the problem is still there, because of referral patterns and intake procedures which for very good reasons result in unsuitable patients not entering therapy. Added to that we have the self-selection bias, with more difficult patients not seeking treatment and not accepting the offer to receive treatment. Yet another problem is dropout[8]: while missing data can be handled by statistical models, they still make prediction models less stable, as it is the post-treatment outcome that we want to predict.

Despite this knowledge gap when it comes to prediction, the development and implementation of Internet-based cognitive behavior therapy is a success story[9]. It may for some readers be a surprising fact that we now have more evidence for Internet treatments than for regular face-to-face therapy for many conditions and disorders[1], at least when it comes to study size and quality of data. Yet, implementation lags behind, as it is still rather rare that Internet treatments are provided on a regular basis in clinical service settings worldwide. When it comes to other digital alternatives, such as mobile phone apps and virtual reality, they are often not evidence-based and seldom implemented in clinical settings. Use of technology in a blended format is fairly common when it comes to administration of services, but still rather rare in the form of combined technology and face-to-face treatments.

With a 25 year history of Internet-based cognitive behavior therapy, there are lessons learned that can help researchers and clinicians to achieve better outcomes. The top tips for successful Internet interventions are the following:

- Start with a proper full assessment. If a patient cannot complete the full pre-treatment questionnaires, he/she is very unlikely to be able to engage in and complete the treatment.
- Move fast. If a patient applies for treatment online, schedule him/her for interview, check him/her for suitability, and inform him/her about inclusion and start of treatment as soon as possible.
- Have a clear deadline for post-treatment assessment regardless of treatment completion and adherence. Schedule a phone meeting that will serve as a deadline.
- Technology should be user friendly and not crash. A good system is crucial and should work for different platforms (e.g., computer and phone).

In the future, more work will have to be done on global mental health and delivery of interventions in non-Western languages. AI will have to be fully investigated. Understudied and marginalized groups will have to come to focus. And, crucially, the treatment-demand gap will have to be reduced.

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The evolving field of digital mental health: current evidence and implementation issues for smartphone apps, generative artificial intelligence, and virtual reality

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The expanding domain of digital mental health is transitioning beyond traditional telehealth to incorporate smartphone apps, virtual reality, and generative artificial intelligence, including large language models. While industry setbacks and methodological critiques have highlighted gaps in evidence and challenges in scaling these technologies, emerging solutions rooted in co-design, rigorous evaluation, and implementation science offer promising pathways forward. This paper underscores the dual necessity of advancing the scientific foundations of digital mental health and increasing its real-world applicability through five themes. First, we discuss recent technological advances in digital phenotyping, virtual reality, and generative artificial intelligence. Progress in this latter area, specifically designed to create new outputs such as conversations and images, holds unique potential for the mental health field. Given the spread of smartphone apps, we then evaluate the evidence supporting their utility across various mental health contexts, including well-being, depression, anxiety, schizophrenia, eating disorders, and substance use disorders. This broad view of the field highlights the need for a new generation of more rigorous, placebo-controlled, and real-world studies. We subsequently explore engagement challenges that hamper all digital mental health tools, and propose solutions, including human support, digital navigators, just-in-time adaptive interventions, and personalized approaches. We then analyze implementation issues, emphasizing clinician engagement, service integration, and scalable delivery models. We finally consider the need to ensure that innovations work for all people and thus can bridge digital health disparities, reviewing the evidence on tailoring digital tools for historically marginalized populations and low- and middle-income countries. Regarding digital mental health innovations as tools to augment and extend care, we conclude that smartphone apps, virtual reality, and large language models can positively impact mental health care if deployed correctly.

Key words: Digital mental health, smartphone apps, virtual reality, generative artificial intelligence, large language models, engagement, implementation science, depression, anxiety, schizophrenia, eating disorders, substance use disorders

(World Psychiatry 2025;24:156–174)

The surge in telehealth related to the COVID-19 pandemic has transformed the behavioral health field[1-3], yet the nature of the emerging domain remains in flux. Synchronous telehealth (video visits) rapidly expanded access to care during the pandemic, and psychiatry recorded the highest use of these visits compared to other medical specialties[3]. However, the reliance of traditional telehealth on clinician availability limited scalability, and growth is already contracting. Recent data indicate that telehealth visits in 2024 were less than 50% of their COVID-19 peak[4]. Few clinics today offer fully virtual practices, with the majority instead providing a blend of online and in-person care options[5,6]. These changes are partly driven by unstable telehealth legislation[7], with many of the regulations that permitted the rapid move to telehealth during the pandemic now expired or in flux. But they also reflect a deeper concern that telehealth alone is insufficient to substantially increase access to care and quality of mental health services.

Asynchronous digital health – such as the use of smartphone apps, virtual reality, and generative artificial intelligence, including large language models (LLMs) – offers unique opportunities to scale care delivery. Unlike traditional telehealth, these tools can function as self-help, coach-guided, or clinician-led interventions, providing flexibility and accessibility outside of immediate clinician interactions[8]. While initial enthusiasm for these technologies remains high, a notable gap in robust, real-world evidence continues to preclude their integration into routine care[9]. Despite significant advancements since our early review published in this journal[1], recent industry failures and research critiques have highlighted the need for more rigorous approaches, including use of digital placebos in controlled trials, generalizable and pre-registered models, and greater transparency in data sharing[10-12]. Much of recent research has focused on how a particular app or artificial intelligence program might work, but has not produced mechanistic and generalizable evidence that the field can utilize to build a strong scientific base. These setbacks, however, lay the groundwork for a new generation of evidence-based digital innovations.

Hybrid models that utilize both traditional telehealth and asynchronous digital health reflect the latest evidence and represent a promising approach to increase access and quality of care. However, blending the use of novel technologies into care requires careful consideration. Emerging usage of digital navigators (technology coaches)[13] to supplement digital mental health interventions and support patients has gained attention with the growing recognition that self-help tools offer limited effectiveness without some degree of human support. The optimal dose and balance of human and digital support, delivered in new hybrid or blended formats, presents a new frontier. It also broadens the concept of digital health

from tools or products to care-delivery platforms. Already successful models have integrated dedicated digital mental health services in Australia[14,15], Denmark[16], Sweden[17], Norway[18], the US[19], and Canada[20], among others. While it is possible that artificial intelligence and LLMs could soon serve some of digital navigator features, the evidence remains scant today, and the importance of the human connection in mental health care should not be underestimated.

To explore the evolution of digital mental health and how this new generation of tools will work with humans to create superior outcomes, this review focuses on five key areas. First, it examines recent advances in smartphones, virtual reality, generative artificial intelligence, and LLMs. Second, it evaluates clinical outcomes for smartphone apps across common mental health conditions. Third, it explores engagement challenges hampering all digital mental health tools, and proposes several solutions. Fourth, it analyzes implementation strategies to support real-world adoption and scalability. Fifth, it addresses how current tools often fail to meet the needs of overlooked populations, including cultural minorities and those living in low-resource settings[21,22], and explores possible ways forward. Common threads across all five themes – around scientific rigor, real-world engagement, community partnerships, and blended-care models – reinforce the transformation of the field from creating tools to improving care.

Looking ahead, innovation in engagement strategies and implementation science will play pivotal roles in advancing the next generation of digital tools. Just-in-time adaptive interventions, digital phenotyping, and personalized approaches are gaining renewed attention for their potential to address long-standing challenges in adherence and effectiveness. This paper offers an optimistic perspective on the field's evolution, and a well-defined roadmap for the years to come.

RECENT TECHNOLOGICAL ADVANCES

Smartphone apps and digital phenotyping

Smartphone apps serving as therapeutics have gained traction, and several of them have been cleared as medical devices by the US Food and Drug Administration (FDA). However, the actual effectiveness of these apps in real-world conditions remains uncertain. To address this complex topic, a subsequent section of this paper will critically review the current evidence available across a range of mental health conditions.

The interest in smartphones extends beyond their potential to deliver apps and interventions. These same devices are also capable of surveying patients in real time, enabling ecological momentary assessment for the vast majority of the population. In addition, data from smartphone sensors can generate behavioral metrics (e.g., sleep patterns, sedentary periods) and information on environmental exposures (e.g., local temperature, light exposure, greenspace) that can provide personalized contexts and temporal trajectories for how individuals experience mental illness. Often referred to as digital phenotyping[23], recent evidence on this approach in youth[24] and adults[25,26] provides promising signals with clinical validity.

A recent review exploring machine learning applied to digital phenotyping noted that mood disorders, anxiety disorders, and schizophrenia spectrum disorders are the three most studied conditions across all health care, even beyond mental health[27]. Relapse detection in schizophrenia and symptom prediction in mood disorders have strong pilot results with replication and external validation[28-30] which provide promising generalizable clinical signals. The vast number of pilot studies suggest that digital phenotyping research should now move towards validation to determine clinical relevance, with larger sample sizes and longer duration studies[31]. Such ongoing efforts include the US National Institutes of Health's Accelerating Medicine Partnership Schizophrenia Study, capturing smartphone digital phenotyping data from over 40 sites around the world in people at clinical high risk for psychosis for up to 12 months[32].

While early evidence suggests that digital phenotyping is feasible and acceptable, key barriers in the field remain a lack of standards for data collection, data processing, and feature creation, with variable data streams derived from different models/brands of smartphones. For example, a recent review of digital phenotyping across mental health found that, even when generating seemingly uncontroversial behavioral features such as sleep duration, each study used a different combination of sensors and processing pipelines, so that comparison of results and generalizability of outcomes were challenging[33]. Efforts to externally validate digital phenotyping work thus remain limited[34].

While research using wearable devices is sometimes labeled as digital phenotyping, this work is best categorized as actigraphy and considered in the framing of that unique field. Core differences include additional needed hardware and results often unique to that hardware and supporting software. While each approach has its merits, digital phenotyping utilizes patients' existing smartphone devices, so it represents a scalable and low-cost method limited primarily by device variance and missing data. Wearable studies offer the benefit of devices with often superior sensors, but are more limited in terms of scalability and longer-term engagement. As smartphone technology and sensors improve, the two fields may continue to blend. Even today, several studies can simultaneously apply both digital phenotyping and wearable devices through Android's Health Connect and Apple HealthKit/SensorKit features.

Given that successful digital phenotyping can support a myriad of other digital health developments, ranging from just-in-time adaptive interventions to precision-guided medication selection, success here will benefit the entire field. A focus on standards around both data collection and data processing in the mental health field, mirroring advances in accelerometry studies generally[35], can generate better science and more synergistic advances. Likewise, standards around protecting privacy and data governance in this sensitive area can engender trust and patient interest in sharing their personal data for research.

Virtual reality

Virtual reality is emerging as a significant innovation in the field of mental health treatment[36]. In using immersive simulations, it addresses a key limitation of traditional mental health interventions, which are often restricted to clinical settings and rely on patients recalling experiences and subsequently applying therapeutic techniques in their daily lives[37]. A recent review of the field[36] found that a growing body of research supports the efficacy of virtual reality-based interventions across different mental health conditions.

The unique capacity of virtual reality to recreate real-world environments has been particularly effective in augmenting cognitive-behavioral therapy (CBT), otherwise known as VR-CBT[38]. The majority of randomized controlled trials (RCTs) of VR-CBT approaches have been conducted in anxiety disorders, with a recent meta-analysis finding that they were superior to waiting lists or psychoeducation controls[39]. However, significant heterogeneity between effect sizes was evident, and active comparisons yielded non-significant differences. A meta-analysis of VR-CBT for social anxiety disorder also demonstrated that it had superior effects compared to waitlist controls for anxiety symptoms and avoidance behaviors[40]. These findings parallel results from studies in other conditions, such as psychosis, post-traumatic stress disorder (PTSD) and specific phobias, which indicate that VR-CBT is generally as effective as traditional CBT[36,41-43].

Virtual reality treatments have also been developed to support psychosocial and functional recovery, with the majority of evidence in mental disorders where routine functioning is challenging, such as schizophrenia, autism, and attention-deficit/hyperactivity disorder (ADHD)[41,42,44-45]. In these conditions, virtual reality has been found to enhance everyday living skills, including social and vocational tasks, by providing a safe space to learn and practice in relevant scenarios[42,45]. However, results have been mixed: a recent RCT of a virtual reality treatment targeting social cognition in psychosis found no significant difference compared to an active virtual reality relaxation condition[46]. This mirrors the findings of another trial comparing VR-CBT targeting social behaviors with virtual reality relaxation in a psychosis sample, which also found no difference between these conditions[47].

Emerging evidence suggests that virtual reality can be effectively integrated into various therapeutic modalities by leveraging its capacity to represent visual stimuli and influence affective states within virtual environments. A recent systematic review[48] found that virtual reality-based relaxation interventions are equally or more effective than non-virtual reality approaches in reducing short-term stress and anxiety, with the added benefit of being more resource-efficient to deliver. Virtual reality has also shown promise in enhancing "third wave" CBT approaches such as mindfulness, acceptance and commitment therapy, and dialectical behavioral therapy (DBT), which have a focus on separating the self from mental events. Similarly, virtual reality-enhanced DBT has shown the potential to help individuals manage emotional dysregulation more effectively by practicing distress tolerance skills in immersive, controlled environments[49].

Despite extensive research supporting the efficacy of virtual reality treatments for various mental health conditions, there remain few consumer-ready applications available on the market. One of the primary challenges is scaling virtual reality interventions to reach a broader population cost-effectively. Although the technology is becoming more accessible, the expenses associated with high-quality hardware, software development, and clinician training remain significant barriers[50]. Additionally, strategies to make these interventions accessible in under-resourced areas are critical [21,51].

Generative artificial intelligence

Few innovations have garnered so much interest in mental health as generative artificial intelligence. This is a unique subset of artificial intelligence in that it can create novel content, such as conversations or images, based on data and patterns on which it has been trained. The public release of ChatGPT 3.5 unleashed interest in the topic and gave rise to a rush for mental health use.

A new generation of artificial intelligence-driven chatbots is becoming increasingly prevalent in digital mental health, evolving from early rule-based chatbots. However, these latter chatbots are still common, and a 2022 review suggested that, across all of health care, 96% of chatbots were driven by decision-tree-like logic and not actual artificial intelligence[52]. Those earlier systems, which relied on predefined scripts and decision trees, were helpful in controlled environments, but faced limitations in handling complex, real-world interactions. Their inability to process free-text inputs or maintain context in multi-turn conversations raised concerns about their broader applicability[1,52]. Examples include psychotherapy chatbots such as versions of *Wysa* and *Woebot*, which, despite their limitations, offered the advantage of predictability and reduced risk of errors. The importance of such reduced risk was highlighted in 2023, when a generative artificial intelligence code embedded in an eating disorder chatbot led it to make harmful statements to users, prompting its removal within days of its public release[53]. The underlying issues of bias, subtle errors, and more overt errors (often labeled as "hallucinations") must be considered in framing the potential of generative artificial intelligence models and assessing the evolving risks that must be weighed with the expanding benefits.

Recent advancements have shifted toward machine learning-powered models, particularly LLMs. These models, trained on vast datasets from the Internet and other sources, address many of the limitations of rule-based systems. Their ability to generate human-like responses has made them valuable not only as tools but also as virtual companions. Users appreciate their capacity to handle diverse inputs, exhibit personality traits, and respond empathetically, which makes them more effective for personalized mental health support. Research shows that LLMs can demonstrate consistent behavior across the Big Five personality traits[54], and even outperform humans in certain tasks, such as recognizing irony and false beliefs[55]. Furthermore, the multimodal capabilities of modern LLMs enable them to process not just text but also voice and image inputs[56,57], expanding their versatility in digital mental health.

Preliminary research has demonstrated the potential of LLMs across various stages of mental health care. While much of this work has not been replicated, these pilot studies underscore the broad range of applications. For prevention, LLMs can offer low-risk, personalized psychoeducation, effectively raising mental health awareness by utilizing high-quality resources[58,59]. For relapse or onset detection, LLMs show promise in risk prediction, with studies indicating that models such as GPT-4 can approach clinical accuracy in identifying suicidal ideation and other crisis indicators, though additional safety measures and bias mitigation are necessary[60-62]. In diagnosis, LLMs can facilitate data-driven assessments of mental health conditions, sometimes matching clinicians' ability, for instance in predicting depression scores based on clinical data[63]. For treatment optimization, LLMs can assist in medication selection and therapeutic interventions by leveraging patient-specific data to help clinicians make informed decisions[64,65]. In high-risk situations, such as crisis intervention, LLMs can provide elements of crisis counseling, although this use carries a higher risk of harm[60,66]. Finally, LLMs have been applied to deliver ongoing therapy and counseling, enhancing access to routine mental health services by analyzing past therapy outcomes to improve care[67,68].

Despite the growing popularity of LLM-powered chatbots for mental health support, this field remains underexplored at its current stage, particularly related to the lack of transparency in training data, explainability of models, and standardized evaluation methods[69]. All base models for LLMs have been trained, at least partially, on social media data. This is understandable given that the newest models need billions, and likely trillions, of parameters (data points) to learn from. But, in learning about mental health mainly from social media, these models have also learned about stigma and bias. This point was well illustrated in a 2022 paper showing a range of stigmatizing images generated in response to prompts around schizophrenia[70].

Studies have also pointed out that, while these models can perform some theory-of-mind tasks, they still struggle with more complex social reasoning, highlighting the gap between artificial intelligence-driven reasoning and human cognition[71]. Finally, while many models have been proposed to evaluate LLM chatbots on criteria ranging from ethics to efficiency, none are well utilized today, and no standard has emerged[72]. Thus, comparison between chatbots, let alone evaluation of evolving chatbots, remains a challenge.

While LLMs have shown promise in providing human-like companionship, their unpredictability remains a major challenge. LLMs highlight the therapeutic potential of conversation and the rule-based nature of human language, meaning that they can produce convincing conversations. However, psychiatry is less rule-based, with debates about nosology and etiology ongoing today. Thus, LLMs will continue to face challenges as they confront a relative dearth of high-quality training data. In the meantime, debates on the delineation between conversation vs. therapy and companionship vs. care will continue to shift. Anyway, regardless of where the line is drawn, it is clear that some people are already finding benefits in talking with LLMs.

The current uncertainty around the patient-facing use of LLMs contrasts with their rapidly evolving use around clinical documentation. While the subject of less media attention and research, the transformative potential of clinician-facing artificial intelligence tools should not be underestimated. There is already enthusiasm for nascent efforts to utilize LLMs to document clinical encounters [73,74], likely saving clinicians' hours per day of note-writing. Other efforts to use artificial intelligence in upskilling of non-clinicians, in training of clinicians, and in offering clinical decision support are also evolving[75-77], and could represent a paradigm shift in workforce and training while facilitating evidence- and measurement-based care.

With so many use cases and such rapid progress, LLMs have the potential to drive research and care trends in mental health, if the field can unify such work under clear standards and safety procedures. We have already seen the emergence of ethical issues calling international attention in relation to LLMs, including the eating disorder chatbot case[53] and a case with help-seeking people explicitly told that they were interacting with a human while it was actually a LLM[78]. Without such standards and safety considerations, impressive technical achievements by LLMs may find a limited role in clinical care beyond documentation.

SMARTPHONE APP INTERVENTIONS

Access to the Internet is now more common via smartphones than computers[79]. The number of smartphone mental health apps has been estimated at 10,000[80] and remains a dynamic landscape, with new apps frequently introduced and others disappearing from the marketplace[81]. Some apps, such as *PTSD Coach*[82], are still functional after several years, but most are far less stable. Since most research in the digital mental health field focuses on smartphone apps, we cover this issue in detail in this section.

While the clinical outcomes of studies are important to consider, any benefits, including those discussed below, must be considered along with risks. Adverse events are often not well reported in digital health studies, despite calls to change this[83-87]. In some cases, assumed adverse events – such as technology making people with schizophrenia paranoid or delusional – have been disproven through specific studies[85]. Of course, negative effects are not unique to apps, but have also been reported for Internet interventions[88], face-to-face psychotherapies[89], and virtual reality treatments[90].

Negative effects from apps can range from mild (e.g., frustration with glitches, boredom) to severe (e.g., symptom deterioration, onset of new symptoms, suicidal ideation). Concerns have been raised that current marketplace offerings have the potential to induce negative effects because many publicly available apps provide content that is either inaccurate or not grounded in evidence-based treatments[91]. It is difficult to quantify the extent of negative effects, given heterogeneous study designs, sample characteristics, and types of apps delivered. Yet, recent clinical trials in people with a severe mental illness have reported rates of negative effects to be as high as 20%[92-95].

This state of research on adverse events makes it difficult to in-

tegrate apps into clinical practice safely[83,96]. In particular, the degree to which adverse events, such as deterioration, are caused by the use of the smartphone device itself or other external factors may be difficult to understand[87,97]. Researchers involved in future clinical trials of apps should plan from the outset to build data-driven risk prediction models, because this would help ensure that relevant data are collected, enabling better opportunities to match patients to appropriate treatments safely.

Well-being enhancement apps

A significant proportion of people who download a mental health app report doing so to acquire adaptive psychological skills useful to improve their overall well-being[98]. Many well-being apps include meditation, especially mindfulness, practices as a prominent element. For example, during the COVID-19 pandemic, one app curation service reported that searches for mindfulness apps rose by nearly 2,500% compared to the 156% increase observed for depression-specific apps[99]. Investment in this space has flourished, with well over 99% of publicly available mental health-related apps marketing themselves as well-being and not health devices[100].

Several RCTs have reported positive effects of self-guided well-being apps on various adaptive psychological attributes, including emotion regulation[101], mindful awareness[102], psychological flexibility[103], subjective well-being[104], social functioning[105], and self-esteem[106]. However, recent meta-analyses have found that these apps produce modest improvements relative to control conditions on subjective quality of life, positive affect, general well-being, mindful awareness, psychological flexibility, and self-compassion[107-109]. Additional high-quality RCTs are needed to confirm the utility of well-being apps, as concerns about the quality of existing research have been raised around small sample sizes, inadequate control groups, high risk of bias, high attrition, and low adherence, which likely explain the different published findings[107,109].

Given that as few as 2% of publicly available well-being apps have scientific evidence supporting their feasibility and efficacy[110], research partnerships could quickly transform this crowded space. Research focusing on mechanisms of action could also be useful. There is evidence that some well-being apps may exert their effects through enhanced mindful awareness[102]. However, a similar degree of evidence has been reported for other possible mediators (e.g., purpose in life, cognitive defusion) of effects on psychological distress[111]. Since multiple mechanisms are likely to be at work, tailoring choice to individual users based on such potential mechanisms may usher in a new era of more rational use of these apps.

Depression and anxiety self-management

Depression and anxiety, at both diagnostic and sub-threshold levels, are the most prevalent mental health conditions, and are linked with significant impairments in psychological, social and occupational functioning[112]. Since few people with depression or anxiety have access to specialized psychological treatments[113], apps that are grounded in an evidence-based framework and offer credible skills, resources or tips have the potential to represent an accessible, cost-effective and viable option for users to manage their symptoms.

Alongside the proliferation of commercially available depression and anxiety apps[114,115], the number of RCTs evaluating these apps has grown exponentially in recent years. The largest and most recent available meta-analysis[114] identified 176 RCTs of standalone mental health apps for depressive or anxiety symptoms, 67% of which have been published since 2020. This meta-analysis found significant although small effects for mental health apps over control conditions in reducing depressive and generalized anxiety symptoms, which corroborates the findings of recent but more narrow meta-analyses on the effects of apps on these symptoms in specific contexts (e.g., mindfulness meditation apps only[116], clinically diagnosed depressed patients[117], the perinatal period[118]). The large meta-analysis[114] also found evidence from a smaller number of trials that apps may be beneficial for reducing social anxiety, obsessive-compulsive, post-traumatic stress, and acrophobia symptoms, although the findings were considered preliminary due to the small sample sizes and high risk of bias.

Research has recently sought to understand the characteristics of apps that make them more or less effective for depression and anxiety. Knowledge of the mechanisms involved and of "active ingredients" is critical for producing more efficient apps. Such mechanisms and components can be prioritized, added or refined, while the ineffective or redundant components can be discarded[119]. The above-mentioned recent meta-analysis[114] showed that effects were larger in trials that delivered apps based on CBT principles (compared to mindfulness or cognitive training) or containing chatbot technology or mood monitoring features. These components could offer greater personalization or foster emotional self-awareness, resulting in more significant clinical benefit.

One methodological design that can help identify effective components of an app is the factorial trial, in which participants are randomly assigned to the presence or absence of a particular treatment component. A factorial trial was recently conducted[120] to test the efficacy of five CBT skills (self-monitoring, cognitive restructuring, assertiveness training, behavioral activation, and problem-solving) delivered through the *Resilience Training* app in 1,093 university students with sub-threshold depression. The authors could not identify whether one CBT skill was more effective than another, as reductions in depressive symptoms were observed for all participants, regardless of the presence or absence of the five CBT skills. However, this trial is noteworthy, and it is encouraging to see further factorial trials on depression apps underway[121]. These trials will ideally shed light on active ingredients, generate hypotheses for future research, and inform the development of more effective self-management apps.

A consistent trend observed in recent research is that the provision of human guidance augments the effect sizes found for depression and anxiety apps[122]. This finding may be due to human support increasing app engagement, offering additional therapy, or mediating/moderating outcomes through the benefits of thera-

peutic alliance. The involvement of digital navigators may be useful in this respect. Moreover, the next generation of chatbots that can better personalize recommendations and simulate emotional and empathic responses may offer a novel and complementary approach to increase the efficacy of digital health tools[123].

Overall, the effects of depression and anxiety self-management apps are now established on the basis of nearly 200 trials, underscoring the need to use ongoing research opportunities for further advancements. Carefully designed studies focusing on mechanisms of change, the impact of engagement on clinical outcomes, the use of automated support systems, and integration into real-world settings will likely prove more valuable than additional trials confirming already available results.

Clinical management of mood disorders

Existing research has mostly focused on the effects of apps as a standalone, low-intensity intervention option among community or student samples screened for mild-to-moderate symptoms of depression. Less is known about the utility of apps in severe mood disorders.

New meta-analytic evidence suggests that apps may enhance the efficacy of conventional treatments for major depressive disorder. A systematic review[124] recently located five RCTs that assessed the added value of integrating apps into standard treatment for this disorder. From seven comparisons, a small but significant effect was found in favor of app-augmented treatment arms, which was robust after removing trials with high risk of bias. Although preliminary, these findings are promising and suggest that apps may offer an incremental benefit to standard care for major depression. Additional research is needed to identify the optimal timing, dosage and content to combine these interventions effectively with established approaches for maximum benefit.

The fluctuations in mood, cognition and behavior that characterize bipolar disorder support the use of data continuously collected through real-time approaches such as digital phenotyping, and indicate a possible value of apps to provide tailored treatment strategies. However, the clinical benefit of apps in the management of this disorder is currently unclear. A recent meta-analysis[125] identified seven RCTs that integrated monitoring apps in the treatment of bipolar disorder, concluding that there was no evidence that they assist in reducing the severity of depressive and manic symptoms. In fact, individual trials have found that, in some cases, monitoring apps may even increase the risk of depressive episodes[126] or be associated with an escalation in manic symptoms[127].

These findings led to recommendations from the International Society for Bipolar Disorders Big Data Task Force that future trials of monitoring apps should consider using more sensitive outcomes, such as mood instability, in addition to relapses and psychiatric hospitalizations[125]. Indeed, a more recent trial evaluating the *LiveWell* self-management app in 205 patients with bipolar disorder[128] found no difference in reduction of relapse risk for those assigned to the app relative to treatment as usual, but did detect positive effects on depressive symptoms and relational quality of life. Overall, while there are some promising trends in the use of monitoring apps for the clinical management of bipolar disorder [129], there is a clear need for further research aiming to better understand how, for whom, and under what set of circumstances these apps can be safely integrated into the clinical management of the disorder.

While the clinical focus of apps for management of mood disorders requires their integration into ordinary care, a core issue today is clinicians' hesitancy and limited awareness. For example, survey research[130] shows that two-thirds of health care providers have little to no knowledge about apps available for bipolar disorder, and only 10% of clinicians surveyed in another study perceived apps to be helpful for patients with severe depression[131], despite the abovementioned empirical evidence. Investment in workshops and educational videos that provide trustworthy, up-to-date information about apps could increase provider confidence[132-134].

Schizophrenia/psychosis

Smartphone technology represents a potential tool to increase access to care of people with schizophrenia, and has been studied as such for over a decade[135]. Concerns that app-assisted monitoring tools and interventions could increase paranoia and delusions are refuted by clear data suggesting that people with schizophrenia are receptive and eager to use smartphone technology as part of their treatment plan[85]. As a consequence, research on apps for early diagnosis, real-time monitoring, psychoeducation, lifestyle, relapse prevention, and intervention among people with schizophrenia has rapidly expanded in the last ten years[136].

Several RCTs of app-supported interventions in individuals with schizophrenia have found positive effects on important clinical outcomes, including reduced fear of relapse[137], and improvement of psychotic symptoms[138], cognitive functioning[139,140], depressive symptoms[141], and medication adherence[139]. However, not all trials have reported favorable results. For instance, incorporating an app that offered a toolbox of behavioral and cognitive skills (*PEAR-004*) conferred no added clinical benefit on symptom scores relative to a non-specific digital sham control among 112 patients with schizophrenia receiving antipsychotic medication[142]. Similarly, the delivery of the self-guided *Temstem* app, designed to provide coping skills to deal with voice hearing, was not superior to a placebo monitoring app in reducing voice hearing distress, and in increasing social functioning and control over voices, among 89 patients with severe mental illness[143]. Likewise, the CBT-informed *Actissist* app study reported no difference in outcomes for people with schizophrenia when compared to a mood-tracking app[144]. The *SlowMo*[145] and *Horyzons*[146] blended interventions also reported null primary results, but some effects on secondary outcomes were promising, underscoring both the potential of blended approaches and the need for more rigorous research.

A recent systematic review and meta-analysis of 26 RCTs considering smartphones and other digital technologies in people with

schizophrenia reported minimal effects, but found that these may increase when the technology is paired with human support[147]. The critical role of human support was highlighted in another recent review paper[148].

The potential for smartphone apps to address the significant physical health inequalities among people with schizophrenia is emerging as a new direction. While digital innovations for physical health have hitherto been neglected in this population, there are signs of renewed interest[149]. Encouragingly, findings of a recent review indicated that digital health behavior change interventions, including apps, were broadly feasible and acceptable to people with severe mental illness[150].

Even if apps are to be integrated into clinical care for schizophrenia spectrum disorders, concerns with their current accessibility and availability have been highlighted. A review of the marketplace[151] identified 25 apps aimed to support people with psychosis. Crucially, 19 of these apps were either non-functional, inaccessible without an access code, or contained outdated, stigmatizing or harmful information. Of the six easily accessible, appropriate and psychosis-specific marketplace apps, five exclusively provided psychoeducation content, while only one offered therapeutic and monitoring features. These findings suggest an urgent need for better translation of apps from research to the marketplace.

Eating disorders

As less than one-quarter of people with eating disorders have access to specialized treatment[152], our early review on digital mental health in this journal[1] highlighted the potential clinical value of apps for these conditions, as evidenced by a handful of RCTs finding CBT apps to be efficacious as either a standalone intervention or as an adjunct to traditional treatment services. Since then, research on apps for eating disorders has been relatively limited, which is surprising, given that these apps are in high demand and are met with great enthusiasm among this clinical population[153,154].

The need for more rigorous research on eating disorder apps has been highlighted recently[154]. A review of the marketplace identified 65 apps aimed to support the treatment of these disorders[154], whose quality was suboptimal, with 92% omitting key in-app features, and only 7% having any research support. Several RCTs evaluating eating disorder apps have emerged since that review. One trial delivered a blended CBT digital intervention for binge-eating disorder, comprised of a web program supported by a mobile app that enabled users to practice homework skills in daily life. The intervention group reported greater reductions in eating disorder symptoms and psychological distress than the control group[155]. Another trial[156] investigated whether a monitoring app enhanced the efficacy of a CBT web program in a symptomatic sample of 293 participants. While no between-group differences emerged on key symptoms, those allocated to the app-augmented intervention were less likely to drop out, suggesting that monitoring apps could help retain users for longer periods in this context.

Recent efforts have explored whether app-enabled micro-intervention prompts in high-risk settings could have therapeutic value in eating disorders. Juarascio et al[157] developed a just-in-time adaptive intervention that provided personalized skill recommendations in real time based on data recorded through digital monitoring mechanisms. In a small pilot trial[158], they compared the presence versus absence of the intervention among 56 patients with bulimia nervosa who were receiving standard CBT. The intervention demonstrated feasibility and acceptability, but did not produce a greater rate of symptom change, possibly because the study was underpowered. It is encouraging to see larger trials of just-in-time adaptive interventions for eating disorders in progress[159], which will ideally shed more light on whether these interventions offer clinical benefit to a population who find it difficult to forecast warning signs of symptom escalation and relapse.

Substance use disorders

People with a substance use disorder are typically reluctant to seek professional help, are prone to relapse, and find it difficult to anticipate those events that trigger cravings[160,161]. This, coupled with the fact that smartphone ownership is as high as 92% among people with these disorders[162], indicates the potential for apps to enhance treatment seeking, mental health literacy, and therapeutic outcomes in this clinical population.

While some of the earliest FDA clearances for apps were around substance use disorders, a 2020 report from the Institute for Clinical and Economic Review suggested that the underlying evidence for these early apps was poor[163]. However, since then, the empirical research exploring the role of apps for these disorders has been continually evolving. In the context of smoking, a recent meta-analysis[124] identified ten RCTs which tested whether apps can increase the efficacy of conventional treatment, and reported a significant moderate effect in favor of augmented treatment conditions. Another recent meta-analysis[164] examined the efficacy of apps as either a standalone or adjunctive intervention on smoking abstinence rates, finding no significant between-group difference from nine RCTs. However, follow-up analysis showed that apps produced higher rates of smoking cessation than control conditions when paired with pharmacotherapy, further demonstrating the potential for apps to augment conventional treatment approaches.

Comparatively, less research has been conducted on apps for other substance use disorders. A systematic review[165] of mobile interventions identified three pilot studies that focused on cannabis use, which all reported positive treatment effects. In contrast, some systematic reviews have synthesized evidence for smartphone interventions targeting risky alcohol use across distinct population groups, concluding that the evidence for their effectiveness is uncertain[166]. The clinical benefit of app-based just-in-time adaptive interventions specifically designed to target illicit substance use was recently summarized in a systematic review[167], which concluded that the evidence for their therapeutic value is mixed and that adequately powered efficacy trials are lacking.

Summary for apps across all conditions

From the rapidly evolving evidence base available, it emerges that app-based interventions have an established efficacy in the self-management of depression and anxiety, while the evidence is mixed concerning their role in well-being enhancement, clinical management of mood disorders, schizophrenia/psychosis, eating disorders, and substance use disorders.

Further research is obviously needed in order to study these interventions with more rigorous methods, such as digital placebos and factorial trial designs; to investigate the working mechanisms of these devices; to explore innovative ways to embed these technologies into practice to ensure that they meet their potential as scalable tools; and to build clinical prediction models helping to select the best available treatment approach for each patient given his/her profile and ongoing progress.

CHALLENGES IN ENGAGEMENT

One of the most widely cited challenges to the utilization of mental health digital tools is low engagement, which refers to a lack of uptake and/or poor adherence to interventions in service users[168,169]. Even among individuals who consent to participate in a study on a mental health app, as many as 50% never download the app[170]. Furthermore, those who download the app are unlikely to use it for more than a few days, and even fewer complete the entire treatment program. For example, one study found that nearly half of the participants allocated to the popular *Headspace* and *Smiling Mind* apps reported never using the app again after ten days[171]. Another study on *Headspace* found that only 2% of stressed employees completed all of the prescribed meditation sessions[172]. Engagement issues in mental health app trials appear to be a problem not localized to specific settings, populations or clinical groups[173].

Poor engagement is an even greater problem in real-world settings. Investigation of real-world objective data on user engagement with 93 popular mental health apps showed a median daily open rate of 4%, with around a 3% retention rate over a 30-day period[174]. A recent naturalistic evaluation[175] of the *HeadGear* depression app showed that, while there were over 26,000 new downloads over the study period, there were only 90 average active daily users, and less than 6% of those who commenced the 30-day challenge component of the app completed it in its entirety. Another recent study[176] examined objective engagement data from 158,930 individuals who downloaded the publicly available *MoodTools* app. Analyses showed that nearly 50% never logged into the app a second time, one-third of active sessions lasted between 0 and 10 seconds, and less than 1% of sessions occurred following a 3-month to 1-year period of inactivity.

Knowing the causes of low engagement is necessary for developing solutions. Factors likely contributing to low engagement include poor usability, lack of user-centric design, concerns about privacy, skepticism about benefits/usefulness, limited digital literacy skills, and lack of personalization features[169,177,178].

Addressing engagement through personalized fit and integration into daily life

Systematic reviews report that customizable, personalized content which aligns with users' values and culture supports better engagement[177,179], while one-size-fits-all approaches are less engaging[179,180]. Digital mental health interventions need to better align with users' needs and expectations[168,180], and be tailored to be inclusive for minority groups[181,182] and by age[183]. Customizable reminders and assessments are reported as beneficial to enhancing engagement[184,185]. It has been suggested[186] that personalized coaching could enable digital mental health interventions to better align with end users' needs.

Time constraints are often mentioned as considerable barriers to engagement with digital mental health interventions[179,180]. For example, a study[187] provided the following end-user perspective: "*I assume a lot of people who are in my situation are in a crazy schedule… and not always have appointments booked for you is good*". People often report forgetting about the digital intervention or struggling to engage with it, particularly during periods of stress, indicating some challenges in integrating these tools into daily life[185,188]. End-users are more likely to engage with digital mental health interventions when these are flexible and can be integrated into their daily routines[177,179-181,184,189].

Addressing engagement through inclusion and trust

Issues about safety continue to be raised as critical factors influencing end-user engagement with digital mental health interventions. Barriers include concerns over privacy[181,185], unauthorized access[181,183], data security and protection[181,183], and lack of confidentiality[179,181-184]. For example, an older person reported[190]: "*Websites being hacked, people's personal details being hacked, y'know it's nothing, nothing is safe. Nothing is secure – and I know that nothing on the web is 100% safe, it can't be*". Greater trust in digital tools can be fostered by providing secure ways to record information[181], and assuring strong data protection measures[183] and clear communication of privacy settings[181,184].

Recent efforts to address these engagement barriers have shown encouraging results. Using co-design principles by gathering the target population's needs, preferences and feedback has generated mental health apps with higher ratings of usability, satisfaction and adherence[177,179,188]. Delivery of acceptance-facilitating interventions – such as training or brief educational videos that provide trustworthy information about the role of digital interventions and address common concerns and misconceptions – has been shown to enhance motivation, positive attitudes and self-efficacy, and reduce digital anxiety, security concerns, and skepticism[133,191,192], which appears to translate into greater uptake and adherence[193].

Addressing engagement through human support: from technical support to coaching

Technical issues – including bugs, usability and accessibility challenges – are major barriers hindering engagement[177,180,182,189]. One young person highlighted[194]: "*So yeah, because I'm not a technical person at all… that's the only downside of it, if it doesn't work okay, then it has quite an impact*". Barriers to engagement include problems with Internet connection ("*Because if Internet connection is not great and you click next then it takes a while for the next page to come up and you know it gets frustrating*"[176]) and digital mental health interventions not being accessible on a smartphone ("*The pages weren't phone friendly – lots of scrolling left to right*"[195]). Rural participants face unique barriers in terms of limited Internet access and poor connectivity[177,184].

Multiple reviews report that professional guidance – whether from therapists, coaches, counselors, or other health professionals – is crucial for user engagement and adherence[177,179,182,183,186,188]. End-users consistently prefer digital mental health interventions that include professional support, finding these more engaging and safer than unguided or self-guided interventions, which could be viewed as impersonal or distressing[177,183-185,189,196]. Some reviews report that end-users prefer a digital mental health intervention as a complement to existing, in-person therapy rather than a replacement[177,185]. For instance, a qualitative study with veterans highlighted that most participants who had used a digital intervention (*PTSD Coach Australia*) had done so as an adjunct to therapy, as it was "*more helpful if you are seeing a psychologist or psychiatrist*"[197]. Importantly, however, negative attitudes from health care providers could diminish end-user engagement[181].

Including human support in digital mental health interventions may be flexible. For example, therapists could be directly involved in facilitating interventions or providing reminders[177]. Some end-users report satisfaction with instantaneous support through digital channels such as chat or email[179], while others emphasize the value of structured interactions with coaches[186]. Infrequent or delayed responses from professionals are reported barriers to engagement[179]. Regular interactions and personalization of feedback from professionals during delivery of digital mental health interventions are found by end-users to be essential for maintaining engagement and feeling supported[179,180,183,186,188]. This reinforces the potential of roles such as that of digital navigators[11,13] in improving engagement rates and therapeutic outcomes[198].

Addressing engagement through just-in-time adaptive interventions

Just-in-time adaptive interventions are an innovative approach that leverages mobile devices to collect real-time data from sensors or user input, allowing them to deliver brief, tailored "micro-interventions" at precise moments when individuals are most in need or receptive to support[199]. For example, an intervention of this kind was designed to support smoking cessation by delivering brief mindfulness exercises when individuals reported increased negative affect or smoking behaviors[200]. By aligning support with the user's immediate needs, just-in-time adaptive interventions may enhance the effectiveness and engagement of treatment through increased personalization.

Although numerous trials have been conducted of just-in-time adaptive interventions for health conditions[201], a significant research gap exists in the development and testing of these interventions for mental health problems. There has been some progress in mental health conditions where behavioral patterns are more discrete and measurable, such as eating disorders[202], suicide prevention[203], and addictive behaviors[204]. For example, a just-in-time adaptive intervention targeting opioid addiction in chronic pain prompted mindfulness exercises when stress was detected via a smartwatch[205]. A just-in-time adaptive intervention for youth depression and anxiety (*Mello*[206]), targeting repetitive negative thinking (rumination and worry), showed moderate to large effects over six weeks in a pilot RCT. Another pilot RCT of a just-in-time adaptive intervention for depressive rumination in adults found that the intervention showed greater improvement in rumination relative to a control condition[207]. Finally, a pilot trial of a just-in-time adaptive intervention targeting sleep in veterans found that using the app in conjunction with clinical support improved sleep outcomes[208].

While early results are promising, more development is needed alongside RCTs to thoroughly assess the efficacy of just-in-time adaptive interventions across a range of mental health conditions, and empirically determine whether they can increase engagement.

Addressing engagement through digital literacy

The effectiveness of digital mental health interventions has been closely tied to factors such as digital literacy, familiarity with technology, and availability of training[177]. Limited technological skills and low digital literacy among users are substantial barriers to effective usage of digital interventions[177,181,183-185,188], and these issues are compounded when end-users are confronted with technological barriers. Programs designed to teach digital literacy to people with serious mental illness have shown promising pilot results [209,210] and offer a tangible solution that should be expanded.

Positive beliefs about technology[177,188] and understanding its benefits[177] increase engagement, while low self-efficacy concerning using technology poses a challenge[183]. Increased exposure to technology improved the comfort of young First Nations people and their families over time with using digital mental health interventions[182]. Training and support are essential in improving digital skills, confidence and overall engagement with digital interventions, particularly for users initially struggling with technology[181,184].

Addressing engagement through social influence

Social influence is reported to play a critical role in end-user engagement with digital mental health interventions. Positive influ-

ence from peers and family consistently emerges as a factor encouraging initial adoption and sustained engagement[177,185,188]. Family involvement increases over time with repeated use of technology [182], and sharing tasks with family or friends supports end-users' regular practice[180]. However, the presence of family or caregivers may inhibit open discussion in older adults[183] and in community forums[179].

Social connectedness-related features in digital mental health interventions – such as peer support, community forums, and family involvement – are valued across studies and found to contribute to user retention[177,181,186]. However, these features might instead give rise to feelings of isolation and disengagement[179]. For example, one young person in a qualitative study commented[212]: "*I felt even if I had something to say, I didn't feel comfortable saying it. I wasn't sure if I wrote something it'd make it worse, or I'm not sure how to feel about giving other people advice*".

CHALLENGES IN IMPLEMENTATION

Translating evidence-based practices into real-world use is an increasingly recognized challenge in mental health research[213]. Notoriously, fewer than 50% of clinical innovations are adopted in practice, and those that are adopted often take up to 17-20 years to do so[214]. This challenge is particularly critical in digital mental health, where the perceived benefits of accessibility, reach and scalability are key drivers of interest, funding and innovation, but few examples of implementation success exist[215,216]. This underscores the need for systematic approaches to bridge the knowledge-practice gap in digital mental health. Implementation science provides these approaches, employing a variety of key theories, models and frameworks[217].

Barriers and facilitators in digital tool implementation

A growing body of research has identified barriers and facilitators at multiple levels in implementation of digital mental health interventions, aligning with the domains outlined in key frameworks such as the Consolidated Framework for Implementation Research[218].

Practitioner level

Clinical staff of mental health services can play a critical role in translating digital mental health interventions into routine care. Factors influencing clinicians' motivation, capability and opportunity are key to successful implementation[219-221].

Despite high interest in digital support generated by the COVID-19 pandemic[1,220], negative perceptions – such as concerns about the quality of digital interventions compared to face-to-face care, and privacy issues – remain significant barriers[181]. Moreover, poor digital literacy and lack of confidence in using digital tools[221,222] can impede clinician adoption, which is compounded by concerns about safety and risk management in digital spaces[223,224]. Further, concerns about the potential impact on the therapeutic relationship, with digital interventions often perceived as impersonal or "cold", also act as barriers[223-226].

Like many professionals with established competencies, clinicians can resist changes to practice, creating an additional obstacle[20,224,227]. This highlights the importance of training in the digital space, which has not kept pace with the rapid development of digital tools and their growing evidence base, especially around generative artificial intelligence and LLMs[228]. While training is among the most cited facilitators for digital implementation at the clinician level[181], recent research reveals a lack of content concerning digital mental health interventions within clinical training programs[229]. Moreover, the high-stress, high-demand nature of many mental health services, and the high burden placed on clinicians, must be acknowledged, which may limit opportunities to learn, understand and integrate digital interventions[20,223,224], further emphasizing the need for digital competency training to occur before clinicians are recruited in mental health services. The above factors also affect motivation, capability and opportunity at the leadership level, where a lack of active support or resources for digital implementation can create significant barriers within services[222,224,230].

Practitioner-level facilitators include training, co-design and co-production with clinicians[226], and a belief in a digital future for mental health care[181]. Involving clinicians in the design process increases their buy-in and ensures that digital tools enhance their work meaningfully. Motivated, innovation-minded leaders who demonstrate, model and are accountable are also critical to driving implementation[20]. In addition, integrating digital mental health into curricula for trainee clinicians would build digital competencies earlier and help shift expectations around future clinical roles, addressing some of the barriers to digital adoption. Together, these strategies can address individual-level barriers and create a workforce better equipped to embrace digital transformation in mental health care.

Service level

Several service level determinants relate to both the characteristics of the setting and the factors involved in implementation delivery. Significant barriers are the lack of alignment between digital mental health interventions and existing workflows, the compatibility between digital and face-to-face care[181], and the perceived priority of digital interventions compared to critical clinical tasks, such as responding to emergencies[20,222,224]. Although interoperability and integration with existing technology systems are proposed as solutions, real-world examples remain scarce, due to the high complexity and variability of technological systems used in care settings.

The value of co-designing digital tools with service stakeholders is clear. In the same way that the field now recognizes the impor-

tance of user-centered design and participatory research in the development and evaluation of digital mental health interventions, an early understanding of contextual factors is key to scalability models that include integration and implementation. The involvement of service stakeholders can better support a fit between technology and practice, and ensure that digital tools enhance and complement, rather than compete with, clinical tasks.

The availability and reliability of technology in mental health services – especially in remote or low-resource areas – is a further barrier[222]. Moreover, staff shortage and personnel turnover also hinder implementation and sustainability, as those who have developed expertise and confidence in digital mental health interventions may be replaced by less experienced professionals[20,224], underscoring the key role of training programs conducted before clinicians are recruited in services[229].

Service setting implementation facilitators include adequate resourcing, infrastructure and staffing[181], as well as collaboration and communication between team members or service staff[221,225]. New roles such as that of digital navigators, discussed above, may also help alleviate the staffing issues when clinicians need support to utilize digital mental health technologies in care optimally.

System level

System level barriers include policy, regulatory and financial issues. Regulatory and reimbursement frameworks remain an ongoing challenge. Unclear, restrictive and not fit-for-purpose regulations pose barriers to digital mental health implementation[223,226]. Conversely, regulations that mandate privacy and data protection can shape the digital health ecosystem, influencing confidence in digital mental health interventions among both clinicians and users.

The certification or endorsement of specific interventions can facilitate their implementation, alongside their integration in clinical guidelines[226]. In many Western countries, such as the US and Australia, regulatory agencies do not actively enforce regulatory or certification requirements for digital interventions that fall under the wellness or low-risk sphere. However, the regulatory landscape is evolving rapidly. For example, the UK National Health Service and the Australian government have introduced frameworks such as the Digital Technology Assessment Criteria[230] and the National Safety and Quality Digital Mental Health Standards[231], respectively, with significant implications for future government funding.

In Germany, the Digital Health Application (DiGA) system has linked regulatory approval with reimbursement[232]. The US FDA has recently issued several new guidances[233,234] for digital health technologies that are likely to preview future regulation and enforcement. Decisions are being made regarding whether the recently announced US Medicare billing codes to reimburse digital mental health interventions will stipulate that these interventions must be FDA-cleared to qualify for reimbursement[235]. Thus, the regulatory and reimbursement space is dynamic, with frequent consultation and revision, indicating that, while progress is being made, keeping abreast of developments requires close monitoring of relevant policies and processes.

New developments

The above-mentioned barriers and facilitators have focused on the implementation of digital mental health interventions into mental health care settings, reflecting the predominant focus of current research and scoping efforts. However, a nascent literature also exists exploring the integration of these interventions across schools and educational environments, workplaces, and community services[236]. Given the flexibility and adaptability of digital interventions to "meet people where they are", it is crucial for implementation research to extend beyond traditional care settings.

Further, most progress in digital mental health implementation research has been in identifying and understanding barriers and facilitators. Less is known about which implementation strategies may facilitate real-world use, and under what conditions[215,237]. A recent notable exception is the *ImpleMentAll* trial, which tested a tailored implementation toolkit for Internet-based CBT (iCBT) against "implementation as usual" across Europe and Australia[216]. Results indicated that the toolkit had a small but statistically significant effect on the degree to which iCBT is considered a normal part of work within the context. While this study provides valuable evidence and resources for tailored implementation, detailed insights into how the tailored strategy differed from "implementation as usual" has yet to be published.

To support research on implementation strategies and outcomes in the digital space, methods of the traditional research pipeline should be replaced by methods that develop and test digital mental health interventions within the real-world contexts in which they will be implemented or scaled[213]. One such design is the hybrid implementation-effectiveness trial, which evaluates both effectiveness and implementation to varying degrees[238]. By adopting these and other novel methodologies and involving multidisciplinary teams – including key stakeholders and implementation scientists – the next generation of digital mental health interventions, particularly in expanding areas such as artificial intelligence and virtual reality, can have a more solid foundation for implementation and impact at scale.

DIGITAL MENTAL HEALTH FOR MINORITIES AND LOW-RESOURCE CONTEXTS

The potential of digital mental health to increase access to care is often discussed around serving the unmet needs for care in historically marginalized communities, cultural minorities, and low-resource settings. However, digital approaches could have unintended effects of exclusion without a concomitant focus on digital access and literacy. This section reviews how digital mental health is evolving to meet these important needs and ensure that no patients are left behind.

Historically marginalized communities and cultural minorities

Communities historically affected by discrimination, marginalization and stigma – e.g., racial and ethnic minorities; lesbian, gay, bisexual, transgender, queer/questioning (LGBTQ+) populations; and low-income communities – experience disparities in mental health access and treatment. For instance, although these minorities tend to have a higher prevalence of common mental health problems, they are less likely to seek professional mental health treatment and more likely to prematurely drop out when they are in care, as well as to experience persistent symptoms[239-242]. Blacks, Asians and Hispanics/Latinos are also more likely to receive a diagnosis of severe mental disorder when they seek mental health services[242]. If implemented skillfully, the rise of digital mental health may help reduce such disparities by increasing access to care, reducing cost, removing the stigma associated with seeking mental health care in in-person settings, and engaging underserved communities[243,244].

Research on mental health apps not customized for these populations suggests that they have not fulfilled the promise of broadening access and utilization. A recent study on a freely available meditation app found that African Americans were much less likely to access and utilize the app[245]. As evidence from psychotherapy research consistently shows, culturally tailored interventions are more efficacious than non-tailored ones[246]. Effectively tailored efforts that appeal to and engage people from underserved communities will be critical in digital mental health as well. A recent systematic review and meta-analysis[247] found that culturally adapted digital mental health interventions for racial and ethnic minorities produced a large and significant effect across outcomes (g=0.90) compared to waitlist and treatment-as-usual conditions, although the average attrition was somewhat high (42%). A lack of research with Black and Indigenous populations was highlighted. Tailored digital mental health programs have also been piloted in sexual and gender minorities, a population heavily affected by discrimination, stigma, early life adversity, and more prevalent mental health concerns compared to their heterosexual counterparts[248-250].

Improving access and engagement is one of the most important challenges for digital mental health program designers when tailoring such efforts to underserved communities. To this end, employing participatory designs, such as the community-based participatory research method, may be fruitful in developing community-specific, culturally relevant content and improving delivery design (e.g., frequency, dosage) and engagement strategies (e.g., reminders, peer interventions, personalized messages)[251]. This may be particularly pertinent to historically marginalized communities to overcome potential barriers such as mistrust of traditional health care systems and medical research, stigma in seeking and receiving mental health services, and literacy and language-related issues.

The development and evaluation of digital mental health interventions for historically marginalized populations are still in their infancy, and much work is needed to understand the best approaches to digital mental health for subgroups of minority populations and outcomes. With the advancement and growth of technology, using artificial intelligence and machine learning in digital mental health with marginalized individuals and groups has been an area of both promise and caution, and requires deeper and purposeful research. For instance, a recent study evaluated a personalized artificial intelligence-facilitated self-referral chatbot in the UK, and found that increases in referrals were particularly pronounced among gender non-binary and ethnic minority individuals, with the participants' need for treatment as well as the chatbot's human-free nature (thus reducing the likelihood of stigmatizing interactions with a provider) being potential contributors[252].

Despite the promise of artificial intelligence and machine learning for personalized interventions, they could exacerbate health disparities by displaying biases against marginalized and underserved groups due to algorithms and predictions built on data that reflect social biases[253]. For example, diagnostic algorithms built on historical data might be more likely to suggest diagnoses of severe mental disorders for Black/African Americans despite displaying similar symptoms to their non-Hispanic White peers. Validating computational models with minority populations, training artificial intelligence to overcome social biases, and exploring how artificial intelligence and machine learning may facilitate or hinder addressing factors that lead to mental health disparities, including structural inequalities, are important issues for this area in the future.

Low- and middle-income countries and low-resource settings

Globally, there are significant disparities in access to mental health care, and the World Health Organization (WHO) has called for action to address this inequality as a major global health challenge[254]. It is estimated that 76-85% of severe mental health cases in low- and middle-income countries (LMICs) do not receive treatment due to the scarcity of resources and trained professionals[255]. Today, people in LMICs increasingly own smartphones and want to use them towards health[256]. However, research in digital mental health remains relatively scarce. A systematic review conducted in 2020 found 22 controlled studies that employed mobile/Internet-based psychological interventions in LMIC settings, with the majority conducted in Asia (59%) and focusing on adults with elevated depression, anxiety, PTSD or substance use symptoms[257].

Another systematic review[258] uncovered 55 studies (including those with only qualitative reports) that conducted cultural adaptation of Internet- and mobile-based mental health interventions in LMIC settings, or with migrants and Indigenous people in high-income countries. The study provided a taxonomy of 17 components of cultural adaptation that range from content to methodological (e.g., functions, aesthetics) and procedural (e.g., who is involved, how information is gathered) aspects, and highlighted the complexity in situating and tailoring digital interventions in new cultural contexts. Further evidence from more diverse regions and populations is needed.

In addition to digital mental health tools in direct clinical roles,

there is also great potential for digital interventions to address training needs, reduce the burden of care for providers and mental health care systems, and build local capacity in low-resource LMIC settings. This may include engaging lay providers (i.e., digital navigators) as part of the prevention-to-treatment spectrum of care[259]. For example, to address the surge of suicide among adolescents in China[260] and the lack of resources in rural school systems in that country, a localized gatekeeper for teachers program was developed and delivered via digital training[261]. In India, the EMPOWER study[262] uses digital tools for training and supervising non-specialist providers. A 2024 review of digital psychiatry in LMIC countries offers further examples[256].

Another relevant area for digital mental health globally is its application for people and communities affected by the growing number of wars and conflicts[263]. To this end, digital mental health may offer scalable solutions to address accessibility issues and provide needed real-time support. Examples of this work include a recent RCT of a WHO-guided digital health intervention for depression (*Step by Step*) for Syrian refugees in Lebanon[264], and an RCT with refugees in Germany[265] which found that a hybrid approach (combining digital treatment with in-person intervention based on symptom severity) was sustainable and cost-effective for depression. A recent review of digital mental health interventions for children and adolescents affected by war found that most interventions suffered from gaps, including that most programs were not culturally or linguistically adapted to their contexts[266]. Appropriate contextual tailoring often takes time and resources, and how to best adapt an evidence-based digital health intervention for conflict-affected communities in times of need remains a challenge. Evaluating and ensuring that such interventions are not only efficacious but also scalable is critical, given the large refugee and migrant populations in need of care.

Given the significant need for addressing mental health needs in LMIC settings and the limited resources, digital mental health efforts in these contexts should adopt a population health approach and expand beyond an individual patient focus. This may involve public education to raise awareness of mental health and reduce stigma, as well as engaging key people in communities, schools, and family and work settings[267]. Employing implementation science perspectives and engaging with policy makers early in the research process could also be beneficial to scaling up effective programs, increasing impact, and fostering translation from empirical evidence to practice[268,269].

CONCLUSIONS

The digital mental health space is rapidly growing far beyond traditional telehealth visits. New tools such as LLMs have rapidly emerged, while relatively older ones such as smartphone apps and virtual reality have quickly expanded. While each tool has offered evidence of clinical impact, broad real-world impact remains aloof for all. This paper has highlighted many of the factors involved and proposed actionable solutions. While it is impossible to summarize such a vast and evolving space neatly, two key points around the scientific nature of digital health research and real-world engagement must be highlighted.

First, the vast majority of research reviewed in this paper focused on individual products, particular apps, unique virtual reality programs, and specific LLM models. This focus on digital health as a tool instead of the generalizable principles behind the tools has hindered scientific progress. Clinical research requires synergies, which remain limited in the digital mental health field because of a lack of common metrics and, in part, a lack of shared tools/softwares.

Second, results of our review underscore that the human connection supporting any of these technologies is critical for real-world impact outside of research studies. The next generation of digital tools must be better co-designed, personalized, and responsive to patient needs. These tools must also be studied, beyond efficacy trials, through methods prioritizing external validity and generalizability, such as hybrid research designs guided by implementation science frameworks. With this approach, new tools may better engage clinicians and achieve integration into complex clinical systems.

There are many pathways to improved clinical research and real-world use of digital mental health tools. The extent to which future digital mental health interventions will be genuinely beneficial for people with mental health conditions will directly reflect the intersection of progress across those two domains.

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Bipolar II disorder: a state-of-the-art review

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Bipolar II disorder (BD-II) is currently identified by both the DSM-5 and ICD-11 as a distinct subtype of bipolar disorder, defined by at least one depressive episode and at least one hypomanic episode, with no history of mania. Despite its prevalence and impact, the literature on BD-II remains relatively sparse. This paper provides a comprehensive overview of the available research and current debate on the disorder, including its diagnostic criteria, clinical presentations, comorbidities, epidemiology, risk factors, and treatment strategies. Patients with BD-II often present with recurrent depressive episodes, which outnumber hypomanic episodes by a ratio of 39:1. The condition is therefore often misdiagnosed as major depressive disorder and treated with antidepressant monotherapy, which may worsen its prognosis. The recognition of BD-II is further complicated by the overlap of its symptoms with other disorders, in particular borderline personality disorder. Although BD-II is often perceived as a less severe form of bipolar disorder, evidence suggests significant functional and cognitive impairment, accompanied by an elevated risk of suicidal behavior, including a rate of completed suicide at least equivalent to that observed in bipolar I disorder (BD-I). Psychiatric comorbidities, in particular anxiety and substance use disorders, are common. The disorder is associated with a high prevalence of numerous physical comorbidities, with a particularly high risk of comorbid cardiovascular diseases. Various genetic and environmental risk factors have been identified. Inflammation, circadian rhythm dysregulation and mitochondrial dysfunction are being studied as potential pathophysiological mechanisms. Current treatment guidelines, often extrapolated from BD-I and depression research, may not fully address the unique aspects of BD-II. Nevertheless, substantial evidence supports the value of some pharmacological treatments – primarily mood stabilizers and atypical antipsychotics – augmented by psychoeducation, cognitive behavioral or interpersonal and social rhythm therapy, and lifestyle interventions. Further research on BD-II should be a priority, in order to refine diagnostic criteria, identify potentially modifiable risk factors, and develop targeted interventions.

Key words: Bipolar disorder, bipolar II disorder, depression, hypomania, misdiagnosis, mixed states, suicidal behavior, borderline personality disorder, mitochondrial dysfunction, mood stabilizers, psychoeducation

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The conceptualization of bipolar disorder (BD) has evolved significantly over time, transitioning from early descriptions of "manic depressive insanity" to a more nuanced understanding of the condition as presenting across a spectrum[1]. The expression "bipolar disorder" was coined in the 20th century to reflect the biphasic nature of mood dysregulation, oscillating between manic and depressive states. The term "hypomania" was first introduced in the DSM-III to describe a syndrome similar but less severe than mania[2]. The DSM-III also introduced the concept of "atypical bipolar disorder" to account for individuals who did not fit neatly into the BD or cyclothymic disorder categories, and it was in this context that the term "bipolar II" was first used[2]. This framing laid the groundwork for the later conceptualization of bipolar II disorder (BD-II) as a distinct clinical entity within the mood disorder spectrum[3], identified as such for the first time in 1994 in the DSM-IV[4].

Since its introduction, BD-II has spurred controversy concerning its diagnostic boundaries and clinical utility[5], also as part of the more general debate about the dimensional vs. categorical approach to diagnosis in psychiatry. Indeed, it has been sometimes argued that bipolar disorder may be better conceptualized as just one diagnostic entity with variations in its expression across individuals[6]. However, BD-II is now widely accepted and recognized as a distinct and valid diagnostic category[7-11].

Studies have consistently documented that BD-II is underdiagnosed[12,13]. For example, the Jorvi Bipolar Study[14] screened 1,630 psychiatric outpatients and found that half of the BD-II cases were previously undiagnosed, with a median delay of almost 8 years from the first episode to diagnosis. Delay in diagnosis can result in progression of illness and provision of inappropriate and potentially iatrogenic treatment. This can compromise the patient's well-being, impede recovery, and affect quality of life[15,16].

Contrary to the perception that BD-II is a milder form of BD, research indicates that patients often suffer from high depressive burden[17-19], poor functioning, and poor clinical outcomes[20-26]. In addition, recent analyses of mortality data indicate that the overall suicide rate and lethality index of suicide attempts in BD-II are similar to or greater than in bipolar I disorder (BD-I)[26,27].

Compared to BD-I, BD-II is still substantially understudied[28,29]. Despite its prevalence and impact, the literature remains relatively sparse, particularly in relation to treatment strategies. This paper aims to provide a comprehensive picture of the available research and current debate on BD-II, by reviewing its diagnostic criteria, clinical presentations, comorbidities, epidemiology, risk factors, and treatment strategies.

DIAGNOSTIC CRITERIA

BD-II is identified as a subtype of BD in both the DSM-5[30] and ICD-11[31], defined by at least one depressive episode and at least one hypomanic episode, with no history of mania. Both systems specify that during the hypomanic episode there is no marked im-

pairment in social or occupational functioning. The DSM-5 criteria for hypomanic episode also require that the episode is not severe enough to necessitate hospitalization, and that there should not be psychotic features (otherwise the episode should be diagnosed as manic). The ICD-11 diagnostic requirements similarly specify that mood disturbance in the hypomanic episode "is not accompanied by delusions or hallucinations"[31], while the fact that the hypomanic episode does not "require intensive treatment (e.g., hospitalization)" is mentioned in the section on the differential diagnosis with a manic episode[31].

In both systems, the symptomatic picture of the hypomanic episode is exactly the same as that of the manic episode (although in the ICD-11 the wording is slightly different in the two descriptions), so that the two episodes differ only in terms of severity. This fact has been subject to some criticism in the past (e.g., "the signs and symptoms of hypomanic episodes as described in DSM-IV are insufficiently discriminatory from those for mania"[32]), but possible qualitative differences between manic and hypomanic episodes have not been clarified. It has been sometimes pointed out that increased goal-directed activity is the key feature of hypomania, even in the absence of a clear mood change[33]. Moreover, it has been noted that hypomanic episodes are often marked by dysphoria ("mixed hypomania"), reported to be more frequent in some clinical samples than euphoric mood[34].

In both diagnostic manuals there is a specification that the depressive episode must last for at least two weeks. For the hypomanic episode, the DSM-5 requires that the symptoms last at least four consecutive days, whereas in the ICD-11 the requirement is less specific ("at least several days"). The threshold of four days for the diagnosis of hypomanic episode has been debated in the past, and a threshold of two days has been instead proposed[32]. This proposal was supported by the observation that the rate of bipolar family history among bipolar II patients – identified by the two-day threshold – was similar to that of bipolar I patients and significantly higher than that of patients with major depressive disorder (MDD)[35]. This change in the threshold for the diagnosis of hypomanic episode was indeed considered within the process of development of the DSM-5, but finally rejected due to concerns about the increased risk of false positives[36].

Both the DSM-5 and ICD-11 specify the minimum number of symptoms in the depressive episode, whereas for the hypomanic episode this specification is only made in the DSM-5 (at least three symptoms in addition to elevated, expansive or irritable mood, and increased activity or energy), whereas in the ICD-11 the minimum number of additional symptoms is not made explicit ("several of the following symptoms").

In the ICD-11, it is acknowledged that "hypomanic episodes are often difficult to distinguish from normal periods of elevated mood", and it is underscored that "in order to be considered a hypomanic episode, the symptoms must represent a significant and noticeable change from the individual's typical mood and behavior"[31].

In fact, the issues of the boundary between hypomanic and manic episode, and between hypomanic episode and "normal periods of elevated mood", remain somewhat in flux. While BD is one of the most stable diagnoses in psychiatry[37-39], field trials for the DSM-5 found a concordance rate of 0.40 for a BD-II diagnosis compared to 0.56 for BD-I[40]. However, the interrater reliability for the diagnosis of BD-II was still higher than that for MDD (0.28)[40]. Moreover, the BD-II diagnosis reliably separates from that of BD-I in careful clinical interviews[41].

CLINICAL PRESENTATIONS

The accurate identification of BD-II is crucial for effective management, but this process is complicated by the overlap of symptoms with other disorders. Patients with BD-II often present with recurrent depressive episodes or symptoms, which outnumber hypomanic episodes or symptoms by a ratio of 39:1[17]. However, this ratio may in reality be lower, due to the underestimation or lack of identification of hypomanic episodes or symptoms[42]. Indeed, while there is a clear change in functioning that is observable by others during hypomanic episodes, the mood disturbance is by definition not severe enough to cause marked impairment in social or occupational functioning[43]. Further, many patients perceive hypomanic episodes as being pleasant and hence do not seek help during these periods. It is also possible that, in a mixed hypomanic episode, the patient believes that he/she is just irritable in the context of depression, without recognizing the presence of other hypomanic symptoms[12].

People with BD-II typically have their first encounter with the treatment system due to depression, which accounts for over 80% of the time ill[17,44]. Therefore, BD-II is frequently misdiagnosed as MDD and treated with antidepressant monotherapy, which may worsen the prognosis, and potentially increase the risk of suicide attempts[45]. The French EPIDEP study reported a BD-II rate of 40% among patients suffering from a major depressive episode when a DSM-IV-based semi-structured interview was used, which was significantly higher than the 22% rate at initial assessment[46].

A careful screening for history of previous hypomanic episodes must be conducted in all patients presenting with a major depressive episode. Further, since the diagnosis of BD-II requires careful clinical evaluation to distinguish it also from other conditions, such as borderline personality disorder and attention-deficit/hyperactivity disorder (ADHD)[47] (see below), detecting the episodic nature of hypomania and depression is crucial. Clinicians must assess not only the presence of symptoms, but also their pattern, duration and impact on functioning.

A greater likelihood of mixed states has been found in BD-II compared to BD-I[48], with estimates suggesting that up to 40% of individuals with BD-II experience these states at some point[34,49-51]. The presence of mixed states is associated with a more severe course of illness, including higher rates of comorbid anxiety and substance use disorders, increased risk of suicidal behavior, more frequent mood episode recurrences and rapid cycling, greater functional impairment, and reduced quality of life[52]. Accurate diagnosis and tailored treatment strategies are essential for managing mixed states effectively, which may include a lower threshold for admission[53-56].

DIFFERENTIAL DIAGNOSIS

Distinguishing hypomanic episodes from other conditions can be challenging. A key element in diagnosing BD-II is to establish a history of disordered mood episodes that represent a clear break from previous functioning, in contrast to the more constant symptoms seen in many other psychiatric conditions.

Major depressive disorder

Depressive episodes of BD-II and MDD both present with symptoms such as depressed mood, lack of interest and motivation, feelings of guilt or low self-esteem, decreased energy, impaired concentration, changes in appetite, psychomotor agitation or retardation, and suicidal thoughts or behavior. The diagnostic distinction relies on the occurrence of hypomania, which is absent in MDD but present in BD-II. To avoid missing BD-II, clinicians should routinely inquire about past episodes of hypomania in patients presenting with depression. Here, obtaining collateral information from family members is essential, as hypomanic symptoms might be more apparent to significant others than to the patient[33,57-61].

Several clinical features can increase the suspicion of an underlying bipolar diathesis in patients presenting with depression. These include the presence of multiple discrete episodes, abrupt onset and offset, psychotic symptoms, severe melancholic features, family history of BD, non-response to antidepressant medication, induction of hypomania by antidepressant medication, early age of onset, and seasonal patterns of mood disturbances[62-68]. These features have been referred to as the "bipolar signature"[69]. BD-II patients also experience more paranoia, anhedonia and guilt than those with MDD[63].

The presence of atypical depressive features – i.e., increased appetite, hypersomnia, agitation and heightened interpersonal sensitivity – is more common in BD-II than MDD[70-73]. Also, patients with BD-II have significantly more atypical symptoms in depression when compared to those with BD-I[74]. There is an approximately 35% prevalence of psychomotor agitation in BD-II depressive episodes[75]. Seasonal variations in mood, often associated with atypical features[76], are more pronounced in BD-II, with depressive symptoms observed to peak in winter and hypomanic symptoms in the fall[77,78]. Furthermore, people with BD-II have been found to be younger and more likely to be educated, compared to those with MDD[63].

Personality and temperament factors may further differentiate BD-II from MDD. Specifically, patients with BD-II exhibit higher levels of cyclothymic and hyperthymic temperaments[63], and are more likely to be sensation seekers[79] compared to those with MDD. They may also show higher irritability, anxious worrying, and self-criticism, and lower social avoidance[57,58]. Studies have found that BD-II patients have more Cluster B personality disorder diagnoses, ADHD, and substance use issues compared to those with MDD[63].

Borderline personality disorder

Differentiating BD-II from borderline personality disorder may pose significant clinical challenges, due to overlapping features such as suicidality, mood symptoms (especially depression), impulsivity, irritability, and risky behaviors. Misdiagnosis can impact treatment outcomes, as patients with borderline personality disorder may be incorrectly treated with biological therapies suited for BD-II rather than psychological therapies, and vice versa[80].

However, there are distinct differences in the presentation and course between these disorders that can aid in accurate diagnosis and appropriate treatment (see Figure 1). Affective instability, while a core feature of borderline personality disorder, is less common in BD-II, especially during periods of euthymia[81]. Also, this instability is often reactive to interpersonal stressors in patients with borderline personality disorder, while affective lability in BD-II tends to be more autonomous and internally driven[82].

People with borderline personality disorder often experience intense fears of abandonment, unstable relationships, chronic feel-

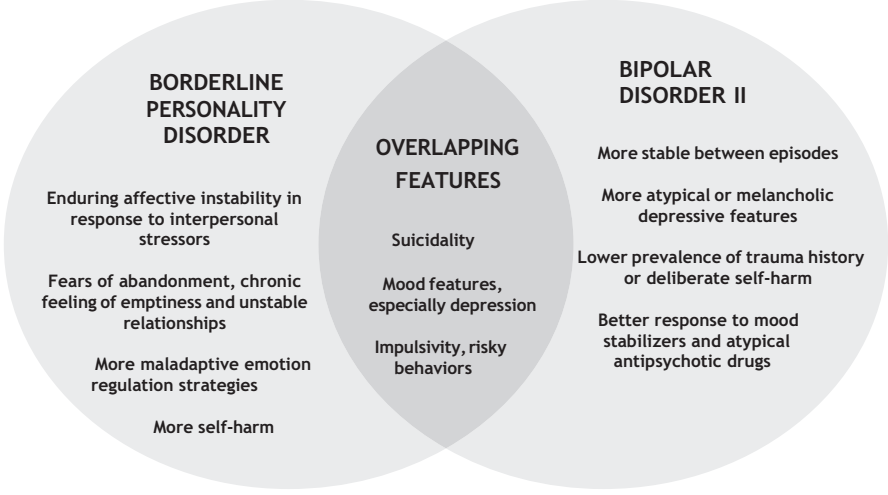

Figure 1 Comparison of symptoms between bipolar II disorder and borderline personality disorder

ings of emptiness, and use more maladaptive emotion regulation strategies compared to those with BD-II[83]. Depressive episodes in the context of BD-II are more frequently melancholic[84] or agitated [75], while depression comorbid with BPD is typically non-melancholic and reactive to interpersonal life events.

In BD-II, compared to borderline personality disorder, there is a lower prevalence of trauma history (although this is a risk factor for both conditions[85]), less likelihood of deliberate self-harm (except in mixed states or depression), more stable relationships, and less sensitivity to criticism[86]. The impulsivity in BD-II is related to hypomanic episodes, while in borderline personality disorder it is mood-independent. BD-II responds better to mood stabilizers and atypical antipsychotic drugs, whereas patients with borderline personality disorder benefit more from psychotherapies[80].

Other psychiatric conditions

BD-I is distinguished from BD-II by the presence of full manic episodes, with the possible occurrence of psychotic features, which are marked by severe functional impairment and may require hospitalization. Cyclothymia is characterized by a long-term (at least two years) pattern of numerous periods of hypomanic and depressive symptoms without meeting full criteria for hypomanic or depressive episodes. Anxiety disorders manifest with constant anxiety and worry, without episodic mood changes, and the presence of a variety of physical symptoms, without the mood elevation observed in hypomania. ADHD is marked by a persistent pattern of inattention and hyperactivity usually starting in childhood, without distinct mood episodes. Complex post-traumatic stress disorder occurs after the exposure to one or more events of a threatening or horrific nature, and is characterized by flashbacks or nightmares, and by heightened emotional responses, such as impulsivity or aggressiveness, but without clear mood episodes. Finally, in substance use disorders, mood changes typically follow substance use rather than occurring independently.

SCREENING

Several tools have been developed to screen for prior manic or hypomanic episodes, and for BD in general. The Mood Disorder Questionnaire (MDQ) is one of the most extensively studied screening tools for BD, with a reported sensitivity of about 60% and a specificity of 85%[87,88]. However, the MDQ has a higher sensitivity for detecting BD-I than BD-II[89]. Relatedly, it performs poorer in community settings than in clinical cohorts[90].

The Hypomania Checklist (HCL-32) was designed to capture the more subtle aspects of hypomania[91]. It has an estimated sensitivity of 80% and a specificity of around 60% in detecting prior hypomanic episodes[92]. It can be used in both clinical and community settings, allowing a broader application for screening purposes[93].

The Rapid Mood Screener (RMS) was developed to screen for BD-I[94]. It queries symptoms of hypomania/mania and depression, with a total of three items allocated to each. In a study aimed to screen for manic symptoms and bipolar I disorder features, when four or more items of the RMS were endorsed, BD-I was detected with a sensitivity of 0.88, a specificity of 0.80, and positive and negative predictive values of 0.80 and 0.88, respectively[94]. The RMS has been subsequently validated in BD-II[95].

These screening instruments have generally shown better performance in clinical settings rather than in population samples, where there is a more substantial false positive rate. Importantly, these tools are not diagnostic instruments, but merely indicators of the need for closer clinical exploration of potential BD[90,96].

EPIDEMIOLOGY

The reported prevalence of BD-II varies significantly across epidemiological studies, likely due to methodological differences. The World Mental Health Survey[97] reported an aggregate lifetime prevalence of 0.6% for BD-I, 0.4% for BD-II, and 1.4% for subthreshold BD. The data, gathered across 11 countries in the Americas, Europe and Asia, indicated a consistent pattern of prevalence, comorbidity and severity across these diverse regions. However, a systematic review and meta-analysis including 276,221 individuals[98] reported a pooled lifetime prevalence of 1.1% for BD-I and 1.6% for BD-II, finding higher lifetime prevalence rates in North Africa and the Middle East.

This disparity likely reflects methodological variability and the lack of gold standard diagnostic criteria for bipolar spectrum disorders, particularly for BD-II. There is also a significant variance in clinicians' diagnostic process, particularly when diagnosing BD-II, as it requires direct information gathering not only from the patient, but also from his/her family and support circle[99].

Furthermore, the fact that BD-II has been included for the first time only in the 11th revision of the ICD, which has still not been adopted in many countries, has complicated and still complicates the estimation of the global incidence and prevalence of the condition[100].

BD-II appears to be more prevalent in females[101]. For example, the Mayo Clinic Biobank, which included 1,465 participants with BD (69% BD-I and 31% BD-II), reported that 66.1% of BD-II patients were female, compared to 58.6% of BD-I patients[102]. Similarly, the BipoläR study, which analyzed data from 7,345 individuals registered in the Swedish National Quality Assurance Register for BD, found that females made up 64.9% of BD-II cases and 57.3% of BD-I cases[103]. This gender disparity in BD-II prevalence may stem from a combination of biological and psychosocial factors, as well as potential diagnostic biases, since the predominance of depressive symptoms may lead to increased recognition of the disorder in females[104].

COURSE

BD-II often begins with non-specific symptoms such as anxiety or sleep disturbances, which precede mood swings and full episodes of depression and hypomania (see Figure 2). These symp-

toms may be accompanied by some degree of functional impairment and distress. Patients typically meet the full diagnostic criteria for BD-II several years after the initial symptoms appear, emphasizing the need for more attention to the at-risk and prodromal stages to facilitate early detection and intervention[57,105-108].

The onset of BD typically occurs during adolescence and early adulthood, with predominant initial depressive symptoms[109]. Indeed, a 10-year follow-up study of individuals with prepubertal depression found that 33% and 15% later met criteria for BD-I and BD-II, respectively[110]. An analysis of large, predominantly European samples indicated an earlier age of onset for individuals with BD-I compared to BD-II, although some studies found the opposite[16].

The World Mental Health Survey reported a mean age of onset of 18 years for BD-I, 20 years for BD-II, and 22 years for subthreshold BD, with the age of onset being inversely correlated with the severity of illness over time[97]. There is evidence that the average duration of untreated BD-II is approximately 10 years[15,111], with BD-I cases showing a significantly shorter delay of diagnosis than BD-II cases, especially when comparing male BD-I patients to female BD-II patients[111].

A comparative analysis of 25 studies found that patients with MDD, BD-I and BD-II were symptomatic 46%, 44% and 43% of the time, respectively, with BD-II patients experiencing depressive symptoms for 81% of the symptomatic time[112]. Indeed, depression takes the largest toll on quality of life and functioning among individuals with BD-II[113]. A naturalistic study found that these patients spent approximately 40% more time in depressive states than those with BD-I[19]. Additionally, BD-II is associated with a higher rate of depressive relapse than BD-I[112]. Longitudinal studies indicate that recovery from depressive episodes is less common in BD-II, and that BD-II patients show greater monthly symptom fluctuation and higher year-round illness severity compared to BD-I individuals[112,114]. For example, a study involving self-monitoring over a median of 310 days found that individuals with BD-II had a lower mean level of mood, and spent more time with depressive symptoms, compared to those with BD-I[18].

Rapid cycling, defined as at least four mood episodes per year, is more prevalent in BD-II than BD-I[115,116]. This pattern is associated with worse long-term outcomes, including higher suicide rates[117]. Rapid cycling may occur during a portion of the life course, but is not necessarily an enduring characteristic.

Psychotic features occur in approximately 15% of BD-II cases, compared to 50% in BD-I[118,119], though the prevalence is higher in some reports[120]. The presence of these features during BD-II depressive episodes is associated with a greater likelihood of hospitalization and more severe melancholic and catatonic symptoms [121]. Approximately half (42-58%) of BD-II patients have never been hospitalized despite several lifetime episodes, a rate significantly lower than that of BD-I patients (21-26%)[25,122].

Compared to individuals with BD-I, those with BD-II report significantly higher functional impairment, higher burden of illness and poorer health-related quality of life, even during periods of euthymia[20]. They also experience more residual symptoms, higher rates of antidepressant use and more lifetime personality disorders compared to people with BD-I[21,22,26,122,123]. These factors raise

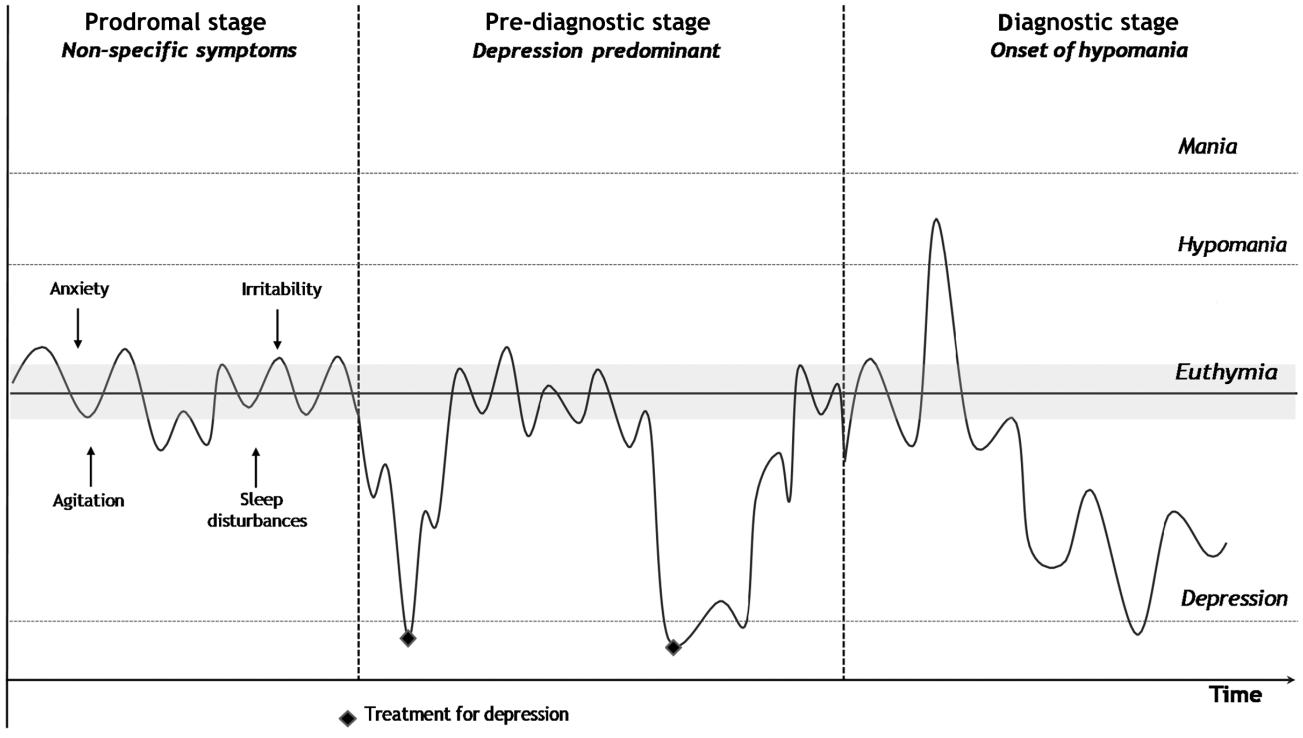

Figure 2 Representation of a typical clinical course of bipolar II disorder

questions about whether it is the disorder itself, the comorbidities or associated factors that are driving the prognosis[21,26].

Individuals with BD-II report higher rates of family dysfunction, divorce and unemployment compared to those with BD-I[23-26,124]. Cognitive impairment has been often found in BD-II[21,24,125-127]. A study reported that approximately half of BD-II patients had some impairment, with 12% of them being severely and globally impaired[128].

PSYCHIATRIC COMORBIDITIES

Psychiatric comorbidities are the rule in BD-II and complicate its diagnosis, leading to poorly targeted treatment and contributing to higher morbidity and disability rates. Data from the World Mental Health Survey[97] revealed that 83% of individuals with BD-II have at least one comorbid psychiatric diagnosis, and that more than 50% of them experience three or more psychiatric comorbidities. A systematic review[25] found that people with BD-II have a 29.5% higher rate of comorbid psychiatric disorders than those with BD-I. The high prevalence of psychiatric comorbidities in BD-II stems from its complex clinical presentation and reflects the limitations of current psychiatric classification systems based on overlapping symptoms.

Anxiety disorders are particularly common in people with BD-II, affecting about 75% of these patients, as estimated by the World Mental Health Survey[97]. Similar prevalence rates have been found in other studies[129-132]. Specific lifetime prevalence rates include 33% for generalized anxiety disorder and 39% for social anxiety disorder[97]. These two comorbidities have been found to be more common among patients with BD-II than in those with MDD[133]. More overall comorbid anxiety disorders have been reported in BD-II compared to BD-I[134], but the relevant evidence remains inconsistent[129]. Anxiety symptoms in BD-II often present as part of the prodrome, preceding mood episodes, and are associated with greater treatment resistance and increased suicidality[134-136]. The frequent co-occurrence of BD-II and anxiety disorders suggests possible shared etiological and pathophysiological pathways, and supports the view that they may represent, at least in part of the cases, different aspects of a single disorder rather than separate conditions[70,135]. Genetic studies further reinforce this view, providing data which may indicate a distinct biological subtype of BD-II with comorbid anxiety[137].

A large-scale, cross-sectional study involving 61,392 adults across 11 countries found that obsessive-compulsive disorder occurred in 12% of patients with BD-II[97], suggesting a strong comorbid link that was influenced by familial history of mood disorders[138].

A complex and controversial comorbidity is that with ADHD[139,140], with rates in BD ranging between 5.1% and 47.1%[141]. The symptom similarity between BD and ADHD can complicate the diagnosis and management of both conditions, leading to poorly targeted treatment and potentially contributing to higher morbidity and disability rates[142,143]. ADHD in BD-II is associated with earlier onset of mood symptoms, increased suicidality, and heightened temperamental instability[141,144]. ADHD treatment with stimulants has the potential to adversely affect mood, while untreated ADHD may worsen mood symptoms through significant functional impairments[144]. Stimulants can effectively treat comorbid ADHD, but should be prescribed alongside adequate mood-stabilizing treatment and during periods of euthymia, to minimize the risk of treatment-emergent hypomania or mixed states[145-148].

Borderline personality disorder is the most complex and diagnostically challenging comorbidity associated with BD-II. Approximately 10% of patients with this condition meet criteria for BD-II, while 20% of BD-II patients meet criteria for borderline personality disorder[149]. Another study reported a 24% lifetime prevalence of borderline personality disorder among individuals with BD-II [150]. This results from the high symptomatic overlap between the two conditions, which includes affective instability, impulsivity, mood dysregulation, and heightened suicidality[86]. However, despite these similarities, key differences in the patterns of mood and behavior can aid in differential diagnosis, as detailed above (see Figure 1).

According to several studies, approximately 50% of individuals with BD-II meet the criteria for substance use disorder, with alcohol being the most common substance of abuse[151-153]. BD-II is associated with a greater risk of alcohol abuse/dependence and benzodiazepine use/abuse[154]. Chengappa et al[154] found that 39% of patients with BD-II are dependent on one or more substances, 17% on two or more, and 11% on three or more. Substance misuse complicates the clinical management of BD-II by mimicking or triggering mood episodes and amplifying hypomanic impulsivity and depressive symptoms, leading to increased morbidity and compromised treatment adherence[155-157].

About 14% of patients with BD-II meet criteria for at least one comorbid lifetime eating disorder[158], and the incidence may be as high as 59% in hospitalized BD-II patients[159]. Binge eating disorder is particularly common in individuals with BD-II, and contributes to obesity, metabolic disturbances, and extended depressive episodes, further complicating the course[160].

RISK OF SUICIDE

Individuals with BD-II are at a significantly increased risk of suicide, with approximately 33% of them having a lifetime history of suicide attempts[54]. The first year following diagnosis is particularly critical, with a high risk of depressive relapse and suicidal behavior[161].

A meta-analysis and systematic review reported that the risk of completed suicide is similar in patients with BD-II compared to those with BD-I[27]. Other studies pointed at a higher prevalence of completed suicide in BD-II[55,117,162]. A Swedish bipolar registry study reported that the rate of suicide attempts was significantly higher in patients with BD-II than in those with BD-I, but no data on completed suicides were provided[26].

BD-II patients often experience a longer duration of untreated illness and more frequent comorbid anxiety disorders, which might exacerbate suicidal risk[163,164]. Functional impairment, high

comorbidity, and a greater tendency to mixed states further contribute to the elevated suicide risk in BD-II[27,54,56].

PHYSICAL COMORBIDITIES

Physical comorbidities are highly prevalent in individuals with BD-II, affecting over 90% of them at some point in their lives[145,165]. They are more frequent than in MDD[63], especially in patients with a body mass index higher than 35[166]. In a study of 1,720 patients with BD[167], those with BD-II exhibited a higher prevalence of gastric ulcer, cardiovascular diseases, Parkinson's disease, and rheumatoid arthritis than those diagnosed with BD-I.

Primarily due to the elevated risk of physical conditions, life expectancy in BD-II is reduced by 10 to 20 years compared to the general population[169-171]. Cardiovascular diseases are a leading cause of morbidity and premature mortality in patients with BD-II[172]. Metabolic disorders – including obesity, type 2 diabetes mellitus, hypertension and dyslipidaemia – are disproportionately common in these patients[165,173,174]. Individuals with BD-II face a threefold increased risk of developing metabolic syndrome compared to the general population[175]. These metabolic disturbances are linked to more frequent mood episodes, greater depressive symptom severity, and a shorter time to relapse[176,177].

Autoimmune diseases frequently co-occur with BD-II, amplifying the burden of illness. Over 20% of individuals with BD-II are affected by autoimmune thyroiditis, with elevated risks also for systemic lupus erythematosus, rheumatoid arthritis, and psoriasis[178-180]. Gastrointestinal disorders, such as irritable bowel syndrome, are also common, with a prevalence of 30% in BD-II compared to 15% in the general population[181,182]. Chronic pain conditions, including migraine, affect 25% to 35% of BD-II patients, worsening depressive symptoms and reducing quality of life[183].

The high prevalence of physical comorbidities in patients with BD-II exacerbates the illness burden, and is associated with greater treatment resistance and higher hospitalization rates[165,176]. This underscores the necessity of regular screening for cardiovascular, metabolic, inflammatory, and pain-related disorders within comprehensive care plans[167]. Effective management of BD-II demands a multidisciplinary approach that integrates psychiatric and physical care in both clinical settings and research[184,185]. Moreover, exploring the bidirectional relationships between BD-II and physical comorbidities is essential to developing targeted interventions[186].

RISK FACTORS AND NEUROBIOLOGY

Trauma is a major risk factor for BD-II[187], with a history of severe childhood abuse being present in about 23% of patients[188]. This abuse often correlates with an earlier age of onset. Ongoing stress and trauma can further exacerbate or trigger episodes, complicating the course of the disorder[189].

Comparative studies show no substantial differences in the prevalence of childhood abuse between BD-I and BD-II, indicating that early trauma is a risk factor across the bipolar spectrum[188-189]. However, offspring of parents with BD-I experience higher levels of childhood trauma compared to those whose parents have BD-II, suggesting that the type of parental bipolar disorder might influence the environmental and emotional conditions experienced by children[190].

Substance abuse is another risk factor. The use of alcohol and drugs can not only precede the development of bipolar symptoms but also complicate the course of the disorder, leading to poorer clinical outcomes and more complex treatment needs[191-194]. Circadian rhythm disruptions, whether due to work, lifestyle, or other disorders, are also linked to a higher incidence of mood disorders, including BD-II. The misalignment of circadian rhythms can exacerbate or trigger episodes of hypomania and depression[195].

Genetic studies suggest that the heritability of BD ranges from 60 to 80%, indicating a strong genetic component[196-198]. Specifically, a 21-67% range is reported for BD-II[199]. Additionally, family studies suggest a higher likelihood of BD-II among first-degree relatives of individuals with BD-II[200,201]. Genome-wide association studies (GWAS) have identified genetic distinctions between BD subtypes: in particular, polygenic risk score (PRS) for schizophrenia is higher in BD-I than BD-II, while PRS for MDD is higher in BD-II, suggesting that BD-II may be more closely related to MDD than BD-I[202].

Inflammation has been highlighted as a possible biological factor in the pathogenesis of BD-II. Studies have identified elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) in individuals with BD-II during depressive and hypomanic episodes[203]. These elevated cytokine levels suggest that inflammation could serve as a biomarker for disease activity and severity, but the evidence for targeted anti-inflammatory treatments is still inconclusive[204-206].

BD-II is increasingly regarded as a disorder of energy regulation. Mitochondrial dysfunction affects cellular energy production, which might lead to the characteristic energy-related mood disturbances seen in BD-II[207-209]. Mitochondrial dysfunction may also be responsible for the observed accelerated biological aging and age-related conditions seen in people with BD, such as autonomic and endothelial dysfunction, increased inflammation, and oxidative stress[210]. This line of investigation could lead to the identification of potential biomarkers for BD-II, as well as novel therapeutic targets[211].

TREATMENT

Most evidence concerning treatment comes from studies on BD-I, with few trials specifically focused on BD-II. This lack of research specifically targeting BD-II is partly due to the absence of regulatory incentives, as drugs approved for BD-I are assumed to be effective for BD-II, even though this assumption is not always justified.

Acute treatment is based on clinical presentation. Maintenance pharmacotherapy beyond acute episodes, accompanied by psychoeducation, is the main treatment strategy. Pharmacological interventions typically involve a mood stabilizer such as lamotri-

gine or lithium, an atypical antipsychotic such as quetiapine, or a combination strategy. Due to its recurrent and chronic nature, the treatment of BD-II for most individuals generally needs to be lifelong. Effective management requires a stable and enduring therapeutic alliance[212], ensuring continuity of care to facilitate treatment adherence and improve outcomes.

Acute treatment of hypomania

Patients experiencing hypomania rarely present for treatment. It is crucial to advise patients on the importance of maintaining mood stabilization as hypomanic episodes often seed subsequent depressive episodes[20]. The goal of treatment of hypomania is to manage the risks associated with impaired judgment and disinhibition, ensuring that patients' behavior and decision-making are consistent with their usual patterns, allowing them to maintain their normal roles and functions.

There are no large randomized controlled trials (RCTs) that examined the efficacy of pharmacological agents for treatment of hypomania. Clinical experience suggests that all agents that are active in mania are also effective in hypomanic episodes. Treatment guidelines from the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD)[213,214] recommend withdrawing any potential mania-inducing medications such as antidepressants, stimulants and corticosteroids, and using mood stabilizers such as lithium, anticonvulsants or atypical antipsychotic agents.

In addition to pharmacotherapy, hypomania may benefit from behavioral interventions. Maintaining healthy daily routines, including a stable sleep-wake cycle and stress avoidance, is valuable in managing hypomanic episodes.

Acute treatment of depression

The treatment of depression in BD-II is particularly challenging and often requires a combination of pharmacotherapy and psychotherapy. In a recent meta-analysis, olanzapine plus fluoxetine, quetiapine, olanzapine, lurasidone, lumateperone, cariprazine, and lamotrigine were found to be more efficacious than placebo in adults with acute bipolar depression across BD-I and BD-II[215].

Quetiapine is the only first-line drug recommended by the CANMAT and ISBD guidelines for the treatment of bipolar II depression[214]. This recommendation is supported by pooled data from four placebo-controlled randomized studies, involving 572 participants, demonstrating that quetiapine monotherapy significantly improves depressive symptoms in BD-II patients[216].

A recent phase 3, randomized, double-blind, placebo-controlled study of patients with bipolar depression and a combined post-hoc analysis of data from two RCTs[217,218] have shown the superiority of lumateperone over placebo in improving depressive symptoms in both BD-I and BD-II patients, suggesting that this agent will gain guideline support for treating depression in BD-II. However, these results need to be confirmed in other trials, as the sample of BD-II patients in both studies can be considered small. Lumateperone is the first drug in 15 years that has been approved by the US Food and Drug Administration (FDA) for bipolar depression associated with both BD-I and BD-II.

Lamotrigine is also an evidence-based treatment for BD-II depression[219]. The CANMAT notes that methodological issues have led to an underestimation of its efficacy, with a slow titration to a 200 mg final dose over an 8-week trial duration, such that participants only had a therapeutic dose for two weeks. In a trial that compared open label lamotrigine monotherapy (N=44) with lithium monotherapy (N=54) in BD-II depressed patients over a 16 week period, therapeutic doses of lamotrigine resulted in a significant reduction of acute depressive symptoms relative to baseline, with no significant differences in efficacy between lamotrigine and lithium[220]. Additionally, a double blind RCT evaluating adjunctive lamotrigine treatment with lithium in 124 patients found clinically significant improvement in depressive symptoms in comparison to placebo in a combined group of BD-II and BD-I depressed patients[221].

Lamotrigine's relatively benign tolerability profile is a notable advantage over atypical antipsychotics, particularly given the metabolic side effects associated with the latter treatments in a disorder characterized by risk for cardiovascular disease and in the context of often lifelong therapy[222]. Moreover, lamotrigine has proven to be effective in women at childbearing age[223] and does not carry the serious teratogenicity risks associated with valproate[224]. However, lamotrigine's prolonged titration regime to start treatment potentially hinders its benefits in acute depression and makes it easier to use for maintenance treatment.

The use of antidepressants in BD-II remains controversial, due to inadequate and conflicting evidence and the potential risk of treatment-emergent hypomanic/manic switch[225]. A systematic review suggests that, while the rates of antidepressant-associated mood elevations are greater among BD-II than MDD patients in acute (8.1% vs. 1.5%) and maintenance (16.5% vs. 6.0%) trials, they are lower in BD-II relative to BD-I in acute (7.1% vs. 14.2%) and maintenance (13.9% vs. 23.4%) studies[226].

Among antidepressants, trial evidence suggests that bupropion is associated with the lowest risk for treatment-emergent hypomanic/manic switch[227]. Further, an RCT of BD-I and BD-II patients showed that bupropion had similar efficacy as sertraline and venlafaxine[228]. There is also RCT evidence that sertraline monotherapy is as effective as lithium and lithium+sertraline combination, while venlafaxine demonstrated greater improvement in depressive symptoms compared to lithium in a trial of 129 BD-II patients[229]. However, venlafaxine seems to have a greater switch propensity than selective serotonin reuptake inhibitors[230].

Based on the above evidence, the CANMAT guidelines[214] recommend bupropion, sertraline and venlafaxine as second-line treatment; and fluoxetine as third-line treatment for BD-II depression. Antidepressants are recommended to be used in conjunction with a mood stabilizer[214,231].

Lithium, traditionally used as monotherapy or in combination

with other pharmacotherapies, has long been a staple in the treatment of BD-II depression[232]. However, recent studies have questioned this approach. One study found no significant improvement in depressive symptoms in BD-I and BD-II patients treated with lithium at doses ranging from 600 to 1,800 mg/day compared to placebo[233].

A recent small non-randomized open-label trial suggested a possible efficacy of psylocibin together with psychotherapy in BD-II resistant depression[234]. Moreover, there are some preliminary data from real-world samples supporting the efficacy of ketamine in the treatment of BD-II depression[235]. Nonetheless, the safety of these interventions, especially in the long-term, is still to be determined.

Overall, the acute treatment of BD-II depression requires a careful balance of pharmacotherapy, lifestyle interventions and psychotherapy, with a focus on individualized treatment plans to manage symptoms effectively and minimize the risk of relapse and treatment-emergent complications.

Maintenance pharmacotherapy

The majority of individuals with BD require maintenance treatment to prevent subsequent episodes, reduce residual symptoms, and restore functioning and quality of life[236]. There is a notable paucity of evidence specifically addressing this subject in BD-II. The clearest guidance has been provided by CAMMAT[214], suggesting that quetiapine (Level 1), lithium and lamotrigine (Level 2) monotherapies exhibit the strongest evidence as first-line agents for maintenance treatment of BD-II.

Lithium is recognized for its efficacy in long-term management. It must be noted, however, that most lithium studies did not report findings separately for BD-I and BD-II. In a systematic review and network meta-analysis examining the comparative effectiveness of medications in maintenance therapy, lithium was indicated as the primary option when prescribing a relapse-prevention medication for patients with BD[237,238]. Lithium reduced time in hypomania/mania by 61%, and time in depression by 53%, in the entire sample, with a lower proportion of time with mood symptoms for BD-II than for BD-I[239].

Patients with BD-I and BD-II have a significantly longer time to relapse into any mood episode and depression with quetiapine relative to placebo[240]. Quetiapine is as effective as lithium when added to treatment as usual for patients with either BD-I or BD-II, with BD-II patients responding better[241]. There are no data for other antipsychotic agents in BD-II, although aripiprazole[242] and asenapine[243] have evidence for maintenance therapy of BD-I and are recommended for long-term treatment of this condition.

Overall, while it is tempting to develop a pharmacological treatment algorithm for BD-II, there is a paucity of robust evidence from clinical trials specifically involving BD-II patients. Clinicians utilize a range of anecdotal and off-label treatments which could be effective but with limited research evidence, highlighting a substantive unmet evidence need.

Psychotherapies

Guidelines emphasize the importance of psychological interventions for the maintenance treatment of BD-II[244]. Combining pharmacotherapy with psychotherapy can significantly improve treatment outcomes, reduce the risk of relapse, and enhance overall patient well-being[244]. Various psychotherapy modalities offer specific benefits, addressing different aspects of the disorder[236].

Cognitive behavioral therapy (CBT) focuses on identifying and modifying negative thought patterns and behaviors that contribute to mood episodes. It helps patients develop and enhance coping strategies and problem-solving skills[245].

Family-focused therapy (FFT) involves the patient's family in the treatment process. It aims to improve family communication, reduce relational stress, and create a more supportive home environment. It educates family members about BD-II and teaches them how to recognize and respond to mood episodes, thereby enhancing the overall support system for the patient[246,247].

Interpersonal and social rhythm therapy (IPSRT) – the only psychotherapy assessed in a randomized controlled trial in a sample consisting of only BD-II patients[248] – targets disruptions in daily routines and social rhythms that can trigger mood episodes[249,250]. It helps patients establish and maintain regular daily routines, including sleep-wake cycle, and improves interpersonal relationships.

A network meta-analysis of 39 randomized clinical trials involving 3,863 participants demonstrated that manualized psychotherapy – such as CBT, FFT and IPSRT – in combination with pharmacotherapy is more effective in reducing recurrences compared to pharmacotherapy alone[248].

Psychoeducation

Psychoeducation is a valuable tool for effective treatment of BD-II, aiming to enhance patient and caregiver understanding of the nature of the condition, treatment options, and management strategies[251,252]. It helps patients and their families to identify early signs of mood episodes, understand the necessity of medication adherence, and manage lifestyle factors that can influence the course of the disorder[253]. In so doing, it empowers patients to take an active role in their treatment.

Lifestyle interventions

Lifestyle interventions play a significant role in managing BD-II. These interventions benefit both mental and physical health, contributing to overall well-being and improved health outcomes[254]. Maintaining a regular sleep-wake cycle and managing stress through mindfulness, exercise, and relaxation techniques can help stabilize mood and enhance emotional resilience[255]. Dietary considerations, such as maintaining a balanced diet, may also contribute to better health outcomes[256]. The ketogenic diet is

an area of interest, although only pilot trial data are available[257,258].

Given the higher prevalence of physical health issues in individuals with BD-II, regular monitoring of activity levels, blood pressure, weight changes, cholesterol and glucose levels is crucial.

CONCLUSIONS

BD-II is a distinct condition within the bipolar spectrum, characterized by recurrent depressive and hypomanic episodes without the presence of mania. Despite its high prevalence and impact, it remains underdiagnosed[12,13], which often leads to prolonged periods of untreated illness, mis-management, and poor clinical outcomes, underscoring the need for improved awareness and tailored treatment approaches[15,16]. Depression is the primary clinical burden in BD-II, with individuals spending over 80% of their symptomatic time in depressive states[17,20], leading to significant functional impairment and a suicide risk comparable to BD-I[54,55].

Currently, treatment guidelines for BD-II are largely extrapolated from studies on BD-I and MDD, limiting the validity and specificity of therapeutic recommendations. Maintenance pharmacotherapy beyond the treatment of acute episodes, in conjunction with psychoeducation, constitutes the primary therapeutic strategy[214,232,251]. The chronic and recurrent nature of BD-II typically requires ongoing management throughout the patient's lifetime, necessitating a stable therapeutic alliance to enhance treatment adherence and improve clinical outcomes[212]. Mood stabilizers such as lamotrigine, lithium, and atypical antipsychotics – particularly quetiapine – have demonstrated efficacy in managing bipolar depression and preventing relapse[213,214].

The role of antidepressants in BD-II remains controversial, due to concerns over treatment-emergent hypomania and mixed states [231]. Evidence suggests that the risk of hypomanic switching is lower in BD-II compared to BD-I, and antidepressants may have a place in the treatment of BD-II when combined with mood stabilizers[226, 228]. Nevertheless, the lack of robust, BD-II-specific clinical trials requires further research to determine the safety and efficacy of antidepressants in this population.

The high prevalence of psychiatric and physical comorbidities in BD-II significantly complicates its clinical management[145]. Common psychiatric comorbidities include anxiety disorders, substance use disorders, and borderline personality disorder, all of which contribute to greater symptom severity and pose unique treatment challenges[97,165]. Physical conditions, such as obesity, metabolic syndrome and cardiovascular diseases, are highly prevalent[145,165]. Cardiovascular diseases are the leading cause of reduced life expectancy in individuals with BD-II[168]. These comorbidities exacerbate the symptomatic burden of the disorder, and highlight the critical need for an integrated, multidisciplinary approach to care[167].

Future research must adopt a systemic approach that integrates fields such as endocrinology, immunology, metabolic regulation, and neuroscience to unravel the complex pathophysiology of BD-II. This systems-level framework is essential for identifying biomarkers that bridge symptomatic and biological profiles, enabling the development of clinical phenotypes to guide targeted treatments and inform personalized care strategies[205].

By addressing the unique challenges posed by BD-II through targeted research and refined clinical practices, we can advance care and improve outcomes for this often-overlooked population.

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Genomics and psychiatric nosology: avoiding hype, maintaining hope

In recent years there have been important advances in our understanding of the genetic architecture of mental disorders[1]. An immediate question is the relevance of such advances for psychiatric nosology. In order to address this question, we can posit a classical, a critical, and an integrative position. These positions are not intended to refer to the work of any particular author in the field, but rather are outlined for heuristic purposes.

A classical position takes a view that emphasizes biological essentialism and genetic determinism. In this view, mental disorders have a natural "essence", this "essence" is closely tied to biology, and genes are key in determining behavioral variation. Given that mental disorders are heritable, it is only a matter of time before we fully delineate the genetic architecture and biological basis of such conditions. As sample sizes increase, for example, polygenic risk scores will account for increasing amounts of the variance.

Those adopting a classical position may point to the genetics of height: we now know which genetic variants contribute to this trait – although food intake also exerts an important role – and we will increasingly be able to outline the biological pathways that account for it. Similarly, for mental disorders, different pathways may be delineated, also accounting for the frequent overlap of these disorders. Indeed, a large-scale analysis of shared heritability in mental disorders found an overlap between major depression and anxiety disorders, and between schizophrenia and bipolar disorder, pointing to an overlap in underlying causal mechanisms[2].

A critical position takes a view that biological essentialism and genetic determinism entail inappropriate reductionism and oversimplification, downplaying the complexity of both neurodevelopment and behavioral traits. In this view, the heritability of a mental disorder simply indicates an association between phenotype and genotype, but tells us little about the underlying mechanisms, which might involve genetic, shared environmental, or non-shared environmental factors[3]. With increases in sample sizes, we have learned that for some phenotypes (e.g., height) polygenic risk score accounts for a relatively large proportion of variance, but for others (e.g., IQ) it accounts for a relatively small proportion.

Those adopting a critical position may emphasize that the heritability of a range of social constructs, such as educational attainment or divorce, tells us little about how genes and environments interact to lead to these outcomes, and, in the absence of such understanding, constructs such as polygenic risk scores are without value. Similarly, genome-wide association studies and gene-by-environment genome-wide interaction studies may be unable to delineate the biopsychosocial mechanisms that lead to mental disorders[4]. Even in the case of rare pathogenic mutations, it is notable that a single damaging variant can be associated with multiple different mental disorders.

An integrative position attempts to draw on the strengths of the classical and critical positions. While natural kinds in physics and chemistry may be defined in terms of necessary and sufficient characteristics, in biology the complexity of organisms often constrains such an approach. Behavioral traits might be considered "soft natural kinds", falling on spectrums of phenotypes, and accounted for by overlapping and distinctive biopsychosocial mechanisms. At one end of the spectrum of orderliness, for example, pathological obsessivity may be due to an acute brain lesion or even a rare damaging variant. At the other end of this spectrum, however, a student may choose to take a very orderly approach to his/her notes to ensure that his/her learning is on track. A pluralistic approach to explaining and understanding behavioral traits is, therefore, needed[5].

From an integrative perspective, both Alzheimer's disease and personality disorders are heritable, and involve the brain and its biology to some extent. But the biopsychosocial mechanisms that account for Alzheimer's disease and personality disorder are qualitatively different. Thus, while mental disorders are heritable, are biological, and involve the brain, they fall on spectrums of phenotypes, and involve a broad range of biopsychosocial difference-makers[5]. Biological/brain differences may be more defining of particular disorders (e.g., Alzheimer's disease often involves amyloid plaques), or far less so (as in personality disorders, for which any particular biomarker has low sensitivity and specificity).

The classical position may be associated with considerable hype. Multiple genomic studies report the involvement of particular genes in specific mental disorders, and argue that this will imminently lead to targeted treatment. The critical position may, on the other hand, lead to too much pessimism about genomic research. Replacing neuroreductionism (brain mechanisms completely explain mental disorders) with cultural reductionism (societal mechanisms completely explain mental disorders) seems unwise. An integrative position allows for a balanced perspective on the relationship between genetics and nosology, avoiding hype and providing hope.

To avoid hype, we should be aware of the "mechanism gap", i.e., the significant challenge of identifying causal mechanisms that explain how genes impact biological pathways and how these in turn lead to spectrums of complex phenotypes[4]. Further, the "gloomy prospect", that non-shared environmental influences are largely unpredictable and idiosyncratic, seems correct[6]. Finally, even with future advances in our understanding of causal mechanisms, genetics cannot solve the "line-drawing problem" of how best to differentiate mental disorder from normality, and mental disorders from one another.

To maintain hope, we should be cognizant that, on occasion, understanding the involvement of a rare variant can lead to a new treatment. For example, rare variants of the PCSK9 protein were noted to cause familial hypercholesterolemia, and this led to use of PCSK9 inhibitors for the treatment of this condition. Further, genetic research has already made important contributions to understanding the structure of psychopathology: the genetic architecture of Alzheimer's disease clearly differs from that of personality traits. Finally, as we understand the genetic architecture of a range of dimensional traits and intermediate phenotypes, iterative progress in our understanding of mental disorders may occur[7].

A balanced perspective on the relationship of genetics to nosology might emphasize that genetics has been important in challenging an essentialist view of mental disorder, by supporting the dimensional nature of psychopathology, and emphasizing the overlapping mechanisms involved in mental disorders. Just as work on family history has contributed to the validation of mental disorders, so will work on their genetic architecture. However, in neither case will this contribution be definitive, and other validators may contradict family/genomic findings[8]. These issues are not peculiar to psychiatry: it is difficult to move from common variants to causal pathways in many conditions, and the substantial genetic overlap of different autoimmune disorders, for example, does not mean that these are no longer classified separately.

Exemplifying a balanced stance, in an early paper on the relationship of genomics to nosology, K.S. Kendler concluded that "whereas psychiatric genetics has and will continue to provide important insights into the etiology of psychiatric and substance use disorders, it is not likely alone to provide deep answers to the complex and multifaceted problems facing psychiatric nosology"[9]. Although genomics has since made considerable advances, and will no doubt continue to do so, this conclusion is likely to remain valid for the foreseeable future. Notably, however, there are non-genetic ways of validating our nosology, and these should certainly be pursued. Similarly, there are many non-genetic risk and protective factors for mental disorder that deserve our attention.

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The interaction between social determinants of schizophrenia and brain dopamine circuitry

It is well established that dopamine plays an important role in the pathogenesis of schizophrenia. A recent meta-analysis confirmed that striatal dopamine synthesis capacity and stress- or amphetamine-induced dopamine release are substantially increased in this disorder, and that both measures correlate with the severity of positive symptoms[1].

Meta-analytic evidence points to several social risk factors for schizophrenia (or proxies for such factors): urban upbringing, childhood trauma, low academic achievement, a personal or parental history of migration from a developing country to Europe, African-American ancestry, hearing impairment, and the presence of autism[2]. An important question, therefore, is whether exposure to these risk factors can influence dopamine function *before* the onset of the disorder. Dopamine function in the living human brain can be assessed using single photon emission computed tomography (SPECT) or positron emission tomography (PET).

We conducted a systematic review of SPECT and PET studies of the relationship between chronic social stressors and striatal dopamine functioning, and obtained fairly consistent evidence of an association between childhood trauma and increased striatal dopamine synthesis and release[3]. This finding suggests that the relationship between childhood trauma and schizophrenia may be mediated by dopamine dysregulation. In contrast, the results of six investigations of the relationship between educational attainment and dopamine D2/3 receptor availability were mainly negative (no association)[3].

A study of first- and second-generation immigrants (healthy volunteers, subjects at high risk of psychosis, and antipsychotic-naïve patients with schizophrenia) and non-immigrants (divided into the same three clinical groups) examined striatal dopamine release after exposure to a psychological stressor while in the scanner. The results showed an increased striatal dopamine release for immigrants in each clinical group[4]. The same researchers also examined striatal dopamine synthesis capacity in immigrants and non-immigrants, divided into healthy volunteers and subjects at high risk of psychosis. The synthesis capacity was higher in immigrants than in non-immigrants and this finding applied, again, to both clinical groups[4].

A study of non-psychotic young adults with severe hearing impairment revealed a greater amphetamine-induced striatal dopamine release, which constitutes evidence of a sensitized dopamine system. An investigation of non-psychotic individuals with autism found, instead, no increase in striatal dopamine synthesis capacity[3].

A PET study of healthy individuals in New York examined the relationship between genetic ancestry and striatal dopamine D2/3 receptor availability[5]. African and European ancestry differentially predicted this availability in the dorsal striatum (caudate nucleus and putamen). African ancestry predicted the availability negatively, while European ancestry predicted it positively. The results remained statistically significant after correction for age, sex, body mass index, level of education, smoking status, and estimated so-

cio-economic status. The effects, of moderate size, were not driven by variation in dopaminergic candidate genes. The reduced dopamine D2/3 receptor availability in individuals of African ancestry probably means that more receptors are occupied by endogenous dopamine, reflecting a more active dopaminergic system.

It is important to clarify whether this putatively greater dopaminergic activity in people of African ancestry is a direct genetic effect or a consequence of their social status. This is not a side issue, because social status (standing, rank, prestige) appears to be the most important single predictor of our health and lifespan, which remains strong after adjustment for behavioral habits such as diet, cigarette smoking, alcohol consumption, and exercise[6]. Social status and economic situation are correlated, but also different. This becomes clear if one considers the ups and downs of migrants from developing countries in Europe: migration improves their economic situation, but is often accompanied by a decline in their social status. Social status affects our health profoundly in that it determines to a large degree how autonomous we are and to what extent we participate socially. The suffering due to a subordinate position or outsider status damages health in ways that are as yet incompletely understood.

Research into the relationship between social status and dopamine function is very interesting, but not easy. First, the phenomenon is complex, because humans belong to multiple hierarchies (e.g., appearance, intelligence, income, social and physical abilities). Second, the measurement of social status requires effort: in the absence of individual measures, one can use group membership as an approximation. This is the approach of the social defeat hypothesis of schizophrenia, which posits that low social status and repeated humiliation increase the risk of developing the disorder in the presence of a poor homeostatic control of dopamine neurons in the dorsal striatum[2].

The results of research in rodents provide strong encouragement to continue this work. The vast majority of this research has relied upon the chronic social defeat stress procedure[7]. This involves placing a male test mouse in the home cage of a larger, male breeder mouse, screened for a sufficient level of aggressive activity. Physical interaction is permitted for 5-10 min, after which the mice are separated for 24 hours by a plexiglass barrier. This is repeated every day for 10 consecutive days, with a different dominant mouse each time. Two out of three defeated mice develop social avoidance and anhedonia-like symptoms, while a third are resilient. The main findings in the brain of sensitive mice are an increase in phasic firing of mesolimbic dopamine neurons that project from the ventral tegmental area to the nucleus accumbens, and an opposite effect in dopamine neurons projecting from the ventral tegmental area to the prefrontal cortex. Resilient mice, in contrast, display normal firing activity after the procedure.

Important for our story is the possibility that social defeat leads to destabilization of the mesolimbic dopamine system via synaptic pruning. Indeed, studies in rodents have shown that social stressors, including repeated exposure to dominant animals, activate microglia and lead to excessive synaptic pruning. The loss of synapses can then disrupt the function of pyramidal neurons in the cortex, disinhibit their projections to meso-striatal regions and destabilize the meso-striatal dopamine system[8].

Among primates, whether low- or high-ranking animals are most stressed is a function of their social organization. In some species, the physical demands of frequent fighting can make a dominant position stressful. In cynomolgus macaques, however, a higher rank is associated with less stress and with a greater amount or availability of striatal dopamine D2/3 receptors, which may reflect a lower level of synaptic striatal dopamine. Well-designed experiments have shown that these aspects of dopamine functioning are the consequence, rather than the cause, of place in the hierarchy[9].

Major problems for human studies in this area are the high refusal rates due to the use of radiotracers, the impossibility to assess several aspects of dopamine function in one session, and the high costs. New techniques such as neuromelanin-sensitive magnetic resonance imaging are emerging, and may help to expand this field of research.

In conclusion, SPECT and PET studies provide preliminary evidence of increased synthesis of dopamine (childhood trauma, migration), increased dopamine release (childhood trauma, migration, hearing impairment) and diminished D2/3 receptor availability (African-American ancestry) in the striatum. This is likely to be relevant for the pathogenesis of schizophrenia and schizophrenia-related disorders. Further research on the relationship between social status and dopamine function, which can also be relevant to other mental health conditions, is needed.

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Measurement-based care: opportunities to improve global mental health care

Measurement-based care (MBC) is a flexible, patient-centered, clinical process that has the potential to improve the quality of global mental health care. It uses standardized and/or individualized patient-reported outcome measures (PROMs) administered routinely and repeatedly during mental health treatment to track progress and guide treatment planning.

We previously proposed an operationalization of MBC called "Collect, Share, Act", derived from the model developed by the US Department of Veterans Affairs, Office of Mental Health[1]. In Collect, collaboratively-chosen PROMs are administered routinely throughout care. In Share, clinicians engage patients in timely discussions of PROM data to ensure a shared understanding. In Act, patients and providers collaboratively use PROM data, along with other sources of information including clinical judgment, to assess progress and make clinical decisions about the course of treatment. Transparency, collaboration and empowerment are integral to the model[1]. MBC can be added to any mental health practice to improve outcomes[2].

Strong research evidence supporting MBC has proliferated in high-income countries (HIC)[2], and MBC has also been studied in middle-income countries (MIC)[3]. There is ample evidence that MBC improves outcomes and reduces treatment dropout when integrated with psychotherapy conducted by specialized mental health providers in HIC[2].

Although the ideal frequency for PROM administration is currently unknown, evidence suggests that more is better. MBC processes must occur frequently enough to detect patient deterioration or lack of response to treatment, so that personalized adjustments can be made[4]. Therefore, providers often integrate MBC at every visit.

Symptom-based PROMs are commonly used[5], but are not required. Practitioners may individually tailor measures assessing a range of outcomes (e.g., quality of life, individualized goals, functioning) to better align with patients' treatment goals[4]. Additionally, two highly-researched MBC outcome measures monitor therapeutic alliance, because of its well-established positive impact on mental health treatment outcomes[2]. It has been hypothesized that, in addition to facilitating personalized treatment adjustments, MBC improves outcomes by strengthening patient-provider communication, engagement and alliance, but there is little direct evidence to support this[6].

It is unclear if and to what extent MBC is used in low-income countries (LICs), as we could not locate examples in the literature. However, a major barrier to identifying global MBC research and practice is semantics. It is possible that MBC is being used in some LICs, but practices are either unpublished, or we are unable to locate published examples because of the varied and sometimes idiosyncratic terms used in the literature – including "performance feedback"[2], "routine outcomes monitoring" or even just "outcome measures"[3] – although confusingly these terms are also sometimes used to describe non-MBC processes. Authors also commonly omit descriptions of assessment processes altogether, aside from stating that self-assessments were utilized.

Without a clear and consistent terminology, we cannot accurately assess the current state of global MBC practice. Nonetheless, it seems reasonable to assume that MBC is not practiced routinely around the world. Because it improves outcomes and can be added to any mental health treatment[2], integrating it more widely and into more models of care has the potential to improve global mental health outcomes.

The absence of mental health specialty care systems in LICs[7] may be a barrier to MBC adoption, as current models of MBC are integrated into psychotherapy and other forms of specialist mental health services. Therefore, increasing integration of MBC into mental health care in LICs likely hinges on the development of creative and innovative adaptations of MBC to enhance models of care currently practiced in those countries, such as task-sharing models that employ trained non-specialist health professionals or non-licensed para-professionals to conduct mental health interventions[7]. MBC might make task-sharing models more effective. Recent implementation research details effective MBC supervision and consultation methods with licensed providers that could be extended and adapted to task-sharing models[8].

Another evidence gap is in non-clinical interventions such as care navigation, therapeutic mentoring, brief early intervention, and peer support. How might we re-envision the basic model of MBC to enhance such interventions? Adaptations to the MBC clinical model that consider the cultures in which they are adopted should also be carefully considered. A full range of research will be necessary to support these ideas, from model development to feasibility, effectiveness and implementation studies.

LIC systems of mental health care may also be deterred from adopting MBC due to concerns around technology infrastructure and funding. MBC is often facilitated by electronic health records. There is a recent proliferation of measurement feedback systems, which are technologies designed to collect and display PROMs[6]. While technology may facilitate implementation, and clinical decision support added to MBC may enhance MBC effectiveness[2], globally there is an incorrect assumption that MBC requires technology. Indeed, many clinicians practice high-quality MBC collecting PROMs with paper forms on clipboards. Technological solutions for MBC that can be developed and scaled up in LIC could be impactful, but should not be considered a prerequisite for adoption.

Underscoring these suggestions is our call for consistent definitions, careful operationalizations, and complete descriptions of MBC practice and adaptations in evaluations and publications[6]. To be effective, PROM data must be used collaboratively with patients to develop goals, monitor progress, and adjust treatment[9]. Innovative models must carefully operationalize the clinical inter-

vention and not assume that providers know how to incorporate PROM data into clinical interventions.

Further, we cannot know to what extent MBC is being implemented when practices are poorly described. The literature is replete with references to using PROMs, but with vague descriptions such as "tracks outcomes with PROMs" or "PROMs were integrated into clinical care" or "feedback was provided", without elaboration on PROM frequency, use and purpose. We must understand how PROMs were used, not just that they were collected. Reaching consensus around terms and operationalizing clinical interventions in research and other scholarly work is critical for identification of best practices and ultimately for advancing the field.

PROM development is another area ripe for investigation globally. Many PROMs were developed as research outcome measures, but are now used clinically because few specific MBC measures exist. Research on what makes a good PROM and how to tailor PROMs, including how to use non-symptom PROMs – such as those measuring recovery, well-being, functional status, quality of life – as well as better understanding of the use of individualized PROMs, would help providers adopt MBC with more patients and treatments, and may add value[5,6]. Co-development of new PROMs with patients would help us measure what patients truly find important[5]. Finally, to expand MBC geographically, we must develop more PROMs in a range of languages, with content incorporating non-Western cultural perspectives[3].

MBC improves mental health outcomes[2] and can make mental health treatment more collaborative[1]. The increased adoption of MBC and development of novel adaptations suitable for a range of mental health interventions may improve global mental health care effectiveness and patient-centeredness. We call on the global mental health community to explore MBC in a wider range of interventions and settings, while using consistent terminology and operationalizations to optimize our ability to communicate with and learn from each other.

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Understanding side effects of psychotherapies: implications for clinical practice and research trials

Based on efficacy and effectiveness data from randomized controlled trials (RCTs) spanning several decades, psychotherapies are considered first-line treatments for numerous psychiatric conditions[1]. There is, however, a remarkable lack of evidence regarding the risks associated with these treatments. This is striking, given the focus on risk assessment and harm mitigation that underpins clinical practice across the fields of psychiatry and psychology.

There have been, therefore, increasing calls to improve the reporting of side effects in psychotherapy trials[2,3]. Here we outline the prevalence and types of side effects of psychotherapies (in both real-world settings and clinical trials), summarize tools and resources used for detecting and reporting these side effects, and provide recommendations aimed to promote consistency in trial practices to better inform clinicians and patients of the risk-benefit profile of these treatments.

When looking into the literature from real-world settings, the side effects of psychotherapies appear to be common. A survey of 224 people who received a psychotherapy revealed the most common side effects to be unpleasant memories (57.8%) or feelings (30.3%), and a perceived lack of understanding by the therapist (18.4%)[4]. When looking into the clinical trial literature, however, the prevalence of side effects appears much lower. One review reported that 5% of participants experienced an (unspecified) adverse event, 2.5% a serious adverse event (e.g., unplanned hospitalization), and 4% attempted suicide[5].

It is difficult, however, to estimate and compare the side effects of psychotherapies, because they are seldom and inconsistently reported and ill-defined in clinical trials. A recent review of 115 psychotherapy trial protocols found considerable variation in what and how side effects and harms were recorded. Most only monitored suicidality, completed suicides or psychiatric admissions[6], which provides an incomplete picture of the potential harms associated with these treatments.

This dearth of evidence is driven by a lack of consensus around what constitutes a side effect of treatment. Side effects can be expressed as adverse events (defined as any untoward medical occurrence), that are commonly self-reported, clinician-reported or researcher-reported, or derived from or validated against medical records in clinical trials in other areas of medicine. What makes psychotherapy trials somewhat unique, however, is that side effects of treatment are more difficult to identify, manifesting for instance as treatment dissatisfaction, lack of therapeutic alliance, anxiety or rumination about therapy, clinical deterioration (estimated to occur in 5% of psychotherapy trial participants[7]) or perceived negative effects of treatment on family/friends. Moreover, contrary to trials of pharmacotherapies – for which adverse events are required

to be monitored, adjudicated or reported as part of regulatory processes required by bodies such as the US Food and Drug Administration – psychotherapy trials are not subject to these regulations, which encourages under-reporting.

There have been some attempts to promote consistency in monitoring side effects in clinical trials evaluating psychotherapies. One example was a 2019 systematic review of tools that can be used to monitor these side effects[8]. Nine instruments, covering seventeen conceptual domains of negative effects of psychotherapy, were identified. They included the Vanderbilt Negative Indicators Scale (VNIS), the Unwanted Event to Adverse Treatment Reaction checklist (UE-ATR), the Inventory for the Assessment of Negative Effects of Psychotherapy (INEP), the Experiences of Therapy Questionnaire (ETQ), the Exploitation Index (EI), the Negative Effects Questionnaire (NEQ), the Unwanted Events and Adverse Treatment Reactions in the context of group psychotherapy (UE-G), the Side Effects of Psychotherapy Scale (SEPS), and the Positive and Negative Effects of Psychotherapy Scale (PANEPS).

Among the most common conceptual domains across these nine instruments were stigma, symptom deterioration, therapeutic relationship (e.g., dependency), and treatment response. It is notable that issues such as therapeutic misconduct and quality of therapy were mixed up with the issue of side effects of treatment.

The UE-ATR covered the highest number of side effect domains. While there were limited data on the psychometric properties of the examined instruments, the test-retest reliability was reported to be 0.76-0.96 for the ETQ, and the inter-rater reliability to be 0.89-0.96 for the VNIS[8].

Despite the availability of these tools, covering a wide range of harm concepts, a review found that only 11% of authors of psychotherapy trials used harm assessment instruments[5]. It is not uncommon for mental health clinical trials to adopt more generic adverse event reporting questionnaires used in other areas of medicine. While this is helpful for comparing the safety profile of a mental health therapy to drugs or devices used in other disciplines, it risks underreporting harms related to psychotherapies, because these questionnaires often neglect the key theoretical domains relevant to psychotherapy evaluation.

For clinical trials of psychotherapies to be clinically salient to therapists and consumers, we recommend as a minimum to embed the following within clinical trial protocols: multiple avenues and opportunities by which to collect data on side effects (e.g., participant self-report aided by validated instruments which include questions about the impact of therapy on the above-mentioned domains; therapist observations/notes/recordings; trial staff interaction with participants; carer- or family-reported effects); the establishment of an independent data safety and monitoring board or equivalent (responsible for assessing participant safety, including the reporting of adverse events, and implementing stopping rules); adequately trained and qualified trial personnel who are responsible for assessing the relatedness of a side effect to the therapy being evaluated, and its seriousness; and reporting the percentages of side effects related to the therapy and the comparator in the manuscript detailing the results of the trial.

Such activities are not without budgetary implications. Prospectively embedding adverse event recording, monitoring, adjudication and reporting activities into clinical trial budgets is critical to allow for accurate detection of these events. Preparing protocols to align with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and with the reporting requirements of CONSORT-Harms (with relevant extensions such as CONSORT-Social & Psychological Interventions[9]) can be considered.

The current practice of under-reporting side effects contributes to the assumption that psychotherapies are without risk. However, the absence of reporting of adverse events does not mean an absence of such events. Identifying adverse events is not a sign of poor, but of good clinical practice[5]. Providing clinicians with evaluations of a therapy which comprise both harms and benefits data will generate a more complete picture, better informing clinical decision-making.

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Women's reproductive mental health: currently available evidence and future directions for research, clinical practice and health policy

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Sex and gender differences in the epidemiology of mental disorders are well documented. Less well understood are the drivers of these differences. Reproductive health represents one of the gendered determinants of mental health that may affect women throughout their life course. In this paper, we review common reproductive events that may be associated with mental ill health, including menstruation (with premenstrual dysphoric disorder appearing for the first time in recent classifications of mental disorders), contraception, abortion, sexual dysfunction, hypersexuality, sexual violence, reproductive coercion, infertility and associated gynaecological conditions, and menopause. Such reproductive events may differentially affect women globally via a range of potential biological and psychosocial mechanisms. These include, for example, vulnerability to the physiological changes in hormone levels across the menstrual cycle; side effects of treatment of mental disorders; inflammation underpinning endometriosis and polycystic ovarian syndrome as well as mental disorders such as depression; intersections with gender disadvantage manifesting, for example, as structural barriers in accessing menstrual products and sanitation, contraception and abortion, underscoring the broader social determinants impacting women's mental health. Greater understanding of these mechanisms is guiding the development of effective interventions, which are also reviewed here. However, key evidence gaps remain, partly as a result of the historic gender bias in mental health research, and the neglect of reproductive health in clinical practice. Furthermore, while several women's health strategies have recently been proposed internationally, they do not usually include a focus on mental health across the life course, particularly for women with severe mental illness. Integrating co-designed reproductive health interventions into primary and secondary mental health care settings, providing tailored care, increasing the evidence base on effective interventions, and empowering women to make informed choices about their reproductive health, could improve not only reproductive health but also women's mental health across the life course.

Key words: Reproductive mental health, menstruation, contraception, abortion, sexual violence, reproductive coercion, sexual dysfunction, compulsive sexual behavior disorder, infertility, menopause

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It is well established that there are sex and gender differences in the prevalence, risk factors and natural history of mental disorders[1]. For example, studies show that the lifetime prevalence of mood and anxiety disorders in women is twice that of men[2,3]. The research evidence is robust, such that these are likely to represent true differences (as opposed to "apparent" differences due to any biases)[1].

The impact of reproductive health on mental health is lifelong and not restricted to childbearing years, and is linked to human rights. Thus, reproductive health represents one of the gendered determinants of mental health impacting women throughout their life course. In recent decades, there have been improvements in public awareness of women's reproductive rights – concepts of "period poverty" (i.e., systemic inequalities in access to menstrual products and education) and sexual abuse, for example, are no longer as taboo as they were in the last century – but stigma around discussion of reproductive health is still common globally. In part related to this, the interface between women's reproductive and mental health across the life course continues to be overlooked by researchers, clinicians and policy makers, despite its centrality in women's lives.

Although several women's health strategies have recently been put forward internationally[4-6], they usually do not include a focus on mental health across the life course. They also fail to address the needs of women with severe mental illness, who are particularly likely to face significant reproductive health inequalities.

Specific mechanisms for the relationship between mental health and reproductive events may involve complex biological, psychological and/or social pathways, which are discussed, where there is evidence, in the specific sections of this paper. These may include shared genetic and environmental (e.g., poverty, social discrimination) factors.

It is well established that sex hormones play a crucial role in brain development and functioning[7], with significant implications for women's mental health[1]. Understanding the neuroendocrine mechanisms underlying women's mental health could uncover valuable new insights into how to optimize exogenous hormonal and non-hormonal treatments for women's mental disorders.

The social determinants of mental disorders are unequally distributed[8]. Gender roles are socialized from an early age, and traditional gender roles are often associated with stigma around discussion of reproductive health, limited education for girls and women, and differential exposure of women to a range of social stressors in the home and workplace[3], including gender harassment and discrimination[1]. Women often perform multiple roles, including caring roles, which are a frequent source of distress. They are also more likely to experience intimate partner violence and sexual abuse, which are known risk factors for mental disorder[9].

Like the risk factors (for mental disorders) that are specific to women, many of the reproduction-related topics considered here have been neglected in mental health research[10,11]. While clinicians fail to routinely ask about sexual functioning and reproductive events, women are unlikely to share information on sexual dysfunction, hypersexuality, or menstrual worsening of depressive or psychotic symptoms, with opportunities thus missed to address such problems with, for example, changes in psychotropic medication. In societies with high levels of gender disadvantage, it is particularly difficult for women to be empowered to speak of their reproductive needs.

Inequities in access to contraception and reproductive coercion experienced by women with mental illness result in increased rates of unwanted pregnancy and abortion. If co-designed reproductive health interventions were integrated into primary and secondary mental health care settings globally, women with mental disorder would be more likely to make informed choices about their reproductive health, which would potentially improve not only their reproductive health but also their mental health.

We hope that this paper and the accompanying commentaries will advance the understanding and treatment of mental health problems in the context of women's reproductive health across the life course. We do not include here events related to pregnancy and the postpartum, as these have been covered recently in another Forum published in this journal[12].

MENSTRUATION AND MENSTRUAL-RELATED DISORDERS

Menstruation refers to the cyclic physiological process in which the endometrium of the uterus sheds through vaginal bleeding, occurring in females of reproductive age as part of the menstrual cycle. This is primarily regulated by fluctuations in levels of oestrogen and progesterone, orchestrated by the hypothalamic-pituitary-ovarian axis.

The cycle can be divided into several phases: the follicular phase, characterized by the development of ovarian follicles and rising levels of follicle stimulating hormone (FSH) and oestradiol; ovulation, triggered by a surge in luteinizing hormone (LH) and involving the release of a mature egg from the ovary; and the luteal phase, marked by the secretion of progesterone and oestradiol from the corpus luteum, which develops from the remnant of the follicle, to prepare the uterus for potential implantation. If fertilization does not occur, hormone levels decline, leading to the shedding of the endometrial lining during menstruation, marking the beginning of a new cycle[13].

The periodic changes that characterize the menstrual cycle are associated with an increased risk for a range of mental health conditions and psychiatric outcomes.

Premenstrual syndrome (PMS) is the most common menstrual disorder, encompassing a range of physical and psychological symptoms occurring in the luteal phase of the menstrual cycle. PMS is estimated to be clinically significant in 20-30% of women[14]. Psychological manifestations may include anxiety, depression, irritability, restlessness, insomnia or excessive sleepiness, and feeling that everything is an effort[15]. However, challenges exist in accurately assessing PMS, due to variability in the type, severity and timing of symptoms across individuals and menstrual cycles; the reliance on self-reported symptoms, which can be influenced by individual perceptions and interpretations as well as by recall bias; the overlap between symptoms of PMS and those of other health conditions, including mood disorders; and a lack of objective diagnostic criteria. Indeed, a systematic review of prospective studies found no convincing evidence for the existence of a distinct premenstrual negative mood syndrome in the general population, and noted that synthesis of study findings was hindered by the diversity of sampling methods, assessment instruments, and cycle phase definitions used in the contributing studies[16].

A minority of women will experience a more severe form of mood disturbance, premenstrual dysphoric disorder (PMDD), which has been included for the first time in the ICD-11[17] and DSM-5[18] classifications. This diagnosis requires that, in the majority of menstrual cycles, at least five symptoms are present in the week before the onset of menstruation, which start to improve within a few days after that onset, and become minimal or absent in the week after menstruation. These must include one or more affective symptoms (marked affective lability, irritability or anger, depressed mood, or anxiety) and one or more additional symptoms (decreased interest in usual activities, concentration difficulties, marked lack of energy, marked change in appetite, hypersomnia or insomnia, a sense of being overwhelmed or out of control, and physical symptoms such as breast tenderness or swelling, joint or muscle pain, and a sensation of "bloating"). The symptoms should be associated with significant distress or interference with social functioning.

When adhering strictly to diagnostic criteria, which requires prospective tracking of symptoms over two cycles, the point prevalence of PMDD is 1.6% of menstruating females[19]. In studies using retrospective reporting of symptoms, this rises to 7.7%[19]. The condition is associated with an increased risk of suicidal ideation[20], and has a similar impact on quality of life as other chronic health problems[21].

The mechanisms underlying PMDD have been examined through experimental manipulation of hormones[22,23]. In women with the disorder, complete suppression of oestradiol and progesterone is sufficient to control symptoms, while the add back of either hormone reproduces the symptoms[24]. Interestingly, high steady levels of these hormones are also sufficient to control symptoms[25]. This has led to a model in which PMDD is caused by vulnerability to the physiological changes in hormone levels across the menstrual cycle[26].

There are various treatments for PMDD. Selective serotonin reuptake inhibitors (SSRIs) are recommended as a first-line treatment by UK[27] and American[28] guidelines. These medications have been shown to be effective in meta-analyses of randomized controlled trials (RCTs), with a larger effect size than in depression (a standardized mean difference of 0.65)[29]. They are as effective when dosed intermittently (during the luteal phase of the cycle) as when they are used continuously throughout the cycle[30], and have a peak effect at 48 hours[31], suggesting a different mechanism of

action than in depression.

Another treatment strategy is to stabilize hormone fluctuations, either through exogenous hormones or by suppression of the cycle using gonadotropin releasing hormone (GnRH) analogues. This is initially recommended in the form of combined oral contraceptives[27,28]. A network meta-analysis has shown that this treatment is effective compared with placebo[32], with no one formulation superior to others. Notably, while these interventions were effective in reducing premenstrual symptoms, reduction in depressive symptoms specifically did not reach statistical significance. Another method is using transdermal oestradiol; although this is recommended by UK guidelines[27], it is based on lower-quality evidence[33] and, notably, it is not recommended by American guidelines[28].

A range of mental disorders have evidence of menstrual exacerbation. Systematic reviews have identified some evidence of menstrual worsening in depression, mania, panic disorder, eating disorders, and emotionally unstable personality disorder[34,35]. In a meta-analysis, the perimenstrual phase was associated with an increased risk of psychosis, with an admission rate 1.5 times higher than baseline[36]. However, firm conclusions are limited by methodological problems. Most studies compared symptom ratings at one or two timepoints in the cycle. This is inadequate, as menstrual cycles show marked variability within and between individuals. Symptom changes should ideally be studied using a within-person design, over multiple timepoints, with robust measurement of cycle phase. Prospective rating of symptoms is needed, as retrospective recall is prone to bias.

While guidelines from the UK Royal College of Obstetricians and Gynaecologists advocate the option of hormonal treatments for mental disorders exacerbated by the menstrual cycle, this is based on limited evidence[27]. Further research into the impact of the menstrual cycle in mental disorders and the effects of hormone-based treatments is needed. It is nonetheless important that health care professionals working with menstruating women enquire as to whether their menstrual cycle is associated with changes in their mental health.

Irrespective of psychiatric diagnosis, the menstrual cycle appears to be related to risk for suicidal behavior. In women with a history of suicidality, the time around menstruation is associated with increased suicidal ideation and planning[37]. Depressive symptoms appear to be the main mediators of this perimenstrual exacerbation[37]. Although a meta-analysis reported that suicidal ideation was unrelated to the stage of menstrual cycle, it found evidence for a 17% greater risk of suicide attempts, 26% greater risk of suicide deaths, and 20% greater risk of psychiatric admission at menstruation, with the menstrual phase more strongly associated with serious mental health outcomes than the premenstrual phase[38]. While completed suicide is more common in men, suicide attempts are more frequent in women[39], and menstrual cycle fluctuations are a potentially modifiable risk factor for suicidality in women.

Although hormonal fluctuations appear to drive the above findings, social factors can profoundly shape women's experiences of menstruation and their mental well-being. Menstruation continues to be stigmatized in societies around the world[40]. Such stigma may prevent women from accessing health care for menstrual problems, as well as being a contributing factor to mental disorders. Sociological studies illustrate how women often conceal menstrual symptoms due to entrenched social expectations, which influences daily activities, dress choices and interpersonal communication[41].

Feminist social scientists have also highlighted how menstruation is embedded within broader socio-cultural contexts, affecting women's gender identity, body image, and social status[42]. Cultural beliefs and media contribute to this broader social context, with profound consequences for women's psychological and sexual well-being[42]. Moreover, so-called "period poverty" – a global health concern estimated to affect up to 15% of young women in even urban high-income settings[43] – highlights systemic inequalities in access to menstrual products, education and sanitation, underscoring the broader social determinants impacting women's mental health.

CONTRACEPTION

The term contraception encompasses all methods to prevent pregnancy. It has been described as one of the most cost-effective health care interventions, in terms of preventing unintended pregnancy (defined as a pregnancy that occurs earlier than desired or is not wanted at all[44]) and reducing maternal and neonatal mortality[45]. Avoiding unintended pregnancy enhances educational opportunities for girls, with far-reaching consequences for life outcomes. Nevertheless, contraception has a complex relationship with mental health and, despite its use by a substantial proportion of the world's population, rigorous investigation of this relationship has been relatively recent[46].

Forms of barrier contraception have been used since antiquity. Modern barrier methods, such as the male condom, offer the advantage of protecting against sexually transmitted infections, in addition to pregnancy[47]. In typical use, barrier methods are less effective in preventing pregnancy than hormonal contraceptives, and generally require the cooperation of both partners[47]. The advent of hormonal contraception has afforded women's reproductive freedom, aided effective family planning, and provided symptom relief for conditions such as acne, endometriosis and the aforementioned PMDD[48]. In 2022, it was estimated that modern contraception prevented approximately 29 million unsafe abortions and 148,000 maternal deaths in lower-income countries in a single year[49].

Although in low- and middle-income countries there has been a clear rise in modern contraceptive use over the past decade, the overall percentage use remains lower than in high-income countries. Shorter-acting forms of hormonal contraception are more common in low- than in high-income countries, while longer-acting formulations are more frequently used in the latter[50]. The most common hormonal method globally is the oral contraceptive with formulations of either combined oestrogen and progestin or progestin-only[51]. Non-oral forms can also be combined (e.g., patches or vaginal rings) or progestin-only (e.g., injections, implants or the levonorgestrel-releasing intrauterine system). Combined contraceptives exert action primarily through the inhibition of ovulation, while progestin-only contraceptives act to thicken cervical mucus

and thin the uterine endometrium[52].

There is most likely a bidirectional relationship between women's mental health and the choice of contraceptive method, the way in which it is used, and its subsequent effectiveness. Hormonal contraception decreases the use of barrier contraception, with a consequent increased risk of sexually transmitted infections[53]. Contraception effectiveness is known to be affected by a range of factors, including adherence, and there is evidence for reduced adherence in women with mental disorders. In severe mental illness such as schizophrenia[54], symptoms such as impaired cognitive function, disorganization and impulsivity may compromise consistent or correct use of contraceptives[55]. There may also be a relationship between depression and not using contraception, contraceptive discontinuation, or inconsistent contraceptive use.

In a cohort of 52,325 women in the US, those with a history of depression in the year prior to contraception initiation were more likely to use it inconsistently, discontinue it, or switch to another form within a year of initiation. In the same study, women with depression were also less likely to use the oral contraceptive pill, favouring other forms of hormonal contraception (e.g., patches or rings)[56]. The wider body of evidence yields mixed findings as to whether longer- or shorter-acting forms of contraception are preferred among women with depression[57-60]. However, evidence from prospective studies confirms a relationship between depression and subsequent poorer contraceptive adherence[57,58,61,62].

While there are clear benefits to women's mental health from having access to contraception, there is mixed evidence of the impact of hormonal contraception on mental health. Some observational studies have suggested an association between the use of this contraception and an increased risk of subsequent depression. In a Danish national cohort, the risk of a first diagnosis of depression or antidepressant use increased among those using any form of hormonal contraception, compared to those who did not[63]. While these associations could reflect reverse causality, subsequent studies have suggested that the risk for depression is most pronounced with progestin-only forms of hormonal contraception[64].

A UK Biobank study attempted to overcome the issue of reverse causality using sister pairings[65]. Compared to those who had never used contraception, oral contraceptive users displayed an increased risk of depression, predominantly within the first two years of initiation (hazard ratio, HR=1.71; 95% CI: 1.55-1.88), and the sibling analysis suggested a causative effect. However, two RCTs (N=348 and N=202) of combined oral contraceptive versus placebo found no associated increase in depressive symptoms, although there was some association with anxiety symptoms[66] and a decline in general well-being[67].

A recent systematic review and meta-analysis concluded that oral contraceptives are not associated with the development of mental health symptoms in the general population, though noting that adolescents and users of progestin-only preparations are potentially at increased risk[64]. Most studies included in the review focused exclusively on depressive rather than anxiety symptoms, and the majority were observational. Another systematic review found a lack of evidence of a relationship between progestin-only contraceptives and depression, though there was a dearth of high-quality studies[68].

Another mental health outcome which has been investigated in relation to contraception use is suicidal behavior, including suicidal ideation, suicide attempts and completed suicide. Three large database studies reported an association between suicidal behavior and oral contraceptive use, particularly within one year of treatment initiation[69-71]. However, a systematic review found that the relationship between hormonal contraceptive use and suicide risk displays considerable variability across studies[72]. Of nine studies reporting on six samples (N=683,198), some suggested no association or even a protective effect against suicide attempts and completed suicide, while others indicated an increased risk of suicide attempts and completed suicide. Inconsistencies in results were attributed to various factors, including variability in samples and consideration of concurrent depressive symptoms. None of the included studies adjusted for family mental health history or childhood adversity as potential confounders. Although the review was unable to draw a firm conclusion regarding an association between hormonal contraceptive use and attempted or completed suicide, it reported some evidence suggesting a higher risk of attempted suicide at initiation of hormonal contraceptive use compared to continued use and that, as such, adolescent women experienced the highest risk. Further research using population-based samples and including exposure to more recent hormonal contraceptive methods is needed to clarify this relationship.

High discontinuation rates have complicated analyses in this field. Many studies have found short-term associations between worsening mental health and hormonal contraception[63,69-71], suggesting that longer duration of use is protective. However, these results could indicate healthy survivor bias, particularly in population-based studies. This is because users experiencing adverse symptoms are more likely to discontinue treatment early, so that the remaining participants will present with more tolerable side effects.

There are benefits and potential risks of contraception to women's mental health, and each individual has the right to make choices over her reproductive health. When considering the mental health risks associated with use of hormonal contraception, there is suggestive evidence that younger women, those with a history of depression, and those using progestin-only preparations are at highest risk. While more definitive research is awaited, an individualized approach to contraceptive decision-making is likely to yield the best outcomes for women and their mental health, including the avoidance of unintended pregnancy.

ABORTION

Induced abortion, also known as termination of pregnancy, is a medical procedure to end pregnancy, which can be done using medication or through surgical intervention. We focus here on induced abortion and do not cover spontaneous abortion, commonly referred to as miscarriage or early pregnancy loss.

Global trends show a decline in rates of unintended pregnancy[72,73], partly due to improved access to contraception. However,

existing contraceptive methods have limitations, and some women who are unable or unwilling to use them may still wish to avoid pregnancy. Additionally, circumstances may make continuing a (planned) pregnancy challenging for some women. Ensuring access to safe and legal abortion, alongside effective contraception, is therefore essential to promoting reproductive autonomy.

One study[74] reported a reduction of abortion rates in Europe and North America between 1990-1994 and 2010-2014, with rates stabilizing elsewhere, regardless of the status of legal abortion[74]. Although another study[75] similarly estimated a reduction of the global abortion rate for approximately 15 years after 1990-1994, it also found that, by 2015-2019, the abortion rate returned similar to that estimated for 1990-1994. Worldwide, in 2015-2019, there were an estimated 121 million unintended pregnancies annually, corresponding to a global rate of 64 per 1,000 women aged 15-49 years. Of these pregnancies, approximately 61% ended in abortion, with a global abortion rate of 39 per 1,000 women aged 15-49 years. Disparities in abortion rates were observed across World Bank income groups, with middle-income countries exhibiting the highest rate (44 abortions per 1,000 women aged 15-49 years) and high-income countries the lowest (15 abortions per 1,000 women aged 15-49 years)[75].

Within each World Bank income group, countries with more restrictive abortion laws reported higher rates of unintended pregnancies compared to those with broader legal access to abortion services. Specifically, high-income countries, where abortion is broadly legal, exhibited the lowest annual average rate of unintended pregnancies (30 per 1,000 women aged 15-49 years), whereas low-income countries with restrictive abortion laws experienced the highest rate (101 pregnancies per 1,000 women aged 15-49 years). Furthermore, the annual abortion rate varied substantially across income groups and legal frameworks. In high-income countries where abortion was broadly legal, the abortion rate stood at 11 per 1,000 women aged 15-49 years, notably lower than in high-income countries with restrictive laws and middle- and low-income countries regardless of legal status.

Several rigorous studies and reviews of the literature[76-85] have consistently concluded that abortion does not increase the risk of mental disorders. For example, in a population-based cohort study utilizing Danish population registry data, researchers compared the psychiatric outcomes of girls and women who underwent first-trimester induced abortion or childbirth between 1995 and 2007, finding that the incidence of psychiatric contact did not significantly increase after abortion (14.6 to 15.2 per 1,000 person years)[83].

Other mental health outcomes have also been examined in Danish registries. When first-time antidepressant prescriptions were considered, there was no evidence of an increase in prescriptions during the year following (incidence rate ratio, IRR=1.54; 95% CI: 1.45-1.62) compared to the year prior to abortion (IRR=1.46; 95% CI: 1.38-1.54) (compared to those not undergoing abortion)[86]. Another outcome used has been first-time non-fatal suicide attempts: there was no evidence of an increase between the year prior to (IRR=2.46; 95% CI: 2.22-2.72) and the year after an abortion (IRR=2.54; 95% CI: 2.29-2.81)[87]. A Dutch prospective cohort study, which compared women who had abortions to women who did not, matched on key confounders, found no evidence for an increased likelihood of incident or recurrent mental disorders over the short (2.5 to 3 years post-abortion) or long term (5 to 6 years post-abortion)[88,89].

Although some studies have suggested a link between abortion and adverse mental health outcomes, they do not support causation, as they failed to adjust for pre-existing mental disorders and other confounders, such as pregnancy intention and intimate partner violence, and/or had other serious methodological flaws[82,85,89-93]. Such flaws include the inadequate measurement of exposure and outcome variables; the use of small, non-representative study samples; low response rates and high levels of loss to follow-up[94].

Women with mental disorders have been found to have a higher risk of unintended pregnancy or abortion[84,95]. A Canadian population-based study reported that, over a three-year period, women with schizophrenia had consistently higher abortion rates than those without this disorder (15.5-17.5 vs. 12.8-13.6 per 1,000 women, and 592-736 vs. 321-341 per 1,000 live births)[96]. Factors associated with increased abortion rates among women with schizophrenia included younger age, multiparity, comorbid non-psychotic mental disorder and substance use disorder.

A Finnish study which also used population-based data similarly found that women with schizophrenia had a higher rate of abortion than those without this disorder, also reporting that terminations performed after 12 weeks of gestation were more prevalent among women with schizophrenia[97]. This study additionally found that the majority of abortions were conducted for social rather than medical reasons.

Several potential mechanisms underlie the above association [61,98-100]. For example, mental disorders can impact contraceptive choices or adherence, increase the risk of sexual coercion, and, in women with conditions such as bipolar disorder, lead to hypersexual behavior. Moreover, amenorrhoea subsequent to antipsychotic-induced hyperprolactinaemia or to anorexia nervosa may lead women to erroneously believe that they are infertile and increase the risk of unintended pregnancy and abortion. Finally, for women with a mental disorder, pregnancy may more often be unwanted, potentially mediated by other factors such as socioeconomic circumstances and impaired self-efficacy[57,101].

Research has examined what predicts poorer mental health outcomes around the time of abortion (a question that is distinct to that of whether abortion increases the risk of mental disorder). While predictors of poor mental health outcomes among women undergoing abortion include prior mental disorder, unstable relationships and adverse experiences such as intimate partner violence[76,82,84,102], these are general risk factors for mental disorders, again suggesting that abortion itself does not pose specific risks for future mental health issues.

Abortion stigma and structural barriers to abortion access have also been identified as predictors of mental disorder among women having abortion[103-105]. Research has also examined the impact of restricting access to abortion services on the risk of mental dis-

order among women of reproductive age[106-109]. In the US, the Turnaway study found that those denied an abortion due to being just over the gestational limit had higher anxiety and stress symptoms and lower self-esteem eight days later compared to those who were able to get an abortion[76,110,111]. Among women eligible to participate in this study, 38% consented to participate, and attrition between baseline and 5-year follow-up was 42% for both groups – an impressive retention for such a long duration of follow-up – and the results were robust to appropriate sensitivity analyses.

Other longitudinal ecological studies conducted in the US, using difference-in-differences analyses, report that abortion restrictions are associated with increased rates of suicide and mental health symptoms among reproductive-aged but not older women[106]. While the design of these studies limits causal inference, these and similar findings suggest that limitations on reproductive autonomy may contribute to an elevated risk of mental disorder for women of reproductive age[106-109]. Indeed, women whose reproductive autonomy is most restricted or who experience most obstacles to abortion services are often those with fewer resources[107-109,112], and those who have been historically marginalized[113]. Ensuring safe and accessible abortion services is of critical importance for women's mental health. Integrated care approaches are likely to be needed, especially for women with mental disorders, to reduce the risk of unintended pregnancy and subsequent abortion.

SEXUAL DYSFUNCTION

Sexual dysfunction is common among women in the general population, with an estimated 41% of women of reproductive age experiencing it during their lifetime[114]. It is characterized by symptoms such as reduced libido, difficulty with arousal and/or orgasm, and genito-pelvic pain or penetration disorder. Risk factors include lack of an intimate relationship, poor body image, low levels of sex education, younger age, lack of exercise, and early life trauma, particularly sexual abuse[115]. A satisfactory sexual life necessitates social interaction skills, an understanding and acceptance of one's sexual orientation, self-confidence, and adequate sexual physiology. Historically, women's sexuality has been undervalued[116-119], leading to limited investigation compared with men's sexuality.

Sexual dysfunction in women is commonly a symptom or manifestation of psychological distress or underlying mental disorders. For example, low libido is a cardinal symptom of depressive disorder, while increased sexual interest is common in mania, as discussed further below. Some treatments for mental disorders are also linked to increased risk of sexual dysfunction[120]. Overall, the prevalence of sexual dysfunction is increased in women with mental disorders, being found to exceed 60% in this group[121-124]. These women are also less likely to have their sexual and reproductive health attended to appropriately[125]. Some risk factors for sexual dysfunction overlap with those for mental disorder. Therefore, women who are at higher risk for mental disorder are also at higher risk for sexual dysfunction.

Normal sexual function involves a complex interplay of central and peripheral neurotransmitters, neuropeptides and hormones, as well as a range of psychological and socio-cultural factors. Many psychotropic medications impact neurotransmitters, affecting mood and sexual function, over and above the dysfunction that might be related to the illness itself. These include benzodiazepines, antidepressants, antipsychotics and mood stabilizers. Recreational substances, including alcohol, are also associated with sexual dysfunction[124,126-128].

Medications can affect sexual function through direct central nervous system (CNS) effects (e.g., dopaminergic increase resulting in increased libido), indirect CNS effects (e.g., sedation secondary to histaminic effects), and hormonal effects (e.g., dopamine blockade causing hyperprolactinaemia).

Dopamine and serotonin, both important neurotransmitters with respect to emotional and mental functioning, play crucial roles in sexual function. Dopamine stimulates testosterone, the hormone of sexual desire (more so than oestrogen in women) in both males and females. Testosterone, in return, stimulates both dopamine and noradrenaline, which both have positive effects on sexual function. Increased sexual activity is therefore seen with dopamine agonists, and reduced sexual activity with dopamine antagonists. As dopamine is the main prolactin inhibitory factor, the reduction of dopamine results in hyperprolactinaemia, which causes low libido and hypogonadal states, with marked negative effects on vaginal response and orgasm[129,130]. Serotonin agonists are associated with sexual dysfunction, with 5HT2A receptor stimulation, in particular, being related to impaired sexual function, and 5HT2C stimulation to increased sexual function. In addition, serotonin stimulates secretion of prolactin, which is inhibitory to sexual function. It is estimated that, on average, 50% of people experience sexual side effects with SSRIs. A small percentage (3 to 5%) report persistent sexual dysfunction despite cessation of the medication. This condition, known as persistent post-SSRI syndrome, is marked by genital anaesthesia and pleasureless orgasm, and is less common in women than in men[131,132].

Thus, the relationship between sexual dysfunction and mental disorders is complex, and may be influenced by the presenting condition or have arisen as a result of treatment[133]. Managing sexual dysfunction is crucial to a satisfactory sexual life, treatment adherence, and better mental health. A sexual and reproductive clinical history before starting medication, as well as psychoeducation about potential sexual side effects, is recommended. Sexual function should be regularly monitored. Dose reduction or switching to medications with fewer sexual side effects can help manage psychotropic-related sexual dysfunction[128,134-137].

For antipsychotic-induced dysfunction, the use of aripriprazole as an alternative or (if unable to stop the current antipsychotic) adjunctive treatment has shown effectiveness[128,134,136]. For antidepressant-induced sexual dysfunction, higher doses of bupropion are supported by moderate-quality systematic review evidence[135]. Evidence to support the use of psychological therapies is sparse[138], although there are some randomized trials indicating improvements in sexual functioning using a cognitive behavioral approach[139]. There is also some limited evidence to support the use of sildenafil, particularly for sexual dysfunction related specifically to arousal[138]. Hormone therapy, for example with testos-

terone, is currently only considered in cases of sexual dysfunction characterized by reduced sexual desire[140]. It is known to increase libido, particularly in post-menopausal women, but with side effects such as hair loss on the head and hair growth on the body.

Broader socio-cultural and structural factors influence women's sexual experiences, highlighting the importance of considering the broad range of social determinants of sexual and mental health[115]. Societies with greater gender inequality are marked by higher levels of sexual dysfunction in women. Women in male-dominated societies report worse sexual health and less sexual satisfaction compared to those in more gender-equal environments. Different risk factors arise globally, influenced by social and religious contexts. For example, in some countries, polygamous relationships and having undergone female genital mutilation are associated with worse sexual function[115].

HYPERSEXUALITY

Hypersexuality is a pathological increase in sexual thoughts and behaviors[141]. It can occur in various mental disorders, but the ICD-11 now also includes a distinct diagnosis of compulsive sexual behavior disorder, classified as an impulse control disorder. This disorder is defined as a persistent pattern of failing to control intense, repetitive sexual impulses or urges, leading to repetitive sexual behavior over an extended period (i.e., six months or more) that causes marked distress and/or impairment in important areas of functioning, including the neglect of other alternative activities[17]. Other features include unsuccessful efforts to reduce the behavior, and its persistence despite adverse consequences and/or deriving little or no satisfaction from it.

Epidemiological data on the prevalence of compulsive sexual behavior disorder in women are scarce, but studies suggest that it is far less common than in men, with a male-to-female ratio of about 3:1[142]. Population-level estimates (not aggregated by gender) range from 1 to 6%[143].

The dopaminergic system is implicated in the pathophysiology of the disorder[142]. Indeed, use of dopamine agonists is associated with compulsive sexual behavior[144]. There may be links to adverse childhood experiences, such as abuse (although more commonly associated with sexual avoidance), underpinned by epigenetic changes in the corticotropin-releasing hormone gene and hypothalamic-pituitary-adrenal (HPA) axis dysregulation[142]. However, most research in this area has been conducted in men. Attachment difficulties, which are also associated with early exposure to sexual abuse, have been implicated in both male and female samples[142].

Social factors, such as societal attitudes towards sexuality, including religiousness and moral conservatism, are also correlated with the disorder[142]. Moral incongruence, where individuals engage in behaviors they disapprove because of their moral beliefs, may also explain the tendency to attribute these behaviors to an addiction, increasing the likelihood of seeking medical attention[145]. The ICD-11 definition clarifies that distress about sexual behavior arising exclusively from religious or moral concerns is not enough to justify a diagnosis of compulsive sexual behavior disorder[17].

Hypersexuality may also arise in the context of other mental disorders. The ICD-11 lists "increase in sexual drive" among the symptoms of mania[17], while the DSM-5 refers to hypersexuality both within "increase in goal-directed activity" and "excessive involvement in activities that have a high potential for painful consequences" when describing a manic episode[18]. For some individuals with bipolar disorder, subtle changes in sexual drive may be an early warning of a manic or hypomanic episode[146]. Studies have observed an increased frequency of sexual intercourse in people with mania[147], and people with bipolar disorder may engage in more frequent extramarital affairs[148-152] and changes of sexual partner[153]. A review highlighted gender differences in the incidence and severity of risky sexual behavior in bipolar disorder, with women engaging in more dangerous behaviors during manic or hypomanic episodes compared to men[154]. Hypersexuality may also occur in borderline personality disorder, in which sex is listed as a potential area of impulsivity in both the ICD-11[17] and the DSM-5[18]. For a diagnosis of compulsive sexual behavior disorder, sexual behavior must be persistent, independent of mood episodes, and not be explained by other organic conditions (e.g., dementia) or use of substances (e.g., cocaine or methamphetamine)[17,143].

Management of compulsive sexual behavior disorder primarily involves psychological intervention, with no pharmacological therapies specifically licensed for it (although many are used to treat comorbid psychopathology, the evidence for which is confined to case studies)[155]. Evidence for psychotherapeutic approaches is sparse[144], with a 2020 systematic review highlighting a complete lack of high-quality literature[156]. Some studies have examined the effectiveness of psychoeducational, cognitive behavioral, and acceptance and commitment approaches, but these have involved predominantly male samples[156].

An emerging qualitative literature describes the experiences of women who have undergone periods of hypersexuality, with many reporting significant shame, particularly in parts of the world with more stigma related to women's sexuality[146]. In some cases, hypersexuality and its consequences (which may include sexual assault) may be associated with post-traumatic stress disorder (PTSD)[157,158]. Yet, like other areas of women's sexual functioning, the experience and phenomenology of hypersexuality is understudied. In borderline personality disorder, most research has focused on sexual impulsivity, which is conceptualized as both an increased number of "casual" sexual partners and an earlier age of first sexual intercourse, with more evidence for the former[159]. In bipolar disorder, it remains unclear the extent to which hypersexuality is experienced in women as increased sexual interest alongside increased energy and disinhibition, or it results from increased impulsiveness and risk taking.

Regardless of its aetiology or underlying diagnosis, it is important that hypersexual behavior is identified by health care professionals, because of its potentially devastating impacts on individuals, partners and families, including increased risks of sexual abuse and exploitation.

SEXUAL VIOLENCE AND REPRODUCTIVE COERCION

Sexual violence refers to any sexual activity that happens without consent, regardless of the relationship between the perpetrator and the victim, and the setting in which it occurs. It includes (but is not limited to) rape, sexual exploitation, sexual assault, sexual harassment, and indecent exposure. Reproductive coercion intersects closely with, but goes beyond sexual violence, aiming to "maintain power and control in a relationship related to reproductive health"[160]. It may be perpetrated by an intimate partner or family member, and disproportionately affects women and girls of reproductive age[161,162]. It encompasses manipulation, emotional blackmail, threats, and various forms of abuse (physical, sexual or financial) that can be promoting pregnancy (e.g., contraception sabotage, forced sex to cause pregnancy, pressured or forced continuation of pregnancy) or preventing pregnancy (e.g., pressured or forced sterilization or use of contraception, pressured or forced abortion, physical violence to induce miscarriage)[163-166]. It is associated with an increased risk of unintended pregnancy, increased severity of intimate partner violence during pregnancy, and intimate partner homicide[167].

Sexual violence is pervasive globally. In the US, the National Intimate Partner and Sexual Violence Survey indicates that 19% of women have experienced rape in their lifetime[168]. In Europe, the European Union Fundamental Rights Survey found that 5% of women had been raped since age 15, with varying rates across countries, ranging from 4 to 17%[169]. Technology-enabled sexual violence is also emerging as an issue of concern: recent research conducted in the UK, Australia and New Zealand found that more than one third of participants in an online panel survey of general community members aged 16-64 years had experienced image-based sexual abuse since age 16[170]. An analysis using Global Burden of Disease data indicates that, although there has been an overall decrease in the rate of sexual violence over time, the rate of decline is slow. In low human development index countries, the trend has been one of increasing sexual violence against women[171].

The prevalence of reproductive coercion in women and adolescent girls ranges from 8 to 30%, with 1 to 19% experiencing pregnancy coercion and 7 to 15% contraceptive interference[164,165,172]. Evidence from low- and middle-income countries is relatively scarce, but studies from Ethiopia, Kenya and India report prevalences from 11 to 28%[173-177]. Risk factors include young age, single status, being non-White, living in poverty, being less educated, and having a partner who has other concurrent partners[172,176,178]. Migrant and refugee women may also be more susceptible[179,180]. US data suggest that women with disabilities face up to a four-fold increased risk[181]. Reproductive coercion is of particular concern in gender-unequal societies, where other intersecting forces – including those based on ability, race and sexual orientation – are involved[182]. Investigation of the epidemiology of reproductive coercion is hindered by the conceptual ambiguity and inconsistent measurement of this form of abuse[164,165,176,179].

Both sexual violence and reproductive coercion have a close (likely bidirectional) relationship with mental health. Risk of sexual violence is particularly high among women with mental disorder. In one study, 61% of women with severe mental illness had experienced sexual violence in adulthood (including 10% in the past year) versus 21% of women in the general population[183]. Research conducted in sexual assault referral centres in England (which provide a single point of access for people who have experienced sexual assault) suggests that up to 40% of attendees are already known to mental health services[184]. Women who experience sexual violence are also at significantly greater risk of mental disorder. The impact of sexual violence goes beyond PTSD to encompass a range of other mental disorders[185,186].

Research has attempted to identify risk and protective factors for mental disorder following sexual violence. Risk appears to be similar across demographic groups, but some assault characteristics appear relevant: weapon use and physical injury are associated with higher risk of mental disorder[186]. There is mixed evidence on whether the characteristics of the perpetrator influences risk for mental disorder in women. While a meta-analysis found that stranger-perpetrated sexual violence was associated with a higher risk of psychopathology in women[186], a more recent study indicated higher risk of depression in women from partner-perpetrated sexual violence[187].

Suicidal ideation and attempts are also more common among survivors of sexual violence[186]. Suicidality is more strongly associated with sexual violence than with other types of traumatic experiences, and the association appears to be independent of other comorbid disorders[188]. Although associations between sexual violence and substance use have been documented, prospective studies that control for pre-assault drinking do not indicate an increased risk of substance use following sexual assault[189,190].

Proposed mechanisms linking sexual violence and mental disorder include direct distress from the violence, negative social experiences such as lack of support and blame, and biological repercussions such as HPA axis dysregulation[191]. Pre-existing coping strategies, genetic vulnerability to mental disorder, and heightened vulnerability of people with mental disorder to sexual violence are also likely to be important[186,191-194].

Studies similarly report associations of reproductive coercion with depression, anxiety, PTSD and substance use[195-197]. There is evidence that mental disorder may moderate the outcomes of reproductive coercion. For example, PTSD and depression could diminish women's self-efficacy, potentially creating a barrier to the use of effective contraception and resulting in unintended pregnancy[198]. Risk is also increased where the economic deprivation and stigma associated with living with mental disorder forces people into vulnerable situations and exploitative relationships, limits access to protective services, and reduces ability to escape abusive environments.

Finally, it is important to acknowledge that mental health services may themselves be sites of sexual violence risk and further re-traumatization: a review by the UK Care Quality Commission of incidents on mental health inpatient wards identified more than 400 cases of sexual assaults or harassment of patients and staff over a three-month period, including 29 allegations of rape[199].

Enquiry about violence and abuse, including sexual violence

and reproductive coercion, is an important part of the health system response. Enquiry should usually be conducted in private settings, excluding intimate partners, family and carers[200]. The World Health Organization (WHO) and the World Psychiatric Association (WPA) recommend a LIVES approach (Listening non-judgmentally and empathically; Inquiring about needs and concerns; Validating experiences; Enhancing safety for victim and family; and Supporting and connecting to information and services)[201]. Health care providers can also play an important role in responding to mental health concerns and offering empathetic and non-judgmental first-line support[202]. The social context is pivotal, with perceived social support and positive regard both important to recovery[203]. Many survivors experience feelings of shame and self-blame, and many report disbelieving, judgmental and stigmatizing attitudes from families, communities and services, which reduce willingness to disclose sexual violence and to access support[204-206].

Recently, the CARE (Choice and control; Action and advocacy; Recognition and understanding; Emotional connection) model was developed specifically as a survivor-centred approach to reproductive coercion, for practical and emotional support[207]. The ARCHES (Addressing Reproductive Coercion in Health Settings) intervention, though lacking a specific mental health focus, has shown promise in reducing reproductive coercion among women experiencing multiple forms of such abuse in US settings[208,209]. Mental health components in such interventions remain a crucial gap.

Technology-assisted interventions that strive to reinforce the importance of accessing health services may be an effective and scalable option, especially in university, school and community settings where rates of reproductive coercion, violence and mental disorder are notably high[210-212]. RCT evaluation of a free safety planning app ("myPlan") found significant reductions in reproductive coercion and suicide risk over 12 months, suggesting some potential as a digital complement to broader responses aimed to support mental health among women exposed to violence and reproductive coercion[213].

Trauma-focused cognitive behavioral therapy and eye movement desensitization and reprocessing (EMDR) are evidence-based interventions to manage the trauma associated with exposure to violence and abuse[214]. Trauma debriefing is commonly practised, but evidence suggests that it does not prevent the onset of PTSD and may even increase risk[215]. Systematic review evidence highlights the importance of the context of psychosocial interventions in shaping how they are accessed and experienced by survivors[216]. These include organizational features, such as the setting or location in which interventions are delivered, and interpersonal factors such as being treated with warmth, kindness and respect.

Systematic reviews from both high- and lower-income settings report a range of psychological interventions that can improve mental health outcomes such as depression and PTSD[214]. However, there is little evidence on psychological interventions for other disorders, such as psychoses, or the extent to which the effectiveness of the interventions is moderated by recent, current or historical abuse.

INFERTILITY AND ASSISTED REPRODUCTION

Infertility is most commonly defined as an inability to conceive after at least 12 months of unprotected sexual intercourse[217]. Primary infertility refers to those who have never conceived, whereas secondary infertility, which is more common, describes those who have at least one child but have been unable to conceive again[217]. Social infertility describes people who are single or in same-sex relationships who require fertility treatment[218].

Infertility affects 8 to 12% of heterosexual reproductive age couples, rising to nearly 30% in low- and middle-income countries[219-221]. Male factors (for example anatomical abnormalities and sperm deficiencies) and factors related to women (for example uterine fibroids, endometriosis, and ovulatory dysfunction) each account for approximately 40% of infertility cases, with the remaining 20% unexplained[217,222].

Demand for infertility treatment has increased, due to delayed childbearing and improved treatment success rates[223], and is expected to continue rising[224]. Common treatments include ovulation induction, OI (in which medications are used to stimulate the ovaries); intrauterine insemination, IUI (in which sperm is injected into the uterus); surgery (for example in endometriosis); and in vitro fertilization, IVF (in which the sperm and oocyte are combined in the laboratory to produce embryos, which are then transferred back to the woman's uterus)[217]. Multiple cycles of treatment are typically required, with up to six cycles of OI[225] and three or more cycles of IVF often recommended[217]. Women may start with less invasive treatments, such as OI or IUI, and progress to more invasive treatments such as IVF if needed. The treatment process can take years[226], and can significantly impact mental health, due to associated emotions of grief, loss, frustration and anger[222,223].

Women with infertility and/or undergoing treatment frequently experience symptoms of mental disorder[219,227]. Up to 78% report anxiety symptoms and up to 56% depressive symptoms[217,219,228-231]. There have been reports of transient psychosis with some infertility treatments[232]. Other mental health consequences include sexual dysfunction, somatization, panic attacks, and eating disorders. Infertility treatments can cause physical side effects such as headaches, dizziness, sleeplessness, breast pain, and joint pain[217,223,227].

Emotions associated with treatment are amplified with multiple cycles[222], which can increase strain on relationships, finances and employment[217]. Approximately 30% of those undergoing infertility treatment will not achieve parenthood[233], and the decision to stop treatment represents a permanent loss of potential parenthood[222]. High psychological burden is a common reason for stopping treatment, even where there is a good medical prognosis and financial capability for further cycles[217,227,233].

The impact of psychological distress on treatment outcomes is unclear. While some women, and those in their social support network, believe that stress can cause infertility and reduce treatment success[234], two of three systematic reviews of emotional state and pregnancy outcome found no association[220,235,236]. Although a systematic review and meta-analysis of cortisol and pregnancy outcomes found associations in eight of twelve studies, the direction

of these associations was mixed[237].

Psychological interventions such as cognitive behavioral therapy, mind-body interventions, counselling, yoga, relaxation, exercise, and positive reappraisal therapy can reduce depression, anxiety and stress, and enhance well-being in women with infertility[219,238-240]. Evidence on whether psychological interventions designed to reduce anxiety and depression in women with infertility lead to an increase in pregnancies is, however, mixed[220,230,238,240-247].

Women with affective and non-affective psychotic disorders exhibit lower fertility rates compared to those without these disorders and those with common mental disorders[248-250]. This has been attributed to several factors, including the impact of the illness on affect and behavior, which can impair the ability to form and sustain stable relationships, and medication side effects such as hyperprolactinaemia. The advent of second-generation antipsychotics, perceived to have fewer side effects impacting fertility, was therefore expected to improve fertility outcomes for women with psychotic disorders. However, a recent retrospective cohort study using UK data found similarly low pregnancy rates regardless of using first- or second-generation antipsychotics, with a notable increase in pregnancy rates upon discontinuation of these medications[251]. This may be due to confounding factors such as illness severity, with healthier women more likely to conceive and stop medication, or to the side effects of second-generation antipsychotics negating potential fertility benefits.

GYNAECOLOGICAL CONDITIONS RELATED TO FERTILITY

Some gynaecological disorders, including endometriosis and polycystic ovarian syndrome (PCOS), reduce fertility and significantly impact women's mental health.

Endometriosis is a chronic disorder, resulting from the presence of endometrium-like tissue outside the uterus, which affects up to 15% of women of reproductive age[252-256]. The aetiology is likely multifactorial, involving hormonal, genetic, inflammatory, environmental and immunological factors[253,254,257,258]. The main symptom is pain, with up to 83% of women experiencing pain during menstruation, sexual intercourse, urination or defecation and/or chronic pelvic pain[253,254,258,259]. Women may also experience heavy or irregular periods[253,254,259]. Other associated conditions include migraine, back pain, fibromyalgia, uterine fibroids, and ovarian cysts[257,259]. Treatments (including hormonal and non-hormonal medication, and surgery) aim to control pain, reduce recurrence, and improve physical functioning, but up to 59% report ongoing pain post-treatment[256,260,261].

PCOS is characterized by hyperandrogenism and menstrual irregularities, and affects up to 20% of women of reproductive age. It is associated with metabolic syndrome[262,263], and may increase the risk of endometriosis via inflammatory mechanisms[264]. Treatments include lifestyle modifications to reduce the risk of metabolic syndrome, and hormonal treatments to reduce the symptoms of hyperandrogenism[263].

Both endometriosis and PCOS can affect women's mental health, due to the burden of symptoms, treatment, fertility concerns, and chronic pain, impacting multiple areas of life, including education, employment and caring[257,260,265,266]. Endometriosis is associated with an increased risk of depression (odds ratio, OR=1.9, 95% CI: 1.6-2.1) and anxiety (OR=2.4, 95% CI: 1.1-5.4)[258,260,262,263,267,268]. Women with PCOS are more likely to have at least one mental disorder compared to those without (OR=1.6, 95% CI: 1.5-1.6)[268-270].

Evidence from meta-analyses shows that women with PCOS have an increased risk of symptoms of depression (ORs range from 2.6 to 3.8)[263,269] and anxiety (ORs range from 2.7 to 5.6)[263,269]. There is also preliminary evidence of a relationship between PCOS and subsequent psychotic disorders from a study using a Northern Finland birth cohort (HR=2.99, 95% CI: 1.52-5.82), with the hypothesized mechanism involving hyperandrogenism[271] and the protective role of oestrogen[272].

Increased risk of mental disorder may be related in part to the impact of PCOS on physical appearance[269,273,274]. There may be also a familial component, as higher rates of mental disorder have been found in siblings of women with PCOS, potentially explained by environmental factors, and alterations in androgen production or steroidogenic pathways[268]. Finally, inflammation underpins both endometriosis and PCOS and a number of mental disorders, such as depression[258,267,275,276].

PCOS may be treated with SSRIs and/or hormonal therapies. Oral contraceptives are used in PCOS to treat symptoms such as body hair growth and irregular periods. While their use has been associated with improvements in some domains of quality of life, evidence of their effects on depression is mixed and requires further investigation[268,269]. If prescribing psychotropic medications in women with PCOS, it is important that metabolic side effects such as weight gain are carefully considered, given the increased risk of metabolic syndrome[263,269,274]. In both PCOS and endometriosis, the use of psychological interventions, including cognitive behavioral therapy, has been associated with improved well-being and reduced symptoms of anxiety and depression[252,263,276,277].

The close relationships between mental health, fertility and associated gynaecological conditions underpin the importance of an integrated approach to clinical management, research and health policy within this area. Only 35% of women with PCOS report discussing mental health with their primary care physician[268]. Regular enquiry about mental health in this population, and consideration of the impact of the conditions and their treatment is critical to providing holistic care[263,268,269,278]. Indeed, there is evidence that depression and anxiety can make it more difficult for those with PCOS to adhere to their treatment plan and engage in lifestyle interventions[263,268,276].

MENOPAUSE

Menopause is defined as the permanent cessation of ovarian function[279], usually indicated by the last menstrual period. The mean age of menopause is 51 years, but this varies widely among individuals and regions of the world[279,280]. The menopausal transi-

tion, characterized by menstrual cycle irregularities and hormonal changes, starts five to eight years earlier[281]; this period through to one year after menopause is also called "peri-menopause". During these years, the ovarian production of oestrogens and progesterone decreases, often with significant fluctuations in blood levels[279].

Common peri-menopausal manifestations include vasomotor symptoms (hot flushes and night sweats, which can affect up to 80% of women), insomnia, poor concentration or "brain fog", low mood and sexual dysfunction, including vaginal dryness, dyspareunia and reduced libido[282-285]. Symptoms can continue for years and significantly reduce quality of life[282]. The hormonal changes that accompany menopause can also negatively influence mental health, as oestrogens have neuro- and psycho-protective properties[286,287]. In particular, 17-β-oestradiol, the natural oestrogen that is most active in the brain, can modulate different neurotransmitter systems – including serotonin, noradrenaline, dopamine, glutamate and acetylcholine[287-289] – with multiple effects on mental functioning[287,290,291]. The presence of 17-β-oestradiol is also associated with improvements in affective symptoms[290,292-294] and cognitive functioning[283-285,292,295-299], as well as antipsychotic properties[272,299,300]. There is also evidence that menopause can impact brain structure[287] and connectivity[301].

Research on the relationship between menopause and mental health suffers from a number of methodological limitations[302]. These include a lack of differentiation between menopause, peri-menopause and post-menopause; incidence and prevalence; mental disorders and symptoms; self-report and clinician assessments; and clinical and community-based samples. Furthermore, it can be challenging to ascertain what is "normal ageing" versus pathological change, and what may be attributable to hormonal versus psychosocial changes (e.g., losses and role transitions)[302,303].

The most methodologically sound studies suggest that peri-menopause (though not post-menopause) is a vulnerable period for depression: most longitudinal, population-based studies have reported an increase in depressive symptoms[304-307] and major depressive disorder, correlating with hormonal changes[304-307]. In a population-based cohort of 231 women aged 35-47 years without previous depression, followed up for eight years, new-onset depressive disorders were 2.5 times more frequent during the menopausal transition compared to pre-menopause[305]. Increased depressive symptoms correlated with higher FSH, LH and inhibin B levels, and greater variability of oestradiol and FSH levels, suggesting that, similar to PMDD, fluctuating rather than absolute hormone levels trigger depressive symptoms.

Likewise, in a population-based cohort of 643 women aged 36-45 years without previous depression, followed up for 36 months, there was a two-fold increase in depressive symptoms and disorders during the menopausal transition, especially in those with hot flushes[304]. Depressive symptoms were also associated with adverse life events[304]. A further two population-based cohorts of 3,302 and 221 women aged 42-52 years, followed up for ten years, observed a significant increase in depressive symptoms and a two- to four-fold increase in major depressive disorder in the peri-menopause and early post-menopause, independent of vasomotor symptoms or stressful life events[306,307].

One investigation that refutes this evidence was a prospective population-based cohort study of 168 women. While irritability and nervousness increased in peri-menopausal women, the prevalence of major depressive episodes did not increase. However, the study was not primarily designed to answer this research question, and only 27% of the sample had reached menopause at the time of assessment[308].

Although there remains some ongoing debate surrounding the relationship between menopause and depression[309], the main risk factor in the peri-menopause appears to be a history of prior depression, particularly related to hormonal changes, for example depression occurring during peripartum or PMDD[310,311]. This suggests that belonging to a subgroup sensitive to oestrogen withdrawal increases the risk for developing depressive symptoms during menopausal transition[312]. Women who suffer from hot flushes, sleep disturbances or vasomotor symptoms also seem to be at increased risk for depressive symptoms[306,310]. The risk is also higher in women who have a very late or prolonged menopause [313,314], or an abrupt surgical menopause with no hormonal substitution[313]. Psychosocial stressors, such as financial difficulties and lack of social support, are additional risk factors and interact with biological changes[304].

There is some evidence of an increased risk of new-onset psychotic disorders following menopause, supporting the "oestrogen protection hypothesis", which postulates that oestrogens are protective against psychoses[315]. In a representative sample of 392 first-admitted patients with psychoses, incidence was higher for young men than for young women but, after age 40, women experienced a second peak of onset, with an incidence about twice as high as in men[316]. These women also had more severe symptoms and a worse course of illness. Epidemiological studies have since confirmed these findings[287,317]. A recent systematic review also concluded that menopause can have a significant impact on women with schizophrenia spectrum disorders, with changes in symptomatology, cognitive function and quality of life[318]. An effect of menopause on the pharmacokinetics and pharmacodynamics of antipsychotics, with consequences on their bioavailability and on response to treatment, has also been reported[319].

Hormone replacement therapy (HRT) has traditionally been associated with managing physical menopausal symptoms, in particular vasomotor ones[279]. This therapy, particularly transdermally applied 17-β-oestradiol, seems also to improve depressive symptoms and may reduce the risk of major depressive disorder, especially if onset is during peri-menopause[320-323]. HRT is not officially approved for the treatment of menopausal depression either in Europe or the US, but clinical guidelines recommend its use for low mood, especially in peri-menopausal women with vasomotor symptoms[321-323]. 17-β-oestradiol may also have indirect positive effects on mental well-being by attenuating peri-menopausal complaints such as hot flushes, night sweats with sleep disturbances, and general irritability. It may thus contribute to a general improvement of the mental state, and to prevention of relapses.

Concerns about risks of treatment have led to controversy about oestrogen replacement. New studies, however, as well as re-analyses of earlier data (e.g., from the Women's Health Initiative study)

suggest benefits when oestrogen replacement is started early in a so-called "window of opportunity"[324]. An individual risk-benefit assessment is always necessary (including comparison with psychotropic medications), alongside close monitoring by an expert[321-327]. Alternatives such as selective oestrogen receptor modulators might also ameliorate symptoms in post-menopausal women with schizophrenia or depression[302,328]. However, results so far are inconsistent. SSRIs can ameliorate both depressive symptoms and hot flushes, and their augmentation with oestrogens seems particularly effective[329].

Psychotherapy is especially important, because this phase of life in women is often characterized by numerous psychosocial stressors, such as the realization of ageing, role transitions, and sexual and relationship difficulties. It may also be a period in which women feel the need to re-evaluate their life expectations, with gender stereotypes often having prevented them from pursuing their goals. Psychotherapy in this age group should also pay attention to women's subjective experience of the menopause, including their physical complaints, their fears and beliefs regarding menopause and the changes experienced, as well as their femininity and sexuality[303].

Cognitive behavioral therapy is recommended and has been adapted for menopause[322,330]. A meta-analysis of 14 RCTs found small-to-medium effect sizes for reductions in symptoms of depression and anxiety[331]. Empowerment and the development of self-confidence are essential elements of therapy[303,309,332,333]. Empowerment can also be achieved through education about menopause[332]. Given the range of physical and mental symptoms that women may be experiencing, an integrated approach considering both biological and psychosocial treatments, and tailored to individual needs, is essential.

IMPLICATIONS FOR RESEARCH

Women's reproductive mental health is under-researched. Stigma and societal taboos surrounding women's reproductive health may have contributed to this[12], along with a lack of women scientists in senior academic positions[10]. Another contributing factor may have been the negative findings of the early studies on women's hormones and mental health, due to their focus on between-person differences, as opposed to the growing body of recent research which has focused on within-person differences, highlighting the critical role of hormonal fluctuations in the genesis and maintenance of mental disorders, within the broader socio-cultural milieu[11]. A "sex and gender neutral" approach, failing to consider this component in the design, conduct and reporting of mental health research, risks undermining its scientific validity and efficiency. This in turn impairs the delivery of sex- and gender-sensitive mental health treatments and services.

Global inequalities in research capacity and in health care access pose challenges to the generalizability of what remains a limited evidence base. Many of the studies on women's reproductive mental health have been conducted in high-income countries, and translating findings to low- and middle-income contexts remains problematic. For some of the issues that are not experienced exclusively by women, for example hypersexuality and sexual dysfunction, there remains a preponderance of studies focused only on men. Moreover, there is a lack of research on how the lesbian, gay, bisexual, transgender, queer or questioning (LGBTQ+) and gender diverse communities experience reproductive mental health issues, including sexual violence, reproductive coercion, and infertility. Addressing these disparities is crucial for advancing understanding of and addressing reproductive mental health issues[218].

Women's reproductive mental health involves complex interactions of biological, psychological, social, cultural and political factors, necessitating interdisciplinary collaboration across fields such as psychology, obstetrics/gynaecology, psychiatry, public health, psychoneuroendocrinology and sociology. Such collaborations can drive innovative methodologies and interventions, shedding light on the mechanisms underlying mental disorders and guiding therapeutic approaches. Research is also urgently needed on the indications and contraindications of hormonal treatments for women with mental disorders, especially on the relative risks of hormones compared to psychotropic medications and/or the best augmentation strategies.

Social and structural determinants are likely to moderate the mental health impacts of reproductive events. Understanding their trajectory will require longitudinal research. To facilitate this, there needs to be routine data collection on exposure to the social determinants of mental health. Research should ensure the measurement and analysis of their impact in trials of (pharmacological and non-pharmacological) interventions, in observational cohort studies, and in the evaluation of public health interventions. More broadly, work is needed to improve the methodological rigour of research, addressing issues such as inconsistent measurement and conceptual ambiguity. Greater use of subgroup analyses is needed to identify specific risk factors, protective factors, and differential intervention effects based on demographic, clinical and contextual factors.

Investigating the complex and multifaceted sexed and gendered determinants of mental health, including those relating to reproductive life events, is essential for advancing understanding and treatment of mental disorders, benefiting women and society as a whole.

IMPLICATIONS FOR CLINICAL PRACTICE AND HEALTH POLICY

The intersection of women's reproductive and mental health, along with their complex biopsychosocial underpinnings, underscores the need for a holistic approach among clinicians caring for women of reproductive age, and among health policy makers considering how to respond to the increasing burden of mental disorder in this population[334]. Such an approach must account for both physical and mental health aspects, as well as for the broader social and economic contexts shaping women's experiences.

Policy change is needed across numerous domains, spanning menstrual health, contraceptive access, abortion rights, sexual vio-

lence prevention, trauma-informed care, fertility treatment access, and menopausal health care. Changes should seek to address social determinants of women's reproductive mental health, dismantling structural barriers, and safeguarding women's reproductive autonomy and mental well-being.

Health services need to be able to respond to the reproductive mental health care needs of their populations, including through the provision of gender-sensitive care. In particular, mental health clinicians should seek opportunities to enquire about reproductive and sexual health, including menstruation, sexual abuse, and access to reproductive interventions such as abortion and hormonal treatments, recognizing their potential impact on mental health. Evidence suggests that many health care professionals avoid these conversations, due to barriers such as lack of knowledge or uncertainty about how to approach them[335,336]. Overcoming these barriers necessitates ongoing training and workforce development, alongside the integration of information on women's reproductive and sexual health, and how this relates to mental health, into undergraduate and postgraduate curricula, particularly within psychiatric, primary care and gynaecological clinical training. It is also critical for prescribers to understand the interaction of psychotropic medications with sex hormones, and how such hormones can be used in clinical practice either as a first step or as an adjunct to existing treatments.

For many women, reproductive life stages may represent important transitions, accompanied by changes in their life circumstances and how they are viewed by themselves and others. Such transitions may provide a catalyst for seeking psychological help. Interventions can be offered at a range of intensities, though psychological therapies differ substantially in their availability worldwide. As a relatively simple and low-cost intervention, there is evidence that psychoeducation about the impact of reproductive life events on mental health can improve outcomes, including response to treatment[277,303].

Trauma is a shared mechanism mediating and/or moderating many of the relationships between reproductive life events and mental health examined here. There is increasing recognition that practices within mental health care – including but not limited to the use of coercion, seclusion and restraint – can be distressing and harmful to those with histories of trauma[337]. Trauma-informed care aims to reduce this risk of re-traumatization[338]. The implementation of trauma-informed interventions and services within mental health care, including the provision of single sex wards, needs urgent evaluation, with input and leadership from trauma survivors[165].

Health policies must support clinicians and health services to deliver integrated and holistic reproductive and mental health care at all points of contact with health services. Ensuring equity of access by women to reproductive and mental health care remains a significant challenge, particularly for marginalized groups, including women with substance misuse, personality disorder, or socioeconomic deprivation. Additionally, understanding the needs and experiences of diverse groups – including racially minoritized, gender diverse, neurodiverse, and LGBTQ+ individuals[339] – is imperative. Health services are often located in cities, leaving women from rural areas and Indigenous communities without access to these services, especially if there is unreliable transport and/or poor mobile phone coverage. However, integrating mental and reproductive health care also presents opportunities, given the prevailing prioritization of physical over mental health care in many regions[340]. Seeking assistance for reproductive health could provide an opportunity to address mental health concurrently.

Finally, stigma remains a significant issue for both mental and reproductive health[40,341]. Societal misconceptions and discriminatory attitudes surrounding mental health conditions and reproductive health choices persist, contributing to feelings of shame, secrecy, and reluctance to seek help. Women, in particular, often face societal judgments and cultural taboos regarding their reproductive health decisions, further exacerbating the stigma surrounding these issues. Moreover, the intersectionality of stigma compounds the challenges faced by marginalized groups, including racial and ethnic minorities, LGBTQ+ individuals, and those from low-income backgrounds. Addressing stigma requires multifaceted approaches, including public education campaigns, destigmatizing language and portrayals in media, and fostering supportive and inclusive health care environments where individuals feel empowered to seek the care they need without fear of judgment or discrimination.

CONCLUSIONS

Reproductive health is foundational for women's mental health and well-being. Violations of reproductive rights – including lack of access to reproductive health care, reproductive coercion, and a lack of gender-sensitive mental health care – can lead to enduring negative mental health outcomes. Psychiatrists are well placed to advocate on behalf of their patients for access to reproductive health care, and also need to ensure that they have the knowledge and skills required to respond to their patients' reproductive health care needs.

By examining the interface between reproductive and mental health, we have highlighted in this paper urgent gaps in research, clinical practice and health policy that need to be addressed to optimize women's health. A concerted interdisciplinary effort is critical to advance the reproductive mental health field, to identify new therapeutic avenues and foci for interventions, and to improve quality of life for women globally.

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Politics and development as drivers of women's reproductive mental health

Howard et al[1] provide an excellent and nuanced overview of women's mental health in relation to life-course and common reproductive events, with careful consideration of complicated bi-directional influences (e.g., mental health in relation to sexual violence and contraception access and choice). Their summary includes some attention to social-political contextual factors as moderators of different reproductive experiences and mental health outcomes, including exposures in low- and middle- vs. high-income countries, gender unequal compared to more equal societies, as well as variables functioning at the group and individual level such as race and sexual orientation.

From an historical perspective, the authors' emphasis on sex-based experiences as fundamental to understanding and treating women's mental health is radical, yet essential for progress in basic and translational research. However, two drivers of women's reproductive mental health deserve amplification: a) the political determinants of health[2], defined as government action (or inaction) and policy, which create the social determinants of health mentioned multiple times in the paper; and b) the role of childhood experiences, particularly adverse ones, as a risk factor for compromised reproductive events and mental health.

In her insightful book *Unwell Women: Misdiagnosis and Myth in a Man-Made World*[3], E. Cleghorn dissects modern scientific medicine as part and product of the culture from which it emanated, with strict gender divisions, ascribing power and dominance to men, and heralding the superiority of the male body. She notes that, as early as Aristotle, the female body was described as inverse of the male's, with genitalia "turn'd outside in". Women were marked as different and thus inferior, except for their reproductive capacities, which were used to define them, and limit them.

Women's different bodies and biology were regarded as the foundation of their nervous constitution, unsteady judgement, and susceptibility to emotional storms. The "mythical" uterus was viewed as influencing all disorders and dysfunctions of women's mind and body. Medicine constructed the ideology that a woman *was* her biology, that she was ruled by it, governed by it, at the mercy of it, and her diseases were linked to the "secrets" and "curiosities" of her reproductive organs, which made her unwell a part of every month, and thus overall unfit for activities outside of domestic ones and those related to childcare.

Throughout history, medicine's focus on female biology, as the defining factor of being a woman, worked against the understanding of illness and disease. Indeed, as penned by Scotland's first licensed woman physician, S. Jex-Blake, near the turn of the 19th century, women needed to be viewed as "human first" to receive unbiased and good medical treatment.

Over 150 years later, the US National Institutes of Health – the largest public funder of biomedical research in the world – began to require the consideration of sex as a biological variable in its funded studies on vertebrate animals and humans. This policy aimed to correct the historic focus on male research and the under-reporting of sex and gender in preclinical studies, which had reflected both ongoing male dominance and the subsuming of women under men, an extreme distortion of a "human first" approach.

The centuries-long fight for women's social, political and economic equality necessitated a "human first" rationale. Today, even in the context of ongoing health inequities and disparities related to identities and demographics, sex-based biology and biologically-based reproductive events can be examined in relation to women's mental health to foster the most rigorous and clinically-relevant research.

Howard et al's life-course approach to women's reproductive mental health provides an opportunity to amplify its implicit developmental perspective. They note that "trauma is a shared mechanism mediating and/or moderating many of the relationships between reproductive life events and mental health" and refer to "early life trauma" as a risk factor for sexual dysfunction as well as attachment difficulties, which in turn is a risk factor for compulsive sexual behavior. In several recent reports, associations have been identified between: a) childhood adversity (abuse, neglect, low socio-economic status, violence, bullying) and earlier age for reproductive events[4]; b) sexual abuse or parental separation and reduced odds of contraception use[5]; c) total childhood adverse events and repeat induced abortion[6]; d) childhood adversity (abuse, neglect, household challenges) and worse verbal memory in peri-menopausal women, with higher inflammation as a mediator[7]. Each of these outcomes is a potential contributor to experiencing a mental health condition.

Mental health conditions should be viewed as emerging from individuals' adaptations to their environments *over time* rather than as something a person "has". Recent research demonstrates that exposure to stressors and other psychosocial experiences "gets under the skin" to influence subcellular processes such as immune and endocrine regulation, with consequences for somatic and brain functioning across the life course[8]. Mitochondria appear to play a critical role in the biological embedding of stress, affecting physical and mental well-being[8]. A biologically informed, developmental perspective applied to women's reproductive mental health underscores the urgency to implement systems focused on early intervention as well as to devise innovative early preventive therapies and approaches.

Throughout the paper, the authors appropriately highlight the social determinants of health as key drivers of women's reproductive mental health outcomes. And yet, as D. Dawes powerfully argues in his book *The Political Determinants of Health*[2], social factors such as access to resources including good education, quality health care, safe environments, and healthy food, are proximal conditions influencing health status. To affect change in population health, it is imperative to look upstream to the drivers of these

social factors, to the politics and policies that then trickle down in the form of implemented systems to shape the quality of lives and the associated health outcomes.

The recent US Supreme Court decision that rescinds the constitutional right to complete reproductive health care including abortion services underscores the role of politics in driving women's reproductive health. The ruling returned to state legislatures the power to regulate abortion access. Following the Supreme Court ruling, one recent study found a small but significant increase in depression and anxiety scores in states with immediate bans on abortion versus those without[9].

To address health inequities in resources related to women's reproductive mental health, and the social-economic factors contributing to disparities in well-being, we must actively engage with the political drivers of health.

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Hormone-sensitive depression in women: a key to precision psychiatry

Reading Howard et al's paper[1] evoked in me a range of emotions, ranging from discouragement to optimism. The evidence is unequivocal: reproductive events shape women's mental health and vice versa. Women with fertility-related gynecological conditions and those undergoing hormonal transitions face a heightened risk of depression. These conditions are often long-term, and the consequences are both overwhelming and impossible to overlook. Initially, I felt discouraged by the sheer magnitude of the evidence presented, and further disheartened by the numerous existing research gaps in this field. However, optimism ultimately prevailed as I began to appreciate the opportunities that this knowledge offers.

In psychiatry, we continue to grapple with the etiology of mental disorders, including depression. Howard et al provide key insights into why women's mental health must be a focal point in research, especially for subgroups defined by specific biological exposures. The paper strongly suggests that some depressive episodes are triggered by fluctuations in sex hormones. These are not confined to one particular stage of life, but span from adolescence through menopause, creating a recurrent exposure that increases vulnerability to mental health challenges.

The link between reproduction and mental health is, of course, also bolstered by research regarding the association between childbirth and the risk of depression[2,3]. Moreover, hormonal contraception use is likely to be another key factor. In a recent study of 149,200 first-time users of hormonal intrauterine systems[4], we found a relatively low absolute depression risk, but interestingly observed that the risk was hormone-dose-dependent. This finding offers novel insights into how hormonal exposure directly contributes to depressive episodes in women. A causal interpretation seems to be supported, which is often difficult to establish in observational studies. The hormone-dose relationship points toward possible mechanisms explaining vulnerability among women, which could drive future research but also therapeutic strategies.

Looking ahead, I propose that we explore several important questions. Why do we see such substantial variations in the incidence and prevalence of depression following various reproductive events? Are these variations indicative of true biological differences, or are they the result of biases, selection, or differences in research methods and settings? These may seem like straightforward questions, but they carry important implications. Addressing these questions can deepen our understanding of the etiology of depression. Variations in depression incidence across subgroups of women, and even across different time periods, may be influenced by cultural, social or environmental factors[5]. Disentangling these influences is one key to improving our understanding of the underlying risk mechanisms.

In addition to the influence of external factors, we face other challenges in untangling the bidirectional associations between reproductive events and mental health. The relationship between abortion and mental health, for example, is complex and often mediated by pre-existing mental health conditions[6]. This bidirectional nature complicates efforts to establish clear causality, further emphasizing the need for sophisticated research designs and comprehensive longitudinal data sources that track women over extended periods.

Future studies should expand on these considerations to enhance our understanding of the intricate bio-social-cultural factors that contribute to depression risk. Pre-post designs, for example, could help assess mental health changes before and after reproductive events, allowing us to more definitively shed light on causality. Co-relative designs, which compare outcomes between related individuals (e.g., siblings), offer valuable insights into the roles of genetic and environmental confounders, providing stronger evidence of causal relationships. Additionally, twin studies have long been recognized as a critical tool in psychiatric epidemiology, and can still be used to further investigate these relationships.

These methods, collectively, can support causal inference and inform etiological models and prevention efforts[7]. Investigation of causality could also benefit from the use of mixed-methods research[8], which combines quantitative and qualitative approaches. This is particularly crucial for capturing the nuanced and subjective experiences of women navigating hormonal transitions or reproductive events and their mental health implications. Quantitative data provide the hard numbers, but qualitative research adds depth to these figures, giving voice to individual experiences that help explain the larger epidemiological patterns. Such mixed methods allow us to better document symptom burdens while considering the broader social, cultural and individual contexts.

Another key element in achieving a deeper level of understanding will be the use of longitudinal data sources that span a woman's entire reproductive lifespan. This is where my optimism grows: the prospect of large-scale international collaborations to establish and maintain cohorts of girls and women who can be followed through various hormonal transitions and life stages. These efforts must aim to capture heterogeneity within populations, particularly how different subgroups of women experience and respond to reproductive events in varied ways. Research should account for intersecting identities, such as race, ethnicity and socioeconomic status, which influence risk and resilience factors in reproductive mental health.

A deeper examination of how these intersecting identities interact with reproductive events will not only help in predicting mental health outcomes, but also lead to more personalized and equitable approaches in both research and clinical practice. Let us hope that both public and private agencies are prepared to fund and support such research initiatives, which require patience but hold the potential for transformative discoveries.

Howard et al highlight the under-researching of women's reproductive mental health. This is not simply a gap in knowledge, but a fundamental oversight in the broader understanding of mental health. Ignoring the connection between women's reproductive health and mental health prevents us from gaining a full understanding of depression, especially in its hormone-sensitive forms.

Prioritizing research in this field could help unravel the broader etiology of depression, paving the way for collaborations that expand into other fields within mental health research. This could help address the heterogeneity of mental disorders, a challenge that has hindered the widespread implementation of precision psychiatry approaches[9].

A unified evidence base that defines the incidence and outcomes of hormone-sensitive depression as a distinct subtype could mark a significant step toward realizing the ambitions of precision psychiatry. Once this depressive subtype is characterized, it could become the target for specific interventions. These efforts could directly inform treatment guidelines and lead to more nuanced health care planning based on both age and sex.

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Sociocultural context and intersectionality are vital to women's reproductive mental health

Howard et al[1] have synthesized, with expertise and sensitivity, the substantial evidence about the links between some reproductive events in women's lives and mental health problems. There is detailed consideration of the role of sexual biology, in particular hormonal factors. Sociocultural context is acknowledged as relevant, but might be considered further in the research agenda that is called for and the proposed health worker training.

Gender refers to socially constructed characteristics – behaviors, roles, opportunities and expectations associated with being a woman (or a man) – and is influenced by culture and context. The term is sometimes used interchangeably, and inaccurately, with sex. Gender interacts with sociocultural norms, ethnicity, socioeconomic position, age, place, and access to resources, in what is termed intersectionality. The social determinants of mental health problems and the provision of comprehensive health care can only be fully understood and addressed through a gender-informed intersectional lens.

As a prominent example, knowledge, facilities and a safe environment are needed to manage menstruation hygienically and with dignity. Disposable sanitary products are not accessible to most women and girls in resource-constrained countries, especially the poorest. They must use cloths to absorb menstrual blood, and require access to water and privacy to wash and dry them for re-use. Cloths are often difficult to secure and so risk of blood stains on clothing or seats is high. Girls are much less likely to go to school when menstruating, because they lack access to essential requirements for safe and dignified management of menstrual blood.

Some cultures have traditional beliefs and practices related to menstruation being polluting. Women and girls who are menstruating may have to avoid men and boys, be precluded from religious functions and prohibited from food preparation. They might not be permitted to use the household toilet while menstruating, because the blood is thought to be contaminating. Where there is no

household water supply and open spaces are used, girls are subject to violence and intimidation while toileting, including managing menstruation. These experiences are persistent sources of anxiety, shame, social avoidance, and hypervigilance.

Women who have migrated from low- to high-income countries view menopause as a normal life stage, and do not see a need to seek menopause-specific health care. Instead, they use self-care strategies and traditional remedies, often from their country of origin, and seek health information from family and friends. They rarely initiate conversations about menopausal health with health workers, because this is considered an intimate topic and is not openly spoken about[4]. Their preference is for clinicians to raise the topic with them, but primary care practitioners report that they do not feel culturally competent to do this, and generally avoid the topic unless a woman raises it[5].

Clinicians' gender stereotypes about what is normal and what is pathological influence their recognition and validation of symptoms and their recommendations[6]. Women with endometriosis have been found to have waited an average of 7.5 years between seeking help for pain and having their condition investigated and treated. Doctors believed that women had endometriosis only when lesions were found on diagnostic investigations, but had not believed much earlier accounts of pain and symptom-related disability. Heavy menstrual bleeding, another serious problem for some young women, is often normalized, leading to delays in investigation and treatment. Being disbelieved while experiencing pain or excessive bleeding is strongly associated with elevated symptoms of depression, anxiety and social withdrawal[7].

In high-income countries, menopause has become stereotyped as a hormone deficiency disease and a problematic life stage in which mental and physical health deteriorate. It is notable that none of the population-based surveys assess the menopause-related benefits for quality of life. None ask about improvements in well-being from cessation of regular bleeding and the expenses of sanitary products, reduced anaemia, and being able to wear light-colored clothing and exercise without constraints.

A recent review[8] of prospective cohort studies on mental health problems over the menopause transition found no compelling evidence for a universally increased risk of depressive symptoms or major depressive disorder. Women with a history of depression are indeed at increased risk of recurrence, and risk can be enhanced by experiencing coincidental adverse life events. No compelling evidence was found that the risk of anxiety, bipolar disorder or psychosis is increased. The authors noted that the stereotyped association of menopause with poor mental health can lead to negative expectations as women approach the menopausal transition. One could also argue that these gendered stereotypes have the further potential social harm of leading employers to view women in mid-life as risky prospects or as unable to be appointed to senior roles.

In the light of all this, the assessment of and response to mental health problems associated with reproductive events require broad considerations. It should not be assumed by clinicians or in health promotion strategies that psychological symptoms, including during the menopause transition, are just attributable to biological changes[9]. It has historically been conveyed to women as "the weaker sex" that biology is destiny, that their intrinsic sex-specific vulnerabilities render them less able to learn, to participate in the non-domestic sphere, to be given public appointments and to lead.

These powerful social stereotypes still prevail. Although more women in high-income countries participate in the economy and politics than in the past, equity is rarely achieved, including in remuneration. Women continue to carry a disproportionate load of unpaid household labour, and are far more likely than men to experience violent victimization. The situation is much worse for women of color, who continue to encounter racism as well as sexual discrimination throughout the life course. In countries in which gender inequality is entrenched and roles are severely restricted, biological vulnerability is often used as a justification.

Women's mental health benefits from equality of opportunities, including for post-secondary education, income-generating work, and promotion commensurate with capability. These are enabled by access to reproductive choice, shared household work, and personal safety. If mental health problems are experienced, rights-based approaches in which women are encouraged to participate socially and economically and are given skills to counter discrimination need to be implemented.

An empowerment model of health care has been proposed[9] in which women's sociocultural experiences and circumstances are assessed explicitly, and potentially modifiable risks are addressed, and in which women's expertise is built through health education and agency fostered, so that they become knowledgeable partners in their care.

Health care workers can promote optimal reproductive mental health by recognizing intersectionality and their gender-based stereotypes, and how these influence what is asked about and how they respond. Whether or not pharmaceutical treatments, including hormone therapies, are offered, it is essential to also provide evidence-based psychological treatments, counter catastrophizing, and promote a solution-focused and optimistic approach to reproductive events.

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Breaking down barriers to conversations about sexual and reproductive health

Howard et al[1] have produced a timely and comprehensive overview of the field of women's reproductive mental health, which offers a stark reminder of the significant work that will need to be done to address the relevant health disparities. Here I focus on the barriers to integrating women's sexual and reproductive health issues into mental health care and propose some possible solutions.

Whilst attitudes towards women's sexual and reproductive health have significantly shifted in mental health care, some of the core beliefs about women's rights to autonomy over their own bodies and reproductive choices may still prevail. I believe that the current mental health system, which is risk-averse and paternalistic, must change significantly in this respect.

Howard et al note that mental health practitioners tend to avoid talking about sexual and reproductive health issues due to lack of knowledge and uncertainty. I would argue that, whilst lack of knowledge is a key barrier, there are other significant and complex reasons why these topics are avoided. Identifying and addressing these issues will be critical if practice is to change.

When I undertook focus groups with mental health clinicians about the sexual health needs of people with mental illness[2], these professionals began to discuss the issue through a lens of risk and safeguarding. They were aware that some people were engaging in risky or abusive sexual relationships, but were uncertain about what their role was in addressing this. There was real concern about raising the topic of sexual and reproductive health, as they feared all sorts of negative consequences. They were worried that people would be offended, or that this could damage the therapeutic relationship up to triggering a trauma reaction (in those with a history of sexual abuse). They were aware that many of the people on their caseloads had sexual violence histories, but they felt that this group should not be exposed to these topics.

Whilst well-intended, this paternalistic attitude neglects the needs of marginalized people who could be at continued risk of harm. In addition, avoidance of the topic removes the opportunity to talk about what has happened, and get some support. In fact, it may be another form of silencing people which is inadvertently replicating the patterns of abusers.

There is evidence[3] that, despite the high levels of sexual violence experienced by women with mental illness, routine enquiry is not taking place. Even if a disclosure is made, the woman is not always referred to appropriate services, and the disclosure is not always believed. Indeed, in the focus groups, mental health practitioners were unsure of available local services and what to do about sexual and intimate partner violence.

In addition to paternalism, another factor can be the gender difference between the staff and the person with mental ill health. In the focus groups, male staff participants expressed concern about asking female patients about sexual and reproductive health: "*To be questioning somebody about an intimate part of their life… outside of the framework of what I'm supposed to do during my assessment makes you feel uncomfortable… you know, you're untested waters*"[2].

In addition, participants of both genders expressed the idea that conversations may be more comfortable if the staff member and the person with mental illness were of the same gender: "*Maybe it is gender specific then, because on the ward where we work with women, I've known males sort of like brush over the question… like the females on the ward feel more comfortable talking to the female members of staff about that*"[2]. In a subsequent survey of mental health nurses regarding sexual and reproductive health[4], it was also noted that male participants were more comfortable talking to male than female patients.

The consequences of avoiding sexual and reproductive health issues for women living with mental illness are stark. They are less likely to take up breast and cervical screening, and this may explain their higher cancer mortality[5]. Whilst fertility is lower in women with severe mental illness, the rates of unintended pregnancy and abortion is higher, and there is evidence that these people are at increased risk of human immunodeficiency virus (HIV) and other sexually transmitted infections. In addition, women with mental illness are more likely to have experienced sexual abuse and violence[6].

In order to address the sexual and reproductive health inequalities for women with mental illness, it is important to overcome the structural and interpersonal barriers that have been identified in mental health care settings. This will require top-down leadership to ensure that women's reproductive health is integrated into mental health holistic assessments. In our focus groups, it was interesting that, after spending some time reflecting on the topic (and discussing how challenging they found it), the participants (without prompting) started to discuss solutions. There was a consensus that sexual and reproductive health should be a part of holistic mental health care: "*Actually, it is something that we need to address, because it does affect a lot of other sort of things about the person's care*"[3].

In order to support integrating this topic into mental health, organizational commitment was seen as important and a way of legitimizing its inclusion. Some participants felt that a standardized form would help them in starting the conversation. Having a "sexual and reproductive health" champion would also help keep this on the agenda. While it would be important for people with mental illness to be able to access specialist sexual and reproductive health services, this should not be simply a case of signposting the person to these services. Participants recognized that people with mental illness might benefit from having an advocate to assist them to connect to the other services in a more supportive and proactive way.

Participants also discussed their own knowledge and training needs. They noted that there was no inclusion of sexual and reproductive health in mental health nurse training. The training just

involved knowledge of sexually transmitted infections and how to support people regarding high risk sexual behaviors. Increased conversations about sexual health in care notes was documented after offering mental health staff some specific training[7].

Of note, very little is known about the perspective of people with lived experience on this topic, including preferences around when and whom to have the discussions with. Whilst mental health practitioners have concerns about how conversations about sexual and reproductive health may negatively impact people, there is little evidence to support this. A randomized controlled study[8] of a sexual health promotion intervention for people with severe mental illness (which included collecting data on sexual risk behavior, and use of contraceptive and sexual health services) demonstrated that it was acceptable and feasible to engage people from secondary mental health care, and no adverse events were reported. In a meta-synthesis[9] of qualitative studies related to sexuality in people with severe mental illness, the participants identified a range of areas of need, including wishes to have children and sexual side effects of psychiatric medication, and expressed the desire to talk to someone about these issues.

So, in conclusion, mental health practitioners are aware that women with mental illness have sexual and reproductive health needs, but are unclear about what their role should be in addressing these issues. This is compounded by policy and practice drivers at an organizational level as well as a genuine concern that raising these topics could have a detrimental impact on people with mental health problems. Any initiatives that aim to improve women's sexual and reproductive health in mental health services will need to address these challenges around knowledge, attitudes and confidence amongst mental health practitioners.

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The harms of imposing barriers to abortion care on people's psychological well-being

The assumption that abortion is detrimental to pregnant people's mental health has long been used to justify policies that restrict or ban legal access to abortion. Such policies often include implementing total abortion bans, banning certain types of abortion procedures, setting gestational limits, mandated waiting period and counseling laws, among others. While these policies claim that they will protect people's mental health by denying them access to abortion or forcing them to wait, they ignore the large body of evidence demonstrating that abortion in itself does not cause mental health harm, and that the restrictions themselves might harm pregnant people's mental health.

The US Turnaway Study is one of the most robust investigations assessing whether abortion causes mental health harm[1]. This longitudinal cohort study examined the consequences of having or being denied an abortion on pregnant people's psychological, physical and financial well-being. From 2008-2010, we recruited 956 participants at 30 abortion facilities across 21 US states who had abortions just below a facility's gestational limit, and compared their psychological, physical and socioeconomic outcomes to people denied abortion because they were just above a facility's limit and carried their pregnancies to term. Using a structured telephone interview tool, we interviewed participants one week after having or being denied abortion and then every six months for five years. Using validated measures, we mapped people's mental health trajectories over this five-year period.

The Turnaway Study improves on prior studies by utilizing a prospective design and an appropriate comparison group. Its two main study groups were similar at baseline on key background characteristics that could confound the relationship between abortion and mental health. In particular, they were comparable with respect to pre-pregnancy history of child abuse and neglect, mental health diagnoses, and drug or problem alcohol use. Other studies have been methodologically limited by relying on comparison groups that differ from the abortion group on key background characteristics, such as people with wanted pregnancies or who are not pregnant. These studies ignore the reality that people seek abortion due to reasons related to their financial, relationship, and mental health circumstances[2], all of which can result in key baseline differences that impact their mental health trajectories. The use of such flawed comparison groups have led authors to erroneously conclude that the abortion, rather than other factors – such as pre-existing mental health conditions and trauma – are the source of adverse mental health outcomes.

The Turnaway Study, which accounted for these background characteristics, found no evidence of mental health harm due to abortion. It was the people who were denied access to abortion who had worse mental health, at least initially. For the first six months after being denied abortion, they reported more stress and symptoms of anxiety, and lower self-esteem than those who got their wanted abortion, while reporting similar levels of depression,

post-traumatic stress, and suicidal ideation[1,3-6]. Both study groups – whether they had or were denied abortion – experienced heightened psychological distress around the time they were seeking abortion, which gradually improved over time. While the study concluded that abortion is not harmful to people's mental health, it did find that the people most vulnerable to experiencing post-abortion-seeking psychological distress were those with a history of mental health conditions, perceived abortion stigma, and history of trauma or abuse[1,5].

What's more, when we examined the effects of abortion denial on other outcomes, such as people's socioeconomic and physical well-being, those who were denied abortion fared worse[1]. When compared to those who had an abortion, they experienced an increase in household poverty, were less likely to have enough money to cover basic living expenses such as food, housing and transportation, had lower credit scores as well as more debt, bankruptcies and evictions. These adverse outcomes extended onto participants' children. Children of people denied abortion were more likely to live in poverty and less likely to achieve key developmental milestones, while children born due to abortion denial were more likely to experience poor maternal bonding.

Being denied abortion and then giving birth was also associated with greater physical health risks than having abortion, including experiencing life-threatening complications such as eclampsia and postpartum hemorrhage, chronic headaches or migraines, joint pain, and gestational hypertension, as well as death (two people denied abortion tragically died following delivery, whereas no people died from abortion)[1].

The Turnaway Study findings provided robust evidence demonstrating that abortion denial is more harmful to people's mental and physical health and financial well-being, than having an abortion. These findings also prompted a need to identify the factors that might contribute to elevated levels of anxiety and depression symptoms at the time of abortion seeking.

The Burden Study aimed to explore whether abortion restrictions and other barriers might be one source of the heightened psychological distress when seeking an abortion[7,8]. In this cross-sectional study, we surveyed 784 people seeking abortion care at four facilities located in the states of California, Illinois and New Mexico – all states with protected access to abortion. We selected these states because they allowed us to capture the experiences of people who traveled from other states with more restricted access to abortion care.

We found that 58% of participants experienced delays accessing abortion care, most often due to the costs of care-seeking (45%), as well as access barriers (43%) and travel time (35%). Furthermore, as many as 42% reported incurring catastrophic health expenditures, meaning that their out-of-pocket costs to pay for abortion-related medical care and travel were so high as to hinder their household's ability to pay for basic living needs such as food and housing. Over one-quarter (27%) of participants reported having to tell someone about the abortion decision unwantedly, due to the many logistical constraints that they endured trying to obtain care[7,9].

In analyses adjusting for pre-pregnancy mental health history and other background characteristics, participants who experienced delays, unwanted disclosure about the abortion, and catastrophic health expenditures reported more symptoms of anxiety, depression and stress[7-9]. While the cross-sectional design limited our ability to determine the direction of these relationships, these findings suggest that facing obstacles to abortion care may be harmful to people's psychological and financial well-being.

This research adds to the body of evidence demonstrating that policies claiming to protect pregnant people's mental health by restricting their access to abortion are not evidence-based. It is critical that policy-makers understand the long-standing impact of abortion restrictions on people's psychological, physical and financial well-being, as well as the rippling impacts that these policies are likely to have on the financial and psychological well-being of their children.

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Embodied distress in reproductive psychiatry

Howard et al's paper[1] highlights the complex interplay between social, cultural, physiological and hormonal factors that influence women's mental health in the context of reproductive psychiatry. Reproductive conditions are not just bodily states. For most women, they are deeply connected with their perception of self, and strongly interlinked with social and cultural expectations of womanhood, roles and identity.

The term "embodiment" refers to the daily experience of both having and being a body[2]. Several gynecological conditions may lead to embodied distress, disrupting intimate interpersonal relationships, motherhood and social life, and contributing to poor quality of life.

Up to a third of women presenting to gynecological services have pelvic pain[3]. Vulvodynia, dysmenorrhea and endometriosis

are the commonest conditions involved. Most women, however, do not report gynecological pain, especially dysmenorrhea, as they believe (often due to social conditioning) that pain is part and parcel of being a woman and having menstrual periods. This often leads to delay in diagnosis. The average delay between the start of symptoms and the diagnosis of endometriosis is 7.5 years, while other chronic inflammatory diseases such as rheumatoid arthritis are diagnosed much sooner, even though they have similar economic and societal costs.

In 2018, "What is endometriosis?" was the third most trending health-related question on Google. However, it is common for women living with this condition to experience dismissal associated with gendered medical discrimination around chronic pain, especially that linked to menstruation.

Qualitative research among women with endometriosis often captures the nature of the embodied distress[4]. These women talk about not feeling like themselves, experiencing reactions from the medical and social environment which prompt feelings that they are "going mad", and perceiving that they are a burden to their loved ones, which often results in self-silencing.

The most common words and themes which appear when endometriosis is described in health care contexts refer to symptoms (fatigue, pain, cramps, heavy bleeding); temporality (time, years, always); actors (doctors, medical systems); challenges (struggle, trying, work); and body (organs). As health professionals, if we are to fully understand the experience of this and other chronic painful gynecological conditions, we have to pay attention to their individual, structural and systemic aspects.

We often talk about diagnostic overshadowing, which occurs when health care professionals misattribute a person's physical symptoms to his/her existing mental illness. This misattribution increases the likelihood of delays in treatment, potentially giving rise to complications that further negatively influence health outcomes. In conditions such as dysmenorrhoea and endometriosis, the opposite kind of diagnostic overshadowing often takes place. Women's psychological and social distress related to these conditions is seldom recognized or addressed, being overshadowed by the physical distress.

Vulvodynia and painful sex (dyspareunia) are two conditions even more shrouded in silence, as women often feel ashamed to discuss them, viewing them as personal failure[5]. Many professionals again do not seem to recognize the severity of the problem or its impact on self-worth, self-image and relationships. The term "epistemological purgatory" has been used[6], referring to a liminal space where women are caught regarding their own lived experience and embodied knowledge about these painful conditions as opposed to expert knowledge.

Howard et al discuss the toll that infertility takes on women's mental health. In conditions such as vulvodynia or endometriosis, which may also lead to infertility, the pressure actually seems to often be on conception rather than on symptom control. Any pain in the pelvic region is often normalized[7]. For many years, conditions such as vulvodynia were considered to be of psychological origin. Even now, it is not unusual for women with vulvodynia or dyspareunia to be told that their pain is just of a psychological nature, thus preventing any investigation or recognition of the symptom. This is a paradox, because on the one hand vulvodynia and dysmenorrhoea may be mistakenly attributed to psychological reasons, and on the other the psychological consequences of these conditions may not be recognized. Both these approaches in the health care system may increase the embodied distress faced by women.

This is also reflected in the constant back and forth on how these disorders are placed in our classificatory systems. Until recently, sexual pain disorders were considered as female sexual dysfunctions. Following much advocacy by patient groups and professional societies, the ICD-11 has now classified them under genitourinary pain disorders. Appropriate treatment, attitudes of health professionals and research funding are often determined by where conditions are located in classificatory systems. How this change in the ICD-11 will influence a better understanding of these disorders remains to be seen.

Another major issue that is rarely addressed in reproductive health is the impact of stigma and taboos related to menstruation on women's mental health. While studies on premenstrual dysphoria are many, the social and cultural aspects of menstruation have been largely neglected. Howard et al refer to the concept of "period poverty", defined as poor access to sanitary products during menstruation, which is known to impact women's mental health even in countries such as the US. In low- and middle-income countries, in addition to period poverty, there is often also water and sanitation insecurity. Research from the WASH (water, sanitation and hygiene) sector has emphasized that limited sanitation and lack of water during menstruation have a negative impact on women's mental health[8].

In many societies, there is still taboo, shame and embarrassment associated with women being impure and polluting the environment during their periods. Studies from several parts of the world have found that women often report humiliation, shame and worry, as well as a perceived loss of dignity, related to water and sanitation insecurity during periods. These concerns are also commonly expressed by women who are homeless and those in disaster and conflict situations. Socially acceptable norms around dignified behavior, purity and cleanliness during menstruation may in the above situations clash with availability of resources. Period and sanitation poverty may well be a gendered risk factor for poor mental health in many communities. It is, therefore, important to move away from a purely biomedical model of premenstrual and menstrual distress to one that also addresses cultural, socioeconomic and environmental conditions.

Finally, one cannot ignore the role of culture and bodily idioms of distress related to reproductive mental health[9]. For instance, women in South Asian cultures often use vaginal discharge as an idiom of expressing psychological distress, including depression. Studies have also found an association between partner violence and report of gynecological symptoms in these cultures. As psychiatrists, we must be alert to such bodily expressions of emotional distress, and educate primary care health providers to the adequate recognition of common mental disorders in women even though they might report mainly reproductive symptoms.

In conclusion, reproductive psychiatry involves a careful understanding of the meaning of pain, bodily distress and the impact of various gynecological conditions on a woman's identity and interpersonal relationships. These vary across cultures and have different expressions and relevance at different stages of a woman's reproductive life.

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The impact of reproductive events on women with severe mental illness: we need more research and professional awareness

Howard et al's masterful review of women's reproductive mental health[1] highlights how neglected this essential component of women's lives has been, and how much gender discrimination and stigma have hampered research on the development of much-needed treatments and preventive strategies.

As a mental health researcher with lived experience of bipolar disorder and postpartum psychosis, my work has focused on women with severe mental health conditions and the times of their lives when they are most likely to experience episodes of illness. These times are frequently related to their sexual and reproductive life: menarche, menstruation, sexual activity, pregnancy and childbirth, and peri-menopause. It is at these times that their mental health problems are often triggered or exacerbated, though disappointingly little research has been done on this.

As someone involved with four maternal mental health charities, I have heard several accounts of women who had been stable for many years and then were suddenly admitted for long hospital stays around the time of menopause. Or others who had a postpartum psychosis 25 years earlier, becoming desperately ill and suicidal completely out of the blue. Yet clinicians seem ignorant of this risk. Why? Because so little research has been done into it.

Premenstrual triggering or exacerbation of mental disorders has received little attention until recently. The research which has actually been done has shown that reproductive cycle-associated mood symptoms are commonly reported in women with major depressive disorder and bipolar disorder[2]. In a US sample of 2,524 women, 67.7% of those with mood disorders reported premenstrual mood symptoms, compared to only 33.7% of women without a psychiatric diagnosis. A systematic review of 35 prospective studies concluded there was clear evidence of premenstrual symptom exacerbation for most serious mental disorders, hypothesizing that there may be a sizeable subgroup of hormonally sensitive individuals who are affected[3].

From women's point of view, the stigma around talking about "periods" (especially for some minority communities) deters them from asking for help with what can often be extremely difficult symptoms. For example, in a survey conducted by the Bipolar UK charity (including over 1,000 women with bipolar disorder), 65% reported that premenstrual syndrome significantly worsened their mood, with increased irritability and anger, and yet over half said that they had not told their doctor.

If women do ask for help, they are often denied it. One woman said: "*I track my mood. It's very clear that 7 days before my period starts my mood is badly affected. I've tried to highlight this with my mental health nurse and psychiatrist. I feel it's been ignored or dismissed*"[4]. The lack of research on the psychiatric effects of hormonal fluctuations encourages clinicians to ignore the problem. An illustration of this was provided by the answer to the UK Bipolar Commission's question: "Has anyone in your health care team ever given you information about how hormones can affect your bipolar disorder?". Eighty-five percent of women answered "No"[4].

Many women with severe mental illness experience a similar lack of information and treatment for hormone-related problems in the menopausal transition. Recent evidence documents that a link exists between peri-menopause and a worsening of mood symptoms as well as an increased risk of new-onset mood disorders. In a population-based UK Biobank study[5] with 128,294 female participants, the first-onset rates of bipolar disorder and major depression significantly increased in the four years around menopause. Bipolar I disorder showed the largest effect (an 112% increase), while the increase was 30% for major depression. No association was found for schizophrenia-spectrum disorders. This lends weight to observational studies reporting a higher risk of relapse in these conditions at peri-menopause[6]. It is essential that women with serious mood disorders, some at risk of suicide, are made aware of these dangers. When the UK Bipolar Commission asked women with bipolar disorder if they knew that peri-menopause could be a time at higher risk of relapse, only 35% said they did[4].

Another area which is largely ignored by clinicians and researchers, but which causes a huge amount of suffering to women with severe mental illness, is that of hypersexuality. This is particularly a problem for people with bipolar disorder, and especially for women, who report increased vulnerability to rape (28%) and sexual assault (42%)[7]. This was highlighted in a recent report[8], drawing attention to the fact that diagnostic classification systems do not recognize the seriousness of this problem and its often devastating consequences: unwanted pregnancies and abortions, marriage breakdown, job loss, and exacerbation of mood swings.

Partly because women behaving in a sexually uninhibited and proactive way is socially frowned upon, there is a reluctance to talk about this issue and, according to survey evidence gathered by Bipolar UK, clinicians are similarly reluctant to enquire about it. Many women thus suffer in silence for decades, crippled by shame and guilt at how "their illness" made them behave (often before they had received a diagnosis or learnt that such behavior was characteristic of their condition). Many report that this problem increased their poor sense of worth and exacerbated their depression[7].

It is dismaying that very little research has been done on this issue. Only one small qualitative study[9] has investigated the experience of three women and two men. No research has looked at the consequences of this behavior, whether any patients are offered psychological treatment or, crucially, why this behavior occurs in mania and hypomania. Many people believe that this is a manifestation of manic high energy, self-aggrandisement and recklessness. Dopaminergic pathways in the brain have also been implicated. Some women report that this behavior "takes them over" at particular stages of their menstrual cycle, so sex hormones may also be implicated. Research focusing on possible biological causes may potentially lead to preventive interventions.

Now that it is more acceptable to talk about "periods" and "menopause", perhaps the research community can begin to more deeply investigate the relationship between women's hormonal fluctuations and their brain chemistry. For those of us who live with severe mental illness, and struggle to adapt our lifestyles to reduce the risk of relapse, greater knowledge about how hormones impact our mental health would be invaluable.

Just as research into the level of postnatal risk faced by a woman with bipolar disorder arms her with the knowledge of how best to prepare for that risk, so research on how hormonal changes at other times in the life course affect severe mental illness would potentially give women more control over the condition that blights their lives.

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A comprehensive vision for women's mental health

Howard et al's scholarly, comprehensive and evidence-based review of women's reproductive mental health[1], across eight related topics, is a welcomed addition to earlier work on perinatal psychiatry, which has long dominated the women's mental health discourse[2].

On reading the paper, I was struck by how interrelated the covered topics are, and how deeply they are impacted by the social determinants of health (consider, for example, contraception, reproductive coercion, sexual violence, and abortion). This brings to mind the syndemic theory proposed by anthropologists[3], which refers to clustering of two or more health conditions, their adverse interactions, and contextual factors that create the conditions for interactions worsening health outcomes. This highlights that health issues are entangled in complex biological and social processes, which often require expertise from diverse fields to engender a more socially conscious medicine for prevention and integrated care[3]. Psychiatrists will recognize these concepts as the biopsychosocial model, in which individual biological and psychological factors are influenced by social, economic, cultural and environmental conditions. These intertwining and multiplicative interactions are richly highlighted in women's reproductive mental health.

To further illustrate this complex intertwining, consider the impact of serious mental illness and its treatment across women's reproductive mental health. Antidepressant medications may dampen women's sexual desire, affecting both fertility and relationships. Depression itself may affect sexual libido, as well as lessen motivation and self-efficacy to use contraceptives or seek abortion for an unwanted pregnancy. Mania may lead to hypersexuality and lack of concern about contraception or possible pregnancy, or damage relationships. Psychosis may render women more vulnerable to sexual violence and reproductive coercion, as well as reduce their ability to use contraceptives or seek abortion. Serious mental illness may also lead to marginalization and economic deprivation, and lessen access to health, reproductive and mental health services. Conversely, intimate partner violence and sexual violence may lead to serious mental illness. Multiple roles at home, as caregivers, and at work may burden many women, leading to anxiety and depression. So, a complex circle evolves.

The impact of social factors, culture, religion and policy across women's reproductive mental health is enormous. For example, social stigma, patriarchy, religion and ultraconservative policies may curtail or prohibit sex education, access to contraceptives, emergency contraception, and surgical and medical abortion. The prioritization of "motherhood" and "family life" may mitigate women's autonomous choices, and promote reproductive coercion. Recent political influences on legal decisions and health policy have severely hampered access to abortion in some US jurisdictions. Increasing evidence shows that abortion restrictions lead to increasing anxiety, depression and suicidality among reproductive-aged women. On the other hand, fatally flawed research by anti-

abortionists alleging negative mental health outcomes of abortion has been cited as "evidence" in related legal proceedings, despite well-conducted research refuting this[4]. In considering women's reproductive mental health, both psychiatry and obstetrics/gynecology have been slow to incorporate the social determinants of health into their education, research and clinical services.

A lifespan perspective is lacking across women's mental health. Life does not begin at initiation of menses or end at menopause. Sex/gender issues related to childhood and old age mental health need more attention, as well as sex/gender issues in efficacy and side effects of psychiatric medications.

Mind-body relationships are belatedly receiving their due attention in psychiatry and medicine in general. Gender/sex based perspectives, instead, are slower to emerge. For example, autoimmune and rheumatologic diseases disproportionately affect females, yet little is known about whether their etiology, symptoms, course, treatments, outcomes and psychological aspects are different in females and males. A sex/gender perspective on etiology and treatments may improve outcomes.

Coronary artery and cerebrovascular disease are major killers, and research has shown that there are sex differences in prevention, etiology, symptoms and treatments. The roles of anxiety and depression in heart disease etiology and outcomes are increasingly understood, but a gender/sex perspective is lacking.

The field of women's health and mental health is relatively recent, with appointment of the world's first chair in women's health occurring only in 1995[5]. The development of chairs and programs in women's health and mental health has now spread to most Western countries. Many psychiatric associations, including the WPA, now have a Section on Women's Mental Health, which promotes education, research and career development in this field. As women gradually become medical leaders, it is not surprising that interest in women's health and mental health is increasing. However, these developments are still absent or only gradually emerging in low- and middle-income countries.

A seminal paper in 2001 stated that "women's mental health can only be understood by considering the context of their lives" and listed a broad range of human rights and public health concerns[6]. The international women's mental health consensus statement approved by the WPA in Cairo in 2004 reinforced this wide scope[7]. Human rights issues start with females being considered equal to males. United Nations data show that worldwide females have a disproportionate share of poverty, child abuse and neglect, lower education levels, and poorer access to quality health services[8].

Education is the key to power, health (particularly reproductive health, as expressed by fertility and maternal mortality rates), better nutrition, higher economic status, education of offspring, participation in democracy, and social status among women, as well as lower intimate partner violence. Violence against women remains a global human rights and public health problem that drastically endangers their mental health, resulting in depression, anxiety, stress disorders, eating disorders and emotional suffering.

The WPA curriculum on intimate partner violence and sexual violence against women, translated into several languages on the Association's website, can help mental health care providers safely identify and manage abused women. Prevention of gender-based violence, however, requires broader human rights and public health perspectives that enforce quality of care, provide policy and legal safeguards, and advocate and model respectful relationships in education and work[9].

In conclusion, Howard et al have made a vital contribution to women's reproductive mental health. There is still much to be done for a comprehensive approach to this area in policy, research and clinical practice.

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The efficacy, mechanisms and implementation of physical activity as an adjunctive treatment in mental disorders: a meta-review of outcomes, neurobiology and key determinants

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Research examining physical activity interventions for mental disorders has grown exponentially in the past decade. At this critical juncture, there is a need to synthesize the best evidence to guide researchers, clinicians and people with lived experience. This meta-review aimed to systematically identify and comprehensively evaluate the current evidence about: a) the efficacy of physical activity interventions on mental, cognitive and physical outcomes for individuals with mental disorders; b) the potential neurobiological, psychosocial and behavioral mechanisms underlying the observed effects; and c) the barriers and facilitators for individuals to successfully engage in these interventions. Our systematic search identified 13 meta-analyses of high methodological quality (i.e., A Measurement Tool to Assess Systematic Reviews, AMSTAR score ≥8) assessing outcomes of physical activity as an adjunctive treatment, which included 256 randomized clinical trials (RCTs) and 12,233 individuals. Large effect sizes were found for adjunctive physical activity interventions in improving attention in children and adolescents with attention-deficit/hyperactivity disorder (ADHD); reducing depressive symptoms in children, adolescents and adults with depressive disorders; and reducing body mass index in adults with schizophrenia. Moderate effect sizes were found for reductions of hyperactivity, impulsivity and anxiety, and improvements of executive and social functioning in children and adolescents with ADHD; reduction of anxiety symptoms in adults with anxiety disorders; improved physical and psychological quality of life and cardiovascular fitness in adults with depressive disorders; improved daily living skills, overall quality of life and cardiorespiratory fitness in adults with schizophrenia; reduction of depressive symptoms in older people with depressive disorders; and improvements in cognition and functional mobility in older people with dementia. There is, to date, no meta-analytic evidence for physical activity as a first-line treatment for people with a mental disorder. Five meta-analyses, including 89 RCTs and 4,575 individuals, investigated potential underlying mechanisms. There is a very preliminary evidence for an effect of physical activity on circulating levels of kynurenine, growth hormone, tumor necrosis factor-alpha and brain-derived neurotrophic factor in people with major depressive disorder. No meta-analytic evidence could be found for psychosocial or behavioral mechanisms. Based on 15 umbrella or systematic reviews, covering 432 studies and 48 guidelines, six implementation strategies, along with the most evidence-based behavioral change techniques to support them, were identified. Recommendations to support implementation research in this area were finally formulated.

Key words: Physical activity, exercise, ADHD, anxiety disorders, depression, schizophrenia, dementia, lifestyle physical activity, aerobic exercise, strength training, implementation

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Mental disorders represent an increasingly significant source of burden on global health, posing substantial challenges to health care systems worldwide[1]. Traditional treatment modalities, including pharmacotherapies and psychotherapies, often fall short in leading to comprehensive and sustainable recovery[2], particularly when considering their limitations in addressing the increased risk of chronic physical problems in individuals living with a mental disorder or, in the case of some medications, their potential to induce adverse somatic side effects[3-10].

In response to these challenges, there is a growing interest in adjunctive approaches. Among these, physical activity has emerged as a particularly promising intervention, in particular when viewed through the lens of a "biopsychosocial model" for treating mental disorders. At the biological level, research has suggested that physical activity can modulate various neurotransmitter systems, reduce inflammatory cytokines, and even promote neurogenesis – all of which are also implicated in the pathophysiology of mental disorders[11-13]. At the psychological level, engaging in physical activity can improve affective states, providing a sense of accomplishment on completion, and enhancing self-esteem and self-efficacy over time[14,15]. At the social level, physical activity can provide opportunities for engaging in meaningful interactions and social settings, which is critical for achieving recovery and maintaining well-being[16].

While much of the evidence supporting these biopsychosocial benefits of physical activity has so far been derived from studies in the general population, a rapidly growing body of literature suggests similar effects in psychiatric populations[17-19]. This multifaceted impact suggests that integrating physical activity into treatment plans may provide a valuable adjunct to conventional therapies, promoting not only emotional and psychological well-being, but also better physical health outcomes and improved physical functioning.

Physical activity has been defined as any bodily movement produced by skeletal muscles that results in energy expenditure[20]. Recently, this narrow biomedical perspective has evolved to encompass a more holistic understanding, defining physical activity as people moving, acting and performing within culturally specific spaces and contexts[21]. Exercise, in turn, is recognized as a specific subset of physical activity that is planned, structured and repetitive[20].

To date, several studies have been conducted on the mental and physical health benefits of physical activity and exercise for individual mental disorders. This meta-review aims to provide a comprehensive and systematic evaluation of the available evidence on physical activity as an adjunctive and/or first-line treatment in people living with a mental disorder.

We specifically focus on three types of physical activity: lifestyle physical activity, aerobic exercise, and resistance or strength training. Lifestyle physical activity encompasses everyday activities in which individuals engage as part of their daily routines, such as walking, cycling as a commuting activity, gardening, and household chores, contributing to overall energy expenditure without the need for structured programs[22]. Aerobic exercise involves rhythmic, repetitive movements that increase the heart rate and improve cardiovascular fitness, such as running or cycling on a cycle ergometer[21]. Resistance or strength training involves exercises that induce muscle contraction against resistance, thereby enhancing muscle strength, endurance, and overall functional capacity. This includes activities such as weightlifting, bodyweight exercises, and resistance band workouts[21]. To date, no evidence synthesis has clearly outlined the differential effects of these distinct forms of physical activity across different mental disorders.

We examined the mental, cognitive and physical health outcomes associated with interventions based on these three types of physical activity for the most common mental disorders, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, anxiety disorders, depressive disorders, dementia, psychotic disorders, and substance use disorders. Additionally, we explored the potential mechanisms through which physical activity may exert its effects, considering the meta-analytic evidence on possible neurobiological, psychosocial and behavioral pathways.

We also reviewed evidence-based techniques for increasing the uptake and engagement with physical activity among people receiving mental health care. Ultimately, physical activity can only improve outcomes if it is implemented in real-world settings[23]. The current research-to-practice gap highlights the importance of addressing the key determinants that impact individual participation in physical activity interventions. Such determinants span individual (e.g., knowledge and skills of patients and providers), social (e.g., social support and reinforcement), and environmental (e.g., availability of resources) factors[24-26].

Finally, through this comprehensive meta-review, we provide evidence-based recommendations to guide future implementation efforts, inform clinical practice, drive future research, and contribute to the development of effective physical activity interventions that can enhance the well-being of individuals living with a mental disorder.

METHODS

Searches

Two authors (DV and ADW) independently searched Medline/PubMed, PsycArticles and EMBASE, from their respective inception dates until August 22, 2024, without language restrictions.

For all searches, we used the following terms: ("meta-analysis" OR "systematic review") AND ("alcohol" OR "Alzheimer" OR "attention deficit hyperactivity disorder" OR "ADHD" OR "anxiety" OR "autism" OR "dementia" OR "depression" OR "depressive" OR "illicit drugs" OR "psychosis" OR "psychotic" OR "severe mental illness" OR "schizophrenia" OR "substance") AND ("physical activity" OR "exercise*" OR "resistance" OR "strength"). For investigating the efficacy of physical activity interventions and the potential underlying mechanisms, we added the terms ("randomized controlled trial" OR "RCT"). Narrative reviews, methodology articles, and papers focusing on assessment tools were excluded.

To explore potential neurobiological, psychosocial and behavioral mechanisms, we also added the terms ("brain" OR "brain structure" OR "brain function" OR "brain plasticity" OR neurogenesis OR neurotransmitter OR BDNF OR biomarker OR "growth factors" OR "stress" OR immunology OR neuroimmunology OR neurons OR glia OR vasculature OR IGF1 OR VEGF OR hormones OR peptides OR metabolism OR imaging OR neuromodulation OR volumetry OR endorphin OR monoamine OR dopamine OR noradrenaline OR norepinephrine OR serotonin OR opioid OR social OR self-perception OR self-efficacy OR self-confidence OR confidence OR competence OR "perceived ability" OR relatedness OR belong* OR autonomy OR choice OR "basic needs satisfaction" OR "psychological needs" OR mastery OR mood OR emotion OR sleep OR nature OR greenspace OR "natural environment").

To explore the key determinants that impact individual participation in physical activity interventions, we added the terms (barriers OR impediment* OR obstacle* OR hurdle* OR hindrance* OR challenge* OR facilitat* OR enabler* OR implement* OR determinants OR "implementation evaluation" OR "process evaluation" OR process* OR "qualitative evaluation" OR "qualitative study" OR "qualitative research" OR qualitative OR "mixed method*" OR perspectives OR experienc* OR translat*).

Inclusion criteria

Inclusion criteria for the meta-analyses investigating physical activity outcomes were organized in accordance with the Patient, Interventions, Comparisons, Outcomes and Setting/study design (PICOS) reporting structure (see also supplementary information). We focused on mental, cognitive and physical health outcomes in children, adolescents, adults and older adults with primary diagnoses (based on DSM/ICD criteria/requirements) of ADHD, autism spectrum disorder, anxiety disorders, depressive disorders, dementia, psychotic disorders, and substance use disorders.

We included meta-analyses of high methodological quality (i.e., A Measurement Tool to Assess Systematic Reviews, AMSTAR[27]

score ≥8) informed by a systematic review of RCTs examining physical activity (i.e., lifestyle physical activity, aerobic exercise, or resistance/strength training) as an adjunctive and/or first-line intervention in any health care setting. Meta-analyses meeting the inclusion criteria were removed if there was a more recent meta-analysis with a larger sample and more than 75% overlapping trials. Yoga, tai chi, qigong and other holistic movement practices were excluded due to their inherently multifactorial nature, complicating the isolation of specific effects of the physical activity component on mental health outcomes. Comparisons were made with relevant control conditions (e.g., placebo, treatment as usual/usual care, waiting list, or no treatment).

Inclusion criteria for the meta-analyses investigating potential neurobiological, psychosocial and behavioral mechanisms, and for the umbrella reviews or meta-analyses exploring barriers and facilitators to implementing physical activity, were organized in accordance with the Sample, Phenomenon of Interest, Design, Evaluation, Research type (SPIDER) reporting structure (see also supplementary information).

Data extraction, outcomes, and data synthesis

To evaluate the efficacy of physical activity interventions, we extracted effect size data with 95% confidence intervals (CIs) for all relevant outcomes, as well as the number of participants in the intervention and control arms. Data for effect sizes of continuous outcomes were extracted or recalculated as standardized mean difference (SMD) using comprehensive meta-analysis (CMA, Biostat, version 3). An SMD is regarded as negligible if it is <0.2, small if it is between 0.2 and <0.5, moderate if it is between 0.5 and 0.8, and large if it is >0.8[28].

We also gathered evidence-based FITT (Frequency, Intensity, Time and Type) recommendations regarding the optimal frequency (number of sessions per week), intensity (light, moderate, vigorous), type (aerobic vs. strength training vs. lifestyle physical activity), and time/duration (expressed as minutes for a single session and number of weeks for the entire duration) of physical activity interventions, when available based on sensitivity analyses.

The potential mechanisms underlying the effects of physical activity were summarized according to age group (i.e., children and adolescents, adults, and older adults) and organized following the conceptual framework of Lubans et al[29] in three categories, i.e., neurobiological, psychosocial and behavioral.

We extracted the main individual, social and environmental factors or intervention components that impact individual participation in physical activity interventions within mental health care settings. We defined facilitators as factors that favor, facilitate or help people to engage in physical activity, and barriers as factors that hinder, limit or prevent people from engaging in physical activity. Barriers and facilitators at individual, social and environmental levels were used to develop theoretically informed and evidence-based implementation strategies, composed of behavior change techniques. To this end, we used the Behavior Change Techniques taxonomy[30] and followed the recommendations by Proctor et al[31].

Quality assessment of included studies

Included meta-analyses investigating physical activity outcomes were assessed using AMSTAR[27] (range: 0-11, with a score of 8 or higher indicating "high quality"). We also assessed the content validity of included trials, using a set of five additional quality items, each ranging between 0 and 1 or 2 (AMSTAR Plus Content)[3]. The item regarding double blindness of the design was removed, as it cannot be realized in physical activity trials. The AMSTAR Plus Content score ranges from 0 to 7, with a score of 4 or higher indicating "high quality".

RESULTS

Evidence on physical activity outcomes for people with a mental disorder

The search resulted in 4,299 hits. After removing duplicates and irrelevant abstracts, a total of 147 full texts were screened. Thirteen meta-analyses of randomized controlled trials[32-44], encompassing 256 RCTs and 12,233 participants, were included (see Figure 1 and supplementary information). All of them investigated physical activity as an adjunctive intervention. There was no meta-analysis investigating physical activity as a first-line treatment in people with a mental disorder.

The AMSTAR score ranged from 8 to 11, and the AMSTAR+ score from 0 to 5. The most common methodological shortcomings of individual RCTs were the small sample size and the lack of intention-to-treat analyses (see also supplementary information).

In meta-analyses concerning children and adolescents, large effect sizes were found for adjunctive aerobic exercise in improving attention among individuals with ADHD (SMD=0.84, 95% CI: 0.48 -1.20), and for adjunctive combined aerobic exercise and strength training in reducing depressive symptoms among those with a depressive disorder (SMD=–1.14, 95% CI: –1.88 to –0.40) (see Table 1).

Moderate effect sizes were found for adjunctive aerobic exercise in reducing hyperactivity (SMD=–0.56, 95% CI: –1.08 to –0.04), impulsivity (SMD=–0.56, 95% CI: –1.08 to –0.04) and anxiety (SMD=–0.66, 95% CI: –1.18 to –0.13), and in improving executive (SMD=0.58, 95% CI: 0.15-1.00) and social (SMD=0.59, 95% CI: 0.03-1.16) functioning among individuals with ADHD (see Table 1). A small effect size was observed for adjunctive aerobic exercise alone (i.e., without strength training) in reducing depressive symptoms among children and adolescents with a depressive disorder (SMD=–0.32, 95% CI: –0.59 to –0.05) (see Table 1).

In meta-analyses concerning adults (all ages), large effect sizes were observed for adjunctive aerobic exercise (SMD=–1.16, 95% CI: –1.46 to –0.85) and strength training (SMD=–1.04, 95% CI: –1.87 to –0.22) in reducing depressive symptoms among people with a depressive disorder, and for adjunctive aerobic exercise in reducing body mass index (SMD=–1.69, 95% CI: –3.26 to –0.11) in people with schizophrenia (see Table 2).

Moderate adjunctive effects of aerobic exercise were found in reducing anxiety symptoms among people with anxiety disorders

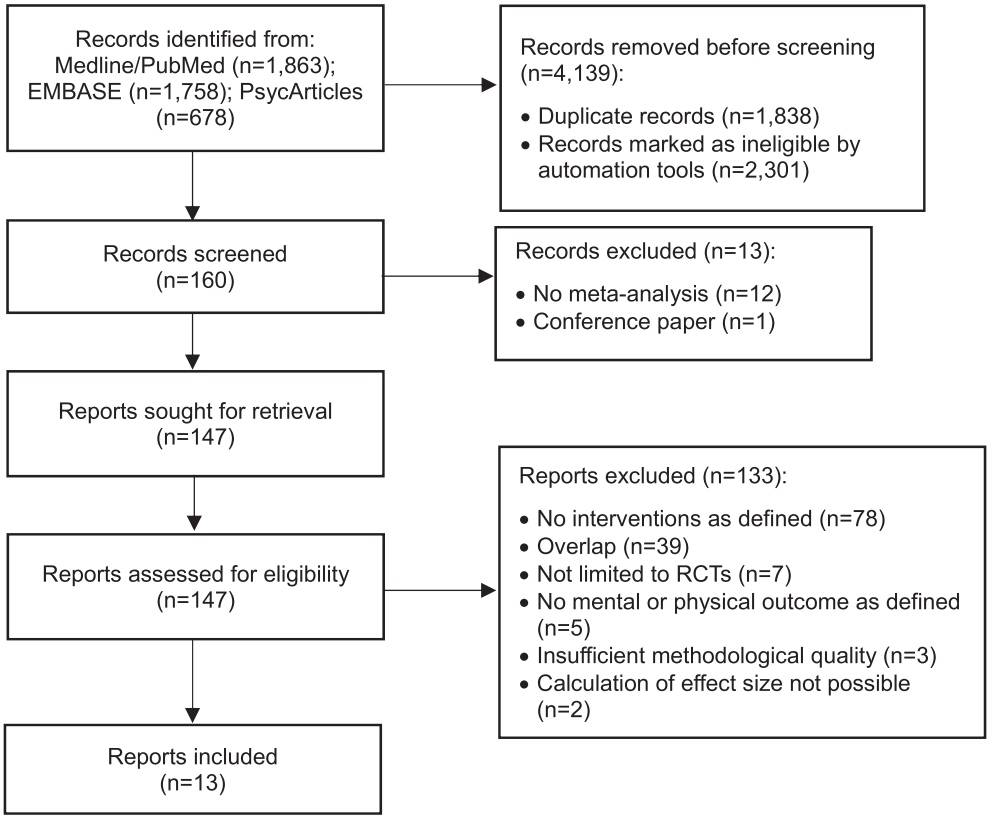

Figure 1 Flow diagram of included and excluded reports on physical activity outcomes in people with a mental disorder. RCT – randomized controlled trial.

(SMD=–0.66, 95% CI: –1.06 to –0.26); in improving overall quality of life in people with schizophrenia (SMD=0.60, 95% CI: 0.08-1.11); and in improving cardiorespiratory fitness both in people with a depressive disorder (SMD=0.64, 95% CI: 0.32-0.96) and in those with schizophrenia (SMD=0.68, 95% CI: 0.34-1.01). Moderate adjunctive effects of aerobic exercise on physical (SMD=0.53, 95% CI:

Table 1 Meta-analytic evidence on outcomes of physical activity as adjunctive treatment in children and adolescents with a mental disorder

	Outcomes	Intervention	N. trials	N. participants	SMD (95% CI)	Effect size interpretation	AMSTAR	AMSTAR+
ADHD								
Cerrillo-Urbina et al[32]	Attention	AE	5	72	0.84 (0.48-1.20)	Large	10/11	2/7
	Hyperactivity	AE	2	29	–0.56 (–1.08 to –0.04)	Moderate	10/11	2/7
	Impulsivity	AE	2	29	–0.56 (–1.08 to –0.04)	Moderate	10/11	2/7
	Anxiety	AE	2	28	–0.66 (–1.18 to –0.13)	Moderate	10/11	2/7
	Executive functioning	AE	3	49	0.58 (0.15-1.00)	Moderate	10/11	2/7
	Social functioning	AE	2	26	0.59 (0.03-1.16)	Moderate	10/11	2/7
Depressive disorders								
Zhang et al[33]	Depressive symptoms	AE	6	231	–0.32 (–0.59 to –0.05)	Small	10/11	0/7
	Depressive symptoms	AE+ST	7	202	–1.14 (–1.88 to –0.40)	Large	10/11	0/7

ADHD – attention-deficit/hyperactivity disorder, AE – aerobic exercise, ST – strength training, SMD – standardized mean difference, AMSTAR – A Measurement Tool to Assess Systematic Reviews, AMSTAR+ – AMSTAR Plus Content

0.22-0.84) and psychological (SMD=0.54, 95% CI: 0.22-0.86) quality of life were observed in individuals with a depressive disorder. A moderate adjunctive effect on daily living skills (SMD=0.65, 95% CI: 0.07-1.22) was also found for aerobic exercise and/or strength training in people with schizophrenia (see Table 2).

Small adjunctive effects were found for strength training in reducing anxiety symptoms (SMD=–0.37, 95% CI: –0.80 to –0.06). Small effect sizes were also observed for adjunctive aerobic exercise and/or strength training in reducing negative symptoms (SMD= –0.24, 95% CI: –0.43 to –0.06), and in improving social (SMD=0.41, 95% CI: 0.08-0.74) and global (SMD=0.41, 95% CI: 0.12-0.70) functioning in individuals with schizophrenia (see Table 2).

In meta-analyses focusing on older adults, moderate adjunctive effects were observed for both aerobic exercise (SMD=–0.73, 95% CI: –1.07 to –0.39) and strength training (SMD=–0.68, 95% CI: –1.00 to –0.36) in reducing depressive symptoms among individuals with a depressive disorder. Moderate adjunctive improvements were also found with strength training for cognition (SMD=0.74, 95% CI: 0.22-1.26) and functional mobility (Time Up Go test) (SMD=0.74, 95% CI: 0.17-1.31) in people with dementia (see Table 3).

No meta-analyses of high methodological quality investigating the efficacy of physical activity using RCTs only were found for autism spectrum disorder and substance use disorders.

Available FITT recommendations in children and adolescents suggest that combined aerobic exercise and strength training yields greater effects on depressive symptoms than aerobic exercise alone, with group exercise further enhancing these benefits. Engaging in exercise for twelve or more weeks is recommended, with individual sessions lasting between 20 and 60 min. A frequency of

Table 2 Meta-analytic evidence on outcomes of physical activity as adjunctive treatment in adults (all ages) with a mental disorder

	Outcomes	Intervention	N. trials	N. participants	SMD (95% CI)	Effect size interpretation	AMSTAR	AMSTAR+
Anxiety disorders								
Ramos-Sanchez et al[34]	Anxiety symptoms	AE and/or ST	13	731	–0.42 (–0.68 to –0.18)	Small	10/11	2/7
	Anxiety symptoms	AE	8	-	–0.66 (–1.06 to –0.26)	Moderate	10/11	1/7
	Anxiety symptoms	ST	4	-	–0.37 (–0.80 to –0.06)	Small	10/11	1/7
	Anxiety symptoms	AE+ST	3	-	–0.12 (–0.34 to 0.10)	NS	10/11	1/7
Depressive disorders								
Heissel et al[35]	Depressive symptoms	AE	30	1218	–1.16 (–1.46 to –0.85)	Large	11/11	3/7
	Depressive symptoms	ST	7	245	–1.04 (–1.87 to –0.22)	Large	11/11	1/7
	Depressive symptoms	AE+ST	10	1195	–0.46 (–0.80 to –0.11)	Small	11/11	5/7
Schuch et al[36]	Physical QoL	AE+ST	5	175	0.53 (0.22-0.84)	Moderate	9/11	1/7
	Psychological QoL	AE+ST	5	175	0.54 (0.22-0.86)	Moderate	9/11	1/7
	Social QoL	AE+ST	3	110	0.29 (–0.13 to 0.71)	Not significant	9/11	1/7
	Environmental QoL	AE+ST	3	110	0.37 (–0.12 to 0.85)	Not significant	9/11	1/7
	Overall QoL	AE+ST	3	104	0.39 (0.05-0.74)	Small	9/11	1/7
Stubbs et al[37]	Cardiorespiratory fitness	AE	8	498	0.64 (0.32–0.96)	Moderate	8/11	1/7
Schizophrenia								
Sabe et al[38]	Negative symptoms	AE and/or ST	17	953	–0.24 (–0.43 to –0.06)	Small	8/11	3/7
	Positive symptoms	AE and/or ST	16	935	–0.18 (–0.34 to –0.02)	Negligible	8/11	3/7
Korman et al[39]	Global functioning	AE and/or ST	17	734	0.41 (0.12–0.70)	Small	10/11	2/7
	Social functioning	AE and/or ST	5	191	0.41 (0.08–0.74)	Small	10/11	1/7
	Daily living skills	AE and/or ST	3	111	0.65 (0.07–1.22)	Moderate	10/11	1/7
Fernandez-Abascal et al[40]	Body mass index	AE	4	141	–1.69 (–3.26 to –0.11)	Large	9/11	0/7
	Overall QoL	AE	3	113	0.60 (0.08–1.11)	Moderate	9/11	1/7
	Cardiorespiratory fitness	AE	3	192	0.68 (0.34–1.01)	Moderate	9/11	1/7

QoL – quality of life, AE – aerobic exercise, ST – strength training, SMD – standardized mean difference, AMSTAR – A Measurement Tool to Assess Systematic Reviews, AMSTAR+ – AMSTAR Plus Content

Table 3 Meta-analytic evidence on outcomes of physical activity as adjunctive treatment in older adults with a mental disorder

	Outcomes	Intervention	N. trials	N. participants	SMD (95% CI)	Effect size interpretation	AMSTAR	AMSTAR+
Dementia								
Li et al[41]	Functional mobility (TUG)	AE	2	105	0.78 (–0.53 to 2.09)	Not significant	9/11	0/7
	Functional mobility (TUG)	ST	2	53	0.74 (0.17-1.31)	Moderate	9/11	1/7
Mendes et al[43]	Quality of life	AE and/or ST	5	661	0.10 (–0.14 to 0.34)	Not significant	8/11	2/7
Zhou et al[42]	Cognitive function	AE	12	795	0.74 (0.22-1.26)	Moderate	8/11	2/7
Depressive disorders								
Tang et al[44]	Depressive symptoms	AE	9	646	–0.73 (–1.07 to –0.39)	Moderate	10/11	1/7
	Depressive symptoms	ST	11	397	–0.68 (–1.00 to –0.36)	Moderate	10/11	0/7
	Depressive symptoms	AE+ST	11	825	–0.21 (–0.52 to 0.11)	Not significant	10/11	2/7

TUG – Time Up Go test, AE – aerobic exercise, ST – strength training, SMD – standardized mean difference, AMSTAR – A Measurement Tool to Assess Systematic Reviews, AMSTAR+ – AMSTAR Plus Content

three or more sessions per week is most beneficial, as well as maintaining at least a moderate intensity during workouts[33]. In adults, FITT recommendations are inconsistent, with only supervised exercise consistently demonstrating larger effects than unsupervised exercise[34-36] (see also supplementary information).

Evidence on potential mechanisms for physical activity effects in people with a mental disorder

The search resulted in 7,282 hits. After removing duplicates and irrelevant abstracts, 29 full texts were screened. Twenty-four studies were excluded (see supplementary information). Five meta-analyses[45-49], covering 89 trials and 4,575 participants, were included. Based on the AMSTAR score, three included meta-analyses were of high methodological quality. The most common methodological problem of individual RCTs was the small sample size (see also supplementary information).

Acute bouts of physical activity produced a large effect size for increased circulating levels of atrial natriuretic peptide, and a moderate effect size for increased growth hormone levels, in people with major depressive disorder (see Table 4). For chronic physical activity, small significant effect sizes were found for increased circulating levels of tumor necrosis factor-alpha (TNF-α), kynurenine, and brain-derived neurotrophic factor (BDNF) in adults with major depressive disorder (see Table 5).

No meta-analytic evidence could be found for psychosocial or behavioral mechanisms.

Table 4 Meta-analytic evidence on neurobiological effects of acute bouts of physical activity in adults with a mental disorder

	Intervention	N. trials	N. participants	Biomarker	SMD (95% CI)	p	Effect size interpretation	AMSTAR	AMSTAR+
Major depressive disorder									
Guimarães et al[45]	AE, ST	3	110	TNF-α	0.29 (–0.54 to 1.13)	0.49	Not significant	9/11	0/7
		4	140	IL-6	0.73 (–0.41 to 1.87)	0.21	Not significant		0/7
		2	74	IL-8	0.51 (–0.25 to 1.26)	0.19	Not significant		0/7
		4	140	IL-10	0.04 (–0.07 to 0.16)	0.46	Not significant		0/7
Schuch et al[46]	AE	2	150	Atrial natriuretic peptide (↑)	1.22 (0.59-1.85)	<0.001	Large	5/11	2/7
		2	161	Cortisol	–0.01 (–0.23 to 0.21)	0.90	Not significant		2/7
		2	161	Growth hormone (↑)	0.78 (0.55–1.01)	<0.001	Moderate		2/7
		2	161	Prolactin	0.19 (–0.03 to 0.41)	0.09	Not significant		2/7

AE – aerobic exercise, ST – strength training, SMD – standardized mean difference, AMSTAR – A Measurement Tool to Assess Systematic Reviews, AMSTAR+ – AMSTAR Plus Content, TNF-α – tumor necrosis factor alpha, IL – interleukin

Table 5 Meta-analytic evidence on neurobiological effects of chronic physical activity in adults and older adults with a mental disorder

	Intervention	N. trials	N. participants	Biomarker	SMD (95% CI)	p	Effect size interpretation	AMSTAR	AMSTAR+
Major depressive disorder in adults									
Guimarães et al[45]	AE, ST	3	175	IL-1β	0.24 (–0.06 to 0.53)	0.11	Not significant	9/11	1/7
		5	427	IL-6	0.08 (–0.44 to 0.60)	0.77	Not significant		1/7
		4	217	TNF-α (↑)	0.29 (0.03-0.55)	0.03	Small		1/7
da Cunha et al[47]	AE, ST	3	123	IL-10	0.24 (–0.72 to 1.21)	NA	Not significant	9/11	0/7
		4	149	BDNF (↑)	0.44 (0.15-0.73)	NA	Small		0/7
		3	243	Kynurenine (↑)	0.29 (0.04-0.54)	NA	Small		0/7
Schuch et al[46]	AE, ST	2	129	Cortisol	–0.17 (–0.52 to 0.18)	0.34	Not significant	5/11	0/7
		2	116	Prolactin	–0.13 (–0.50 to 0.23)	0.73	Not significant		0/7
Dementia in older adults									
Kress et al[49]	AE, ST	3	139	Total hippocampal volume	0.18 (–0.16 to 0.51)	0.30	Not significant	5/11	1/7
Huang et al[48]	AE	2	98	TNF-α	–0.47 (–1.05 to 0.11)	-	Not significant	8/11	0/7

AE – aerobic exercise, ST – strength training, SMD – standardized mean difference, AMSTAR – A Measurement Tool to Assess Systematic Reviews, AMSTAR+ – AMSTAR Plus Content, TNF-α – tumor necrosis factor alpha, IL – interleukin, NA – not available

Evidence on barriers and facilitators for individuals to successfully engage in physical activity interventions within mental health care settings

The search resulted in 18,031 hits. After removing duplicates and irrelevant abstracts, 24 full texts were screened. Nine studies were excluded (see supplementary information). Fifteen umbrella reviews or systematic reviews[50-64], covering 432 studies and 48 guidelines, were selected. Four reviews focused on children and adolescents, ten on adults and one on older adults. The AMSTAR score ranged from 3 to 11. Eleven reviews had an AMSTAR score of 8 or higher, indicating that they were of high methodological quality (see also supplementary information). All evidence was based on studies from high- and middle-income countries.

The most reported facilitators were having access to a structured/supervised physical activity program (n=5), having a social support network (n=4), access to physical activity facilities (n=3), having the autonomy to choose (n=2), experiencing enjoyment (n=2), and trained staff (n=2).

The most reported barriers were the presence of a physical comorbidity (n=6), low self-efficacy (n=5), lack of social support (n=4), financial constraints (n=3), poorly trained staff (n=2), safety issues (n=2), sensory or behavioral dysregulation (n=2), lack of knowledge by patients about physical activity (n=2), side effects of medication (n=2), and lack of time (n=2).

The identified facilitators and barriers were used to develop six theoretically informed implementation strategies, composed of behavior change techniques[29]. These strategies were: a) enhance access to physical activity facilities and opportunities; b) provide trained and engaged staff to facilitate interventions; c) ensure a psychologically and physically safe environment; d) develop tailored interventions; e) foster autonomous motivation, and f) facilitate a resilient social support network (see Table 6).

Most evidence was available for fostering autonomous motivation. Twelve included reviews[50,51,53-55,57-60,62-64] referred to this topic. Fostering commitment to behavior change, providing reg-

Table 6 Evidence-based implementation strategies for physical activity in mental health settings (with behavioral change techniques supporting them)

1. Enhance access to physical activity facilities and opportunities (ensure that physical spaces are designed to encourage activity; add necessary equipment or objects that facilitate physical activity).
2. Provide trained and engaged staff to facilitate interventions (equip staff with motivational interviewing and cognitive behavioral principles to provide general social support; train staff to serve as credible sources for promoting physical activity, ensuring that they can guide participants effectively).
3. Ensure a psychologically and physically safe environment (use social and emotional support to enhance safety; eliminate discomfort or barriers to participation; create a physically and socially supportive environment for physical activity; ensure access to objects that promote physical activity).
4. Develop tailored interventions (set behavior and outcome goals tailored to individual needs; plan concrete actions to meet these goals; encourage self-monitoring to track progress; provide general support and instructional guidance; ensure that staff are seen as credible sources).
5. Foster autonomous motivation (foster commitment to behavior change; provide regular feedback on behaviors and outcomes; offer general and emotional social support to motivate participants; educate participants on the health benefits of physical activity; reinforce identity changes that result from behavior change).
6. Facilitate a resilient social support network (establish a network of social support, including practical, emotional and general support; create social environments that encourage ongoing physical activity).

ular feedback on behaviors and outcomes, offering general and emotional social support to motivate participants, educating participants on the health benefits of physical activity, and reinforcing identity changes that result from behavior change were the main supporting behavioral change techniques (see Table 6).

Evidence for developing tailored interventions was based on data from eleven reviews[51-53,56,57-60,62-64]. Setting behavior and outcome goals tailored to individual needs, planning concrete actions to meet these goals, encouraging self-monitoring to track progress, providing general support and instructional guidance, and ensuring that staff are seen as credible sources were the main supporting behavioral change techniques (see Table 6).

Next, most evidence was found for ensuring a psychologically and physically safe environment, which could be derived from ten reviews[50,53,54,56,58-61,63,64], and for facilitating a resilient social support network, which was reported in eight reviews[53-56,58,62,63,64]. Finally, providing trained and engaged staff to facilitate interventions[53-55,62,63], and enhancing access to physical activity facilities and opportunities[52-54,56,64] were considered important in five reviews each. The main supporting behavioral change techniques relevant to these latter four strategies are listed in Table 6.

DISCUSSION

This meta-review systematically and comprehensively evaluated current evidence on the efficacy of physical activity for individuals living with a mental disorder. The preliminary evidence concerning possible neurobiological effects of physical activity in these individuals was also summarized. We additionally identified within the existing scientific literature the barriers and facilitators for people living with a mental disorder to participate in physical activity interventions in real-world settings, and used this evidence to develop six theoretically informed implementation strategies.

The available meta-analytic literature clearly demonstrates that physical activity is a transdiagnostic efficacious adjunctive intervention. Large effect sizes were found for the adjunctive effects of aerobic exercise in improving attention in ADHD, and of combined aerobic exercise and strength training in reducing depressive symptoms in children and adolescents with depressive disorders. Similarly, large adjunctive effects were seen for aerobic exercise and strength training in adults with a depressive disorder, and for aerobic exercise in reducing body mass index in people with schizophrenia. Moderate adjunctive effects were observed in reducing hyperactivity, impulsivity and anxiety, and in improving executive and social functioning among children and adolescents with ADHD. Adults with anxiety disorders benefited from moderate adjunctive reductions of anxiety symptoms through aerobic exercise. Moderate adjunctive effects were also found in improving daily living skills and overall quality of life in people with schizophrenia, physical and psychological quality of life in individuals with a depressive disorder, and cardiorespiratory fitness in people with schizophrenia or a depressive disorder. Similarly, moderate adjunctive effects were observed in reducing depressive symptoms among older adults with a depressive disorder, and in improving cognition and functional mobility in older adults with dementia.

Of interest, meta-analytic evidence of high methodological quality investigating the efficacy of aerobic exercise and/or strength training only using RCTs is currently lacking for children and adolescents with autism spectrum disorder, and for adolescents and adults with substance use disorders. Besides this, while our current findings are based on meta-analyses of high methodological quality, the evidence base itself is not limited to trials of high methodological quality. Thus, it could be further strengthened through larger trials with greater power and using intention-to-treat analyses.

Important for clinicians is that there is currently no meta-analytic evidence base for physical activity as a first-line intervention in people living with a mental disorder. The existing evidence for physical activity as a first-line treatment is, to date, limited to only one RCT[65] in people with a depressive and/or anxiety disorder. This RCT reported that remission rates were similar following 16 weeks of at least twice weekly running therapy as a first-line treatment versus treatment with escitalopram or sertraline. Only running therapy and not pharmacotherapy had a significant beneficial effect on cardiometabolic parameters[65]. Rigorous, large-scale randomized controlled trials are, therefore, needed to ascertain the efficacy of physical activity as a first-line treatment in people with mental disorders.

Sensitivity analyses suggested that combined aerobic exercise and strength training yields greater effects on depressive symptoms than aerobic exercise alone in children and adolescents. Additionally, exercising in a group setting has been shown to enhance these benefits, indicating the importance of social aspects of physical activity as a critical component of mental health improvement. To maximize the effects on depressive symptoms, engagement in twelve or more weeks of regular exercise is recommended. Optimal single-session durations range from 20 to 60 min. Furthermore, frequency plays a crucial role, with three or more sessions per week associated with the most significant improvements in mood. Finally, maintaining at least a moderate intensity during these sessions seems to be important for achieving the largest effects.

In adults living with a mental disorder, the existing evidence regarding the optimal frequency, intensity, type and duration of physical activity interventions remains inconsistent, making it challenging to formulate clear clinical guidelines. However, one consistent finding across the literature is that supervised exercise yields more significant benefits compared to unsupervised exercise. This suggests that the presence of a qualified facilitator can enhance motivation and foster a supportive environment, ultimately leading to improved outcomes.

Although our meta-review clearly shows that physical activity should be considered as an evidence-based adjunctive treatment modality, in routine care only a small proportion of people receiving mental health care are asked about their physical activity levels[66] and offered related interventions[67]. Future research should focus on how to close this translation gap, including at the health care policy level, where resource decisions and clinical priorities are determined.

One of the reasons for the above gap might be that clinical practice guidelines do not usually consider the adjunctive value of

physical activity, with only a few exceptions[68-70]. Only recently the World Federation of Societies for Biological Psychiatry[26] and the European Psychiatric Association[71] have published guidance documents concluding that physical activity should be used as an adjunctive treatment modality to improve psychotic symptoms and cognition in adults with schizophrenia, and depressive symptoms in adults with a depressive disorder. These guidelines recommend that patients living with a severe mental disorder aim to achieve a minimum of 150 min of moderate-to-vigorous intensity physical activity per week to improve mental health. It is important to note, however, that also lower levels of physical activity have been shown to confer mental health benefits[72]. Given that previous high-quality studies have shown beneficial effects of both light- and high-intensity exercise on mental health outcomes, future research should explore the dose-response relationship (considering frequency, intensity, type and time) in more detail, and its implications for clinical practice.

Future meta-analytic research could also focus on the efficacy of lifestyle physical activity counseling, i.e. integrating physical activity in daily life, as meta-analyses of RCTs investigating the efficacy of this counseling are currently lacking. In this respect, recent research in the general population[73-75] underscores the importance of distinguishing between various domains of physical activity (i.e., leisure time, commuting, occupational activity, and domestic physical activity), exploring their respective impacts on mental health. Evidence suggests that leisure time physical activity is particularly beneficial for mental well-being, often yielding greater psychological benefits compared to activities performed in other contexts. Mental health benefits of leisure time physical activity may stem from its association with increased social interaction and opportunities for enjoyment[76]. A nuanced understanding of how different types of lifestyle physical activity influence mental health in people living with a mental disorder will be essential for developing effective clinical interventions and public health strategies.

It has also been recommended to assess lifestyle from a 24-hour perspective[77,78]. This approach highlights the importance of considering time spent being physically active, sedentary and asleep, since each of these components influences overall health. For children and adolescents, guidelines recommend at least 60 min of moderate-to-vigorous physical activity daily, no more than two hours of recreational screen time, and sufficient sleep (9-11 hours for children, 8-10 hours for adolescents), as this balance positively impacts mental health by reducing anxiety and depression, and improving emotional regulation[77,78]. In adults, the recommendation is 150-300 min of moderate-intensity aerobic activity weekly, along with breaking up sedentary time and ensuring 7-9 hours of quality sleep, as these habits lower the risk of anxiety, depression, and cognitive decline[77,78]. Future research should investigate the impact of complying with the 24-hour guideline in people living with a mental disorder.

Further research should also explore which patients will benefit most from physical activity. There may be subgroups with certain neurobiological characteristics who respond better. Therefore, it is important to know how physical activity works, and to identify potential neurobiological, psychological and behavioral pathways. Overall, we found that the meta-analytic evidence on the neurobiological effects of physical activity in people with mental disorders is very preliminary, and limited to adults with major depressive disorder. Larger studies are obviously needed.

We found some evidence that chronic exercise stimulates the kynurenine pathway, which involves the breakdown of tryptophan, an amino acid crucial for serotonin production. Regular exercise increases the metabolism of tryptophan into kynurenine, leading to the production of metabolites, such as kynurenic acid, that can protect brain function[79]. A meta-analysis in people with age-related diseases[80] also found that structured physical activity had a significant concomitant effect on kynurenine pathway metabolite levels and psychological outcomes, reinforcing the current meta-analytic findings.

Meta-analytic evidence was also available showing a small effect of chronic exercise in promoting an increase of TNF-α. Of note, this increase was observed in adults with depression, but not in older adults with dementia. It has been hypothesized that the intensity of the intervention might play a role[81], with only higher intensity exercise, which is less suitable for older adults, resulting in increases of TNF-α levels. Chronic exercise-induced increases in TNF-α might play a beneficial role in regulating immune function and metabolic health by promoting a balance between pro-inflammatory and anti-inflammatory responses[82].

Effects on the hypothalamic-pituitary-adrenal (HPA) axis activity were inconsistent, with no physical activity-induced changes of cortisol levels in people with a major depressive disorder, but a large acute effect on natriuretic peptides. These peptides play a role in inhibiting HPA axis activity, but they are also a diagnostic and prognostic biomarker of cardiovascular diseases[83].

Our meta-review suggests that physical activity has a moderate acute, but not chronic, effect on growth hormone levels in people with major depressive disorder. Growth hormone regulates several important physiological functions in the brain, including neural plasticity[84]. We also found evidence of small effects of physical activity in increasing BDNF circulating levels.

No meta-analytic evidence could be found for psychosocial or behavioral moderators of the benefits of physical activity in people living with a mental disorder. Indeed, most individual trials did not adequately measure or control for psychosocial factors such as social support, motivation, and changes in self-esteem or coping skills, nor for behavioral factors such as individual goal-setting. A recent systematic review[85], in which only three out of 22 included studies were RCTs, did find that the strongest available evidence was for psychosocial mechanisms, including increased self-esteem, self-efficacy and self-concept, but further research is needed to confirm these findings in controlled trials. With regards to behavioral pathways, it has been proposed that better sleep quality might moderate the mental health benefits observed following physical activity[29]. For instance, a previous meta-analysis of RCTs[86] found that physical activity has a large statistically significant effect on sleep quality in those living with a mental disorder.

Research on individual, social and environmental factors, as well as intervention components, that impact individual participation in physical activity interventions within mental health care settings has grown considerably. Based on our meta-review, we were able to derive six implementation strategies, along with the behavioral change techniques to support them. These strategies include enhancing access to physical activity facilities and opportunities; providing trained and engaged staff to facilitate interventions; ensuring a psychologically and physically safe environment; developing tailored interventions; fostering autonomous motivation; and facilitating a resilient support network. The most extensive evidence was available for fostering autonomous motivation, which involves encouraging commitment to behavior change through goal-setting, regular feedback, and education on the health benefits of physical activity, while also reinforcing identity transformations associated with these changes.

Despite the large body of evidence of high methodological quality supporting the efficacy of physical activity interventions on mental and cognitive health in people living with a mental disorder, there is a lack of clinical practice guidelines, including clearly defined referral pathways, to inform the integration of physical activity into routine mental health care. This meta-review highlights that most existing studies have primarily focused on the question "Does it work, and how?", by evaluating efficacy under ideal conditions. Most studies do not reflect real-world circumstances, with resources, staffing and less complex disorder severity of participants that are not representative for everyday contexts[87,88], although there are exceptions[89]. Moreover, efficacy trials are typically conducted in high-resource settings, raising concerns about their ecological validity in low-income countries.

Future research should focus on strengthening evidence for the implementation strategies identified in this meta-review. We need reviews and meta-analyses that incorporate effectiveness studies [90], which allow to capture critical factors that cannot be fully identified under controlled conditions, such as contextual, organizational and systemic determinants. There is, for example, preliminary meta-analytic evidence that being physically active in nature is more beneficial for a range of psychological outcomes than being physically active in an urban environment[91]. Collaboration between researchers investigating physical activity for mental health and urban planners will be essential in the future, because the green and built environment significantly influence physical activity levels in people with a mental disorder, which in turn directly impact mental health outcomes[92], also in low-income countries[93]. Urban planners should help design and modify spaces to promote active lifestyles, ensuring that interventions are context-specific, sustainable and equitable.

To support implementation research in physical activity for mental illness trials, we formulate the following main recommendations:

- Available information on the implementation of interventions should be reported, also in efficacy studies. Fidelity (i.e., the extent to which the intervention was implemented as intended) is a critical element for determining whether (in)effectiveness can be attributed to the intervention itself. Additionally, details such as the strategies used, the context, and any adaptations to the intervention during the study should be reported. This information supports the interpretation of findings in a way that is useful for clinical practice and replication studies.
- For groups/settings with sufficient evidence of efficacy, the next step is to move on to effectiveness studies representing real-world practice. For this, alternative designs should be considered capturing real-world practice within methodologically-sound research, such as stepped-wedge trials and ecological momentary assessments. Preferably this should be done by hybrid designs where the implementation is evaluated in addition to health-related outcomes[94].
- Internationally agreed-upon methods and frameworks for implementation outcomes, determinants and strategies should be used. For outcomes, models such as RE-AIM[95] could be considered. For determinants, including their identification as barriers and facilitators, broad frameworks such as the Consolidated Framework for Implementation Research[96] could be used, or specific models such as the Theoretical Domains Framework[25] or the Capability, Opportunity, and Motivation model (COM-B) [97] for more individual-level behavioral analysis could be adopted. To target barriers, the Expert Recommendations for Implementing Change (ERIC)[98] are recommended. There are also frameworks that incorporate multiple steps and even offer tools that can be used by teams from the design to maintenance of interventions (e.g., iPRISM)[99]. This will also improve consistent terminology within implementation science as well as comparability and transferability between studies.
- Implementation starts with the design of the intervention, by involving key stakeholders relevant to real-world context. Therefore, recognizing and amplifying the contribution of people with lived experience to physical activity and mental health research may also help facilitate translation into practice and ensure that implementation strategies meet the needs of affected individuals and their families. This includes, for example, the co-design and co-delivery of interventions and the shared generation of research priorities[100-102]. Likewise, it is of value to recruit health care practitioners prescribing or supervising physical activity in mental health care settings. Based on frameworks mentioned above, the relevant team of stakeholders can already identify potential barriers, facilitators and needed strategies from the start.
- As indicated, more research on the implementation of physical activity within mental health care settings should be conducted in low-income countries. It can be hypothesized, however, that implementing physical activity interventions in these settings presents additional challenges, due to a shortage of trained facilitators and appropriate facilities, and the lack of environments that are both psychologically and physically safe for physical activity.

In conclusion, this meta-review sought to aggregate the vast but disparate evidence base around physical activity in the treatment of mental disorders. From this, we can show how the efficacy of exercise interventions is well-established across a broad spec-

trum of mental disorders. Alongside this, the preliminary evidence emerging around the neurobiological effects of physical activity in people with mental disorders has been reviewed. Finally, the literature examining the central determinants of uptake and adherence among people living with a mental disorder has become substantial enough to distill the main barriers and facilitators and develop implementation strategies to inform effective integration into care services. Overall, the findings and conclusions from each part of this meta-review may be used to expose critical gaps for future research, produce a case for dedicating further resources towards including physical activity interventions in mental health care, whilst also presenting the most evidence-based strategies available to date for delivering them successfully.

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Risk of relapse during tapering of antipsychotic medication after a first psychotic episode: association with D2 receptor affinity but not with tapering speed

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While antipsychotic maintenance treatment effectively prevents relapse after a first psychotic episode, many remitted antipsychotic users wish to reduce or discontinue their medication, due to side effects, long-term health concerns, stigma, or the desire to regain autonomy. Current guidelines suggest gradual tapering, but what the optimal speed of this tapering should be, especially in patients who remitted from a first psychotic episode, remains unclear. Furthermore, D2 receptor affinity of the antipsychotic drug may also affect relapse risk. This study examined relapse risk and time to relapse, within the first 18 months after remission from a first psychotic episode, in 227 individuals who tapered antipsychotic medication. Relapse was defined dichotomously using consensus criteria based on the Positive and Negative Syndrome Scale, hospitalization for psychosis, or explicit clinical judgement of the treating psychiatrist. Tapering speed (in olanzapine equivalents mg/day) was calculated as the difference of antipsychotic dose between the start and the end of tapering, divided by the number of days in between. Antipsychotics were classified into partial D2 agonists, or antagonists with low or high D2 affinity. Logistic and Cox proportional hazards regression analyses were controlled for age, sex, cannabis use, and duration of first psychotic episode, as well as for differences in clinical and sociodemographic characteristics between the three drug D2 affinity groups using inverse probability of treatment weighting. During the follow-up period, 45.8% (N=104) of participants experienced a relapse after tapering. The average tapering speed was 10 mg olanzapine equivalents over 75 days, with an average tapering duration of 124 days (range: 6-334 days). Logistic regression analysis showed that the tapering speed did not predict the risk of relapse (z=0.989, p=0.323). Compared with users of high D2 affinity antagonists (N=57), patients using low D2 affinity antagonists (N=116) and partial D2 agonists (N=54) had a lower risk of relapse (respectively, z=–2.104; odds ratio, OR=0.48, p=0.035; and z=–2.278, OR=0.44, p=0.023). Users of high D2 affinity antagonists had a shorter time between the end of tapering and relapse (mean: 280 days) than low D2 affinity antagonist users (mean: 351 days, p=0.027) and partial D2 agonist users (mean: 357 days, p=0.040). Thus, D2 receptor affinity of the antipsychotic was more important than tapering speed in predicting psychotic relapse risk in individuals remitted from a first psychotic episode. Users of high D2 affinity antipsychotics had an about twice higher risk of relapse than users of other types of antipsychotics. This higher risk of relapse after tapering should be regarded as a relevant factor when selecting an antipsychotic drug for people with a first psychotic episode. For patients using strong D2 antagonists after remission from a first psychotic episode, extra monitoring during tapering is required.

Key words: Antipsychotic medication, first episode psychosis, tapering, dose reduction, D2 receptor affinity, partial D2 agonists, dopamine supersensitivity, relapse

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Preventing relapse is a crucial treatment target following a first psychotic episode, since up to 85% of individuals experience a psychotic relapse within 5 years after remission[1], and relapse after a first psychotic episode is associated with a poorer long-term outcome[2]. There is ample evidence documenting the efficacy of antipsychotic medication in reducing the risk of relapse[3]. Consequently, international guidelines recommend the continuation of antipsychotic medication for at least one year following remission from a first psychotic episode[4].

On the other hand, many individuals who remit from a first psychotic episode have a strong desire to reduce or completely discontinue their medication. This desire may be partly fueled by side effects and long-term health concerns, but may also reflect stigma and the need for self-determination and autonomy[5,6]. On average, 50% of people who remitted from a first psychotic episode discontinue medication prematurely, often without clinical guidance[7-9]. A previous study reported better long-term social functioning after early tapering, compared to longer use of medication[10]. Dose reduction has also been experienced to aid in the development of better stress management strategies and in regaining a sense of autonomy[11]. This preference to discontinue antipsychotic treatment needs to be balanced against the increased risk for psychotic relapse that follows cessation of medication[12]. Knowledge on how to taper antipsychotic medication with minimal risk of relapse is essential for clinicians to guide the much-desired antipsychotic dose reduction or discontinuation as safely as possible[13].

An optimal protocol for antipsychotic tapering has not yet been established. There is consensus that gradual tapering is preferable to abrupt discontinuation[14,15]. Currently, "gradual" is generally described as "not abrupt"[16], and lacks a clear definition. A meta-analysis showed that dose reduction over >10 weeks – resulting in end doses about half of the initial dose, but generally still not

below therapeutic levels – was equally effective in preventing psychotic relapse compared to maintenance treatment[12], suggesting that a period of 10 weeks may be sufficiently gradual for reducing the dose by half. However, others have advocated even slower tapering, especially when aiming to discontinue low doses[16,17].

The idea behind slow tapering is that it may reduce the risk of rebound phenomena due to the development of dopamine supersensitivity following the long-term antagonism of striatal D2 receptors by antipsychotic treatment[18]. This supersensitivity may be more pronounced with D2 receptor blockade by high affinity antagonists, compared to low affinity antagonists and partial D2 agonists[19,20]. So far, D2 receptor affinity has not gained particular attention in relation to relapse risk. In a single naturalistic cohort study, a significantly lower hospitalization rate was found for aripiprazole (6.3%, N=17) compared to olanzapine (37.9%, N=29) as the first antipsychotic received for first psychotic episode, but the authors attributed this effect to potential bias by indication (i.e., people who function relatively well may be more likely to be prescribed aripiprazole)[21].

In this study, we aimed to investigate both antipsychotic tapering speed and D2 receptor affinity as predictors of relapse risk and time to psychotic relapse in patients in remission from a first psychotic episode. We hypothesized that a higher tapering speed would be associated with a higher relapse risk, and a shorter time between end of tapering and relapse. In addition, we hypothesized that use of high D2 affinity antagonists would be associated with a greater relapse risk than use of low D2 affinity antagonists or partial D2 agonists, and with a shorter time to relapse after complete discontinuation. We included 227 individuals recently remitted from a first psychotic episode, who tapered antipsychotic medication as part of the Handling Antipsychotic Medication: Long-term Evaluation of Targeted Treatment (HAMLETT) trial, the largest randomized controlled trial worldwide on antipsychotic dose reduction/discontinuation after a first psychotic episode[22].

METHODS

Study design and participants

The data for this study are part of the HAMLETT study, a multicentre single-blind randomized controlled trial of antipsychotic medication reduction/discontinuation, whose protocol has been previously described in detail[22]. All participants provided written informed consent after oral and written explanation of the study. Ethical approval was obtained from the research and ethics committee of the University Medical Center Groningen (NL 62202.042.17).

Patients were screened by clinicians from 26 specialized psychosis centers throughout the Netherlands, and were included in the HAMLETT trial if they: a) were aged 16 to 60 years; b) had received a DSM-5 diagnosis of first episode of schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, or unspecified schizophrenia spectrum and other psychotic disorder; c) had been in symptomatic remission for 3-6 months (i.e., there had been sustained improvement of psychotic symptoms, and any remaining psychotic symptoms did not interfere with daily functioning) according to their treating psychiatrist; d) were using antipsychotic medication. Patients were excluded from the trial if they had displayed harmful behavior during the psychotic episode or if they needed coercive treatment. Eligibility criteria were assessed by trained researchers using the Comprehensive Assessment of Symptoms and History interview (CASH)[23]. Up to one year after randomization, each diagnosis was reassessed on the basis of information collected from the clinical file, the CASH interview, and the Global Assessment of Functioning scale (GAF)[24] at different time points, as well as (when needed) additional information from the treating clinician.

Participants were randomized with a 1:1 ratio to maintenance (≤ 25% dose reduction for at least 12 months) or dose reduction/discontinuation (>25% dose reduction within 6 months). Participants and their clinicians were informed of the randomization outcome. Those randomized to the dose reduction/discontinuation group received recommended tapering schedules based on gradual discontinuation in a period of 3-6 months (see Table 1). Data were collected between September 2017 and May 2024. They concerned the screening, the baseline measurement at 3-6 months after remission, and follow-up visits at 3, 6 and 12 months after baseline, i.e. up to 18 months after remission.

In this specific study, we included HAMLETT participants who tapered antipsychotic treatment between remission and 12-month follow-up, who did not discontinue antipsychotics abruptly or without supervision, and for whom sufficient pharmacy data were available to calculate the speed of the first tapering trajectory after remission (N=304). Participants were excluded from the study if: a) there was no relapse information for the entire observation period (N=1); b) dose reduction was not initiated within the first 12 months after remission (N=39); c) only one dose reduction step was taken on a single day during the first 12 months after remission (e.g., a dose correction from 15 to 12.5 mg olanzapine/day) (N=37).

Assessments

Demographic characteristics, cannabis use in the month before baseline and during the 12-month follow-up, and global functioning and symptomatology at all time points were assessed with the CASH interview, the GAF questionnaire, and the Positive and Negative Syndrome Scale (PANSS)[25], used by raters who were blinded to the patient's condition.

The frequency of contact with a clinical team member (psychiatrist, psychologist or nurse) in the month prior to baseline was assessed with the Treatment Inventory of Costs in Patients with psychiatric disorders (TIC-P) questionnaire[26]. The duration of the first psychotic episode was calculated as the number of days between the dates of onset and remission, which were provided by clinicians from electronic patient records. Medication use was evaluated by means of a self-report questionnaire, and detailed data on medication dispense were provided by the Foundation for Pharmaceutical Statistics, from which olanzapine equivalents were calculated[27-29].

Table 1 HAMLETT antipsychotic tapering schedules (all doses are in mg/day)

	Max. dose	Available doses	Start tapering	After 2w	After 4w	After 6w	After 8w	After 10w	After 12w	After 14w	After 16w	After 18w	After 20w	After 22w	After 24w	After 26w	After 28w	After 30w
Risperidone	10	0.5, 1, 2, 3, 4, 6	10	8	6	5	4	3	2	1.5	1	0.5	0.5	0.25	0.25	0.25**	0.25**	stop
Olanzapine	20	2.5, 5, 10, 15, 20	20	17.5	15	12.5	10	7.5	5	5	2.5	2.5	1.25	1.25	1.25**	1.25**	stop	stop
Quetiapine	800	25, 100, 200, 300	800	600	500	400	300	200	150	100	75	50	25	12.5	12.5	stop	stop	stop
Aripiprazole	20	5, 10, 15	20	17.5	15	12.5	10	10	7.5	7.5	5	5	2.5	2.5	2.5**	2.5**	stop	stop
Haloperidol	20	1, 5, 10	16	12	10	8	6	4	3	2	1	1	0.5	0.5	0.5**	0.5**	stop	stop
Zuclopenthixol	40	2, 10, 25	40	32	28	24	20	16	12	8	6	4	2	1	1	1**	1**	stop
Sulpiride	800	400, 50*	800	600	500	450	400	350	300	250	200	150	100	50	50	50**	50***	stop
Paliperidone	12	3*, 6*, 9*	12	12**	9	9**	9**	6	6	6**	3	3	3**	3**	3***	stop	stop	stop
Pimozide	20	1, 4	20	16	12	10	8	6	4	3	2	1	1	0.5	0.5	0.5**	0.5**	stop
Lurasidone	148	18.5, 37, 74	148	111	92.5	92.5	74	74	55.5	55.5	37	37	18.5	18.5	9.25	9.25	9.25**	stop
Clozapine	900	12.5*, 25, 100, 200	900	700	500	400	350	300	250	200	150	100	50	25	25	12.5	12.5	stop
Amisulpride	800	50, 100, 200, 400	800	700	600	500	400	350	300	250	200	150	100	50	25	25	25**	stop
Brexpiprazole	4	1*, 2*, 3*, 4*	4	3	2	2	1	1	1**	1**	1***	1***	1***	stop	stop	stop	stop	stop
Flupentixol	18	0.5, 1, 3, 5	18	15	12	9	6	4	3	1.5	1	1	0.5	0.5	0.25	0.25	0.25**	stop
Cariprazine	6	1.5*, 3*, 4.5*, 6*	6	4.5	4.5	3	3	1.5	1.5	1.5**	1.5**	1.5***	1.5***	1.5***	stop	stop	stop	stop

w – weeks, * undividable, ** one dose on alternate days, *** one dose every 4 days

Relapse was defined dichotomously on the basis of hospitalization for psychosis, explicit clinical judgement of the treating psychiatrist, or an increase of ≥12 points in the total score of the PANSS, or a score ≥4 and a ≥1 point increase on at least one positive PANSS item, including P1 (delusions), P2 (conceptual disorganization), P3 (hallucinations), G5 (mannerisms/posturing) or G9 (unusual thought content), during one of the follow-up assessments compared to baseline[30].

Tapering and categorization of antipsychotic use

The tapering trajectory was determined for the first 12 months after remission. Tapering speed (in olanzapine equivalents mg/day) was defined as the difference of antipsychotic dose between the start and the end of tapering, divided by the number of days in between. A tapering period started after remission, when the participant first assumed medication at a reduced dose relative to the prior prescribed one. This period lasted until the date on which the participant completely discontinued medication or assumed the lowest dose that either preceded dose increase or remained stable for at least four months.

The total time on antipsychotic medication was calculated as the number of days between remission and the end of tapering. In case multiple antipsychotics were used simultaneously, dose reduction was regarded as the decrease in the combined olanzapine dose equivalent of the antipsychotics. Additionally, tapering speed was categorized as either slower or faster than the recommended HAMLETT tapering schedules (see Table 1), which advise tapering 10 mg of daily oral olanzapine over 20 weeks (cut-off: 10 mg/day / 140 days = 0.071 mg/day).

Antipsychotic drugs were classified into "high D2 affinity antagonists" (K_i < 10 nM), including flupentixol, haloperidol, pimozide, risperidone, zuclopenthixol, sulpiride, paliperidone, penfluridol, amisulpride and lurasidone; "low D2 affinity antagonists" (K_i ≥ 10 nM), including olanzapine, clozapine and quetiapine; and "partial D2 agonists", including aripiprazole, brexpiprazole and cariprazine[31].

As participants were not randomized by type of antipsychotic drug, inverse probability of treatment weighting (IPTW) was applied to correct for bias by indication and balance baseline clinical and sociodemographic characteristics between the groups of antipsychotics[32].

Data analysis

Logistic regression analysis with IPTW was performed to assess whether the risk of relapse was associated with antipsychotic tapering speed (both continuous in olanzapine equivalents mg/day, and in the two categories of faster/slower than recommended tapering speed), and with D2 receptor affinity of the used antipsychotic. High D2 affinity antagonist use was included as the reference group, and post-hoc comparisons were performed to assess whether the risk of relapse differed in users of low D2 affinity antagonists versus D2 partial agonists.

The model was corrected for sex at birth, duration of first psychotic episode (in days), cannabis use between baseline and 12-month follow-up[33], and the start and end dose of tapering. Mean imputation was applied in case of missing duration of first psychotic episode (N=2) or duration of antipsychotic use (N=1). The most extreme values of the duration of first psychotic episode (N=2) and time on antipsychotics (N=2) were winsorized by replacing them with the 95th percentile value, maintaining their relative ranking while reducing their statistical impact[34]. Sensitivity analyses included a logistic regression with IPTW to test the relationship of antipsychotic tapering speed and D2 affinity with the risk of hospitalization.

A Cox proportional hazards analysis with IPTW was performed to assess whether tapering speed, antipsychotic D2 affinity, and the start and end dose of the tapering trajectory were associated with the time to relapse. Time to relapse was defined as the number of days between the end of the tapering trajectory and the onset of the first relapse. If participants did not relapse, they were included as censored with the time to no relapse being the number of days between the end of tapering and the end of follow-up. Participants who experienced a relapse during the tapering trajectory (N=13) were included in the Cox proportional hazards analysis with a time to relapse of zero. The model was corrected for sex at birth, cannabis use, duration of first psychotic episode, antipsychotic dose at the start and end of the tapering trajectory, and the duration of antipsychotic medication use (in days) from remission to the end of tapering.

Statistical analyses were all performed in R (version 4.3.2) via Rstudio (version 2023.12.1.402)[35].

RESULTS

The study included 227 participants in remission from a first psychotic episode who tapered antipsychotic medication, with 32.2% females (N=73) and an average duration of the episode of 193 days. The sociodemographic and clinical characteristics of the participants are shown in Table 2.

Antipsychotic tapering characteristics

Of all participants, 23.8% used partial D2 agonists (N=54), 51.1% used low D2 affinity antagonists (N=116), and 25.1% used high D2 affinity antagonists (N=57). The average antipsychotic dose was 12.7±6.4 mg/day olanzapine equivalents at the start of tapering, and 1.8±3.3 mg/day olanzapine equivalents at the end of the tapering trajectory. The average dose reduction at the end was 88.3±20.6% of the starting dose, and 69.6% (N=158) of the participants fully discontinued their antipsychotic medication. The sociodemographic and clinical characteristics of the three antipsychotic D2 affinity groups are presented in Table 3.

Table 2 Sociodemographic, clinical and tapering characteristics of the study population

	No relapse (N=123)	Relapse (N=104)	Overall (N=227)
Sex at birth, N (%)			
Male	79 (64.2)	75 (72.1)	154 (67.8)
Female	44 (35.8)	29 (27.9)	73 (32.2)
Age (years), mean±SD	28.2±8.8	27.0±7.9	27.6±8.4
Education (years), mean±SD	14.4±2.2	14.2±2.0	14.3±2.1
Duration of first psychotic episode (days), mean±SD	147±178	248±617	193±440
Diagnosis, N (%)			
Schizophreniform disorder	42 (34.1)	27 (26.0)	69 (30.4)
Schizophrenia	41 (33.3)	56 (53.8)	97 (42.7)
Schizoaffective disorder	36 (29.3)	17 (16.3)	53 (23.3)
Brief psychotic disorder	4 (3.3)	4 (3.8)	8 (3.5)
Mental health care contacts (per month), mean±SD	4.01±6.50	3.13±3.38	3.60±5.31
Baseline PANSS score, mean±SD			
Total	43.6±8.8	45.4±10.6	44.4±9.7
Positive	8.6±2.2	9.2±2.8	8.9±2.5
Negative	11.8±4.1	12.4±4.4	12.1±4.2
General	23.1±5.0	23.8±5.9	23.4±5.5
Baseline GAF score, mean±SD	65.7±10.3	65.1±13.1	65.4±11.6
Cannabis use, N (%)			
Yes	33 (26.8)	32 (30.8)	65 (28.6)
No	90 (73.2)	72 (69.2)	162 (71.4)
Antipsychotic drugs used, N (%)			
High affinity D2 antagonists	24 (19.5)	33 (31.7)	57 (25.1)
Low affinity D2 antagonists	67 (54.5)	49 (47.1)	116 (51.1)
Partial agonists	32 (26.0)	22 (21.2)	54 (23.8)
Time between remission and start of tapering (days), mean±SD	103±74.4	105±65.9	103±70.5
Antipsychotic dose at the start of tapering, mean±SD	12.6±6.2	12.9±6.7	12.7±6.4
Antipsychotic dose at the end of tapering, mean±SD	1.9±3.7	1.5±2.9	1.8±3.3
Duration of tapering (days), mean±SD	128±77.8	118±76.2	124±77.0
Average dose reduction per day, mean±SD	0.121±0.126	0.147±0.143	0.133±0.135
Percentage of tapered dose, mean±SD	87.5±21.8	89.1±19.1	88.3±20.6
Tapering type, N (%)			
Dose reduction	37 (30.1)	32 (30.8)	69 (30.4)
Full discontinuation	86 (69.9)	72 (69.2)	158 (69.6)

Antipsychotic doses are reported in olanzapine equivalents mg/day. PANSS – Positive and Negative Syndrome Scale, GAF – Global Assessment of Functioning

The average tapering speed of all participants was 0.133±0.135 mg/day olanzapine equivalents, corresponding to a discontinuation of 10 mg/day olanzapine over 75 days. On average, a tapering trajectory lasted 124±77 days (see Table 2). The fastest tapering trajectory was a dose reduction of 4.88 mg/day olanzapine equivalents to full discontinuation in 6 days. The longest tapering trajectory spanned 334 days, in which a dose of 9.52 mg/day olanzapine equivalents was reduced to 2.38 mg/day (see also supplementary information).

When categorizing the tapering speed, we found that 30.8% tapered slower and 69.2% tapered faster than the recommended tapering trajectory (see Table 1). Among all participants, tapering was finished by 0.9% (N=2) within one week, by 3.96% (N=9) within two weeks, by 7.5% (N=17) within one month, and by 25.1% (N=57) within two months. Tapering lasted between 3 and 6 months for 50.2% (N=114) and lasted longer than 6 months for 24.7% (N=56) of participants.

Tapering speed, antipsychotic D2 receptor affinity, and risk of relapse

Within the first 18 months after remission from the first psychotic episode, 45.8% (N=104) of participants experienced a relapse after dose reduction or complete discontinuation, and 16.3% (N=37) were hospitalized. Logistic regression analysis showed that the speed of antipsychotic tapering (in olanzapine equivalents mg/day) was not associated with the risk of relapse (z=0.989, odds ratio, OR=2.86, 95% CI: 0.38-26.24, p=0.323) (see Table 4). When tapering speed was dichotomized as faster or slower than recommended in the tapering schedules, it still did not significantly relate to the risk of relapse (z=–1.058, OR=0.71, 95% CI: 0.37-1.33, p=0.290) (see also supplementary information). Logistic regression analyses in participants who fully discontinued antipsychotic medication, or which used hospitalization as outcome, also showed no association with tapering speed (see supplementary information).

A significantly lower risk of relapse was observed in users of low D2 affinity antagonists (z=–2.104, OR=0.48, 95% CI: 0.24-0.95, p=0.035) and partial D2 agonists (z=–2.278, OR=0.44, 95% CI: 0.21-0.88, p=0.023) compared to those using high D2 affinity antagonists (see Table 4). There was no difference in the risk of relapse between persons using partial D2 agonists and low D2 affinity antagonists (z=0.291, OR=1.10, 95% CI: –0.57 to 2.17, p=0.771). Overall, 57.9% (N=33) of users of high D2 affinity antagonists, 42.2% (N=49) of users of low D2 affinity antagonists, and 40.7% (N=22) of users of D2 agonists relapsed during the follow-up period (see Figure 1).

The risk of relapse was marginally associated with antipsychotic dose at the end of the tapering trajectory (z=–1.666, OR=0.92, 95% CI: 0.84-1.01, p=0.096), but not with antipsychotic dose at the start of the trajectory (z=1.267, OR=1.03, 95% CI: 0.98-1.08, p=0.205), duration of first psychotic episode (z=1.179, OR=1.00, 95% CI: 1.00-1.00, p=0.239), cannabis use (z=–0.426, OR=0.88, 95% CI: 0.47-1.61, p=0.670) and sex at birth (z=–0.161, OR=0.95, 95% CI: 0.52-1.75, p=0.872) (see Table 4).

Table 3 Sociodemographic, clinical and tapering characteristics per antipsychotic D2 affinity group

	High D2 affinity antagonists (N=57)	Low D2 affinity antagonists (N=116)	Partial D2 agonists (N=54)	Overall (N=227)
Sex at birth, N (%)				
Male	42 (73.7)	79 (68.1)	33 (61.1)	154 (67.8)
Female	15 (26.3)	37 (31.9)	21 (38.9)	73 (32.2)
Age (years), mean±SD	27.6±10.1	27.7±8.0	27.5±7.3	27.6±8.4
Education (years), mean±SD	14.0±2.2	14.4±1.9	14.5±2.3	14.3±2.1
Duration of first psychotic episode (days), mean±SD	277±785	138±185	222±290	193±440
Baseline PANSS score, mean±SD				
Total	44.9±9.7	44.3±9.9	44.2±9.6	44.4±9.7
Positive	9.1±2.7	8.7±2.3	9.0±2.6	8.9±2.5
Negative	12.8±4.6	12.1±4.1	11.4±4.1	12.1±4.2
General	23.1±4.8	23.5±5.9	23.8±5.3	23.4±5.5
Baseline GAF score, mean±SD	65.2±11.9	65.2±11.8	66.2±11.2	65.4±11.6
Antipsychotic dose at the start of tapering, mean±SD	9.9±6.6	13.4±5.1	14.2±7.7	12.7±6.4
Antipsychotic dose at the end of tapering, mean±SD	1.5±2.6	1.6±3.0	2.3±4.6	1.8±3.3
Duration of tapering (days), mean±SD	104±78.6	140±75.9	108±71.1	124±77.0
Average dose reduction per day, mean±SD	0.153±0.195	0.116±0.110	0.149±0.0989	0.133±0.135
Percentage of tapered dose, mean±SD	87.9±19.9	89.1±19.0	86.9±24.6	88.3±20.6
Tapering type, N (%)				
Dose reduction	19 (33.3)	36 (31.0)	14 (25.9)	69 (30.4)
Full discontinuation	38 (66.7)	80 (69.0)	40 (74.1)	158 (69.6)

Antipsychotic doses are reported in olanzapine equivalents mg/day. PANSS – Positive and Negative Syndrome Scale, GAF – Global Assessment of Functioning

Table 4 Logistic regression analysis on the relationship of tapering speed and antipsychotic D2 affinity with relapse rate in patients remitted from first psychotic episode (N=227)

	z value	Odds ratio	95% CI	p
Intercept	−0.404	0.85	0.39-1.85	0.686
Tapering speed	0.989	2.86	0.38-26.24	0.323
Low D2 affinity antagonist*	−2.104	0.48	0.24-0.95	**0.035**
Partial D2 agonist*	−2.278	0.44	0.21-0.88	**0.023**
Start dose (olanzapine equivalents mg/day)	1.267	1.03	0.98-1.08	0.205
End dose (olanzapine equivalents mg/day)	−1.666	0.92	0.84-1.01	0.096
Duration of first psychotic episode (days)	1.179	1.00	1.00-1.00	0.239
Cannabis use (yes)	−0.426	0.88	0.47-1.61	0.670
Sex at birth (female)	−0.161	0.95	0.52-1.75	0.872

*reference category: high D2 affinity antagonist; significant p values are highlighted in bold prints

Tapering speed, antipsychotic D2 receptor affinity, and time to relapse

The Cox proportional hazards model showed that tapering speed did not relate to the time to relapse (z=0.755; hazard ratio, HR=1.55, 95% CI: 0.50-4.83, p=0.450) (see Table 5). The tapering speed categorized as faster or slower than the recommended tapering speed also was not related to the time to relapse (z=–0.411, HR=0.89, 95% CI: 0.50-1.57, p=0.681) (see also supplementary information). Logistic regression analysis including only participants who fully discontinued antipsychotic medication showed similar results (see supplementary information).

The time to relapse was shorter for users of high affinity D2 antagonists than users of low affinity D2 antagonists (z=–2.211, HR=0.57, 95% CI: 0.34-0.94, p=0.027) and partial D2 agonists (z=–2.054, HR=0.54, 95% CI: 0.30-0.98, p=0.040) (see Table 5). The time to relapse did not differ between users of low affinity D2 antagonists and partial D2 agonists (z=0.209, HR=1.06, 95% CI: 0.62-1.80, p=0.835). The restricted mean survival time at 18 months was 280 days for high affinity D2 antagonists, 351 days for low affinity D2 antagonists, and 357 days for partial D2 agonists.

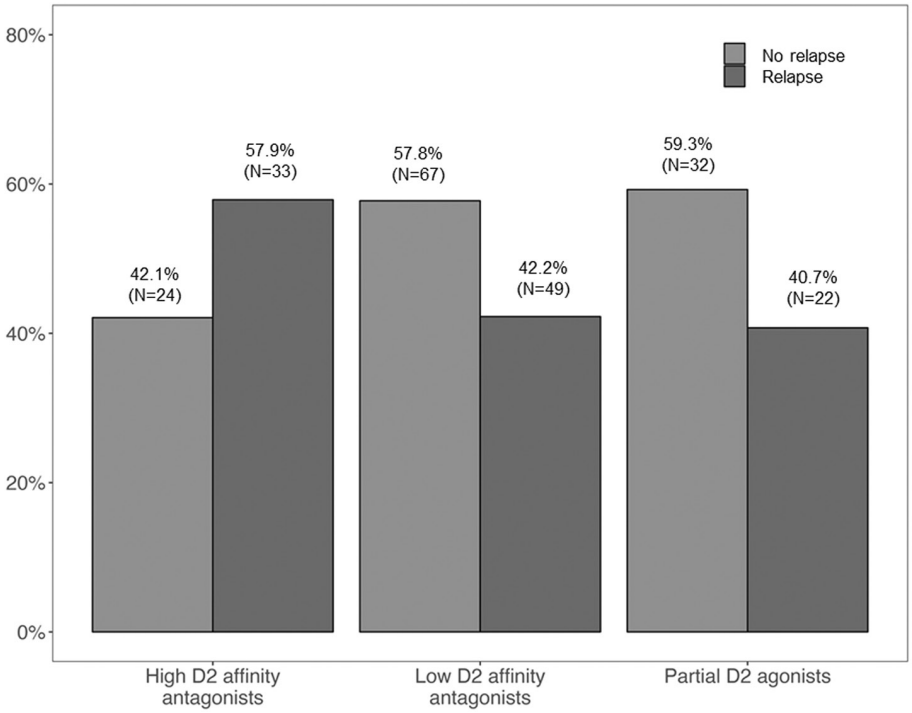

Figure 1 Antipsychotic D2 receptor affinity and prevalence of relapse (N=104) and no relapse (N=123) in participants who tapered antipsychotic medication within 18 months after remission

DISCUSSION

This is the first study to investigate the relationship of both tapering speed and antipsychotic D2 receptor affinity with risk of psychotic relapse and time to relapse in a large sample of individuals remitted from a first psychotic episode, who were followed over the course of 18 months with a detailed reconstruction of the first tapering trajectory based on pharmacy dispensation data. Of 227 participants who reduced (30.4%) or discontinued (69.6%) antipsychotic treatment within 18 months after remission, 45.8% (N=104) experienced a relapse and 16.3% (N=37) were hospitalized. Our results indicate that antipsychotic D2 affinity, but not tapering speed, was associated with relapse risk. Specifically, individuals who tapered off high D2 affinity antagonists were at greater risk of relapse and experienced relapse sooner after discontinuation than those who tapered off low D2 affinity antagonists or partial D2 agonists.

Table 5 Cox proportional hazards regression analysis on the relationship of tapering speed and antipsychotic D2 affinity with time to relapse in patients remitted from first psychotic episode (N=227)

	z value	Hazard ratio	95% CI	p
Tapering speed	0.755	1.55	0.50-4.83	0.450
Low D2 affinity antagonist*	−2.211	0.57	0.34-0.94	**0.027**
Partial D2 agonist*	−2.054	0.54	0.30-0.98	**0.040**
Start dose (olanzapine equivalents mg/day)	1.157	1.02	0.98-1.07	0.247
End dose (olanzapine equivalents mg/day)	−1.668	0.94	0.87-1.01	0.095
Duration of first psychotic episode (days)	0.906	1.00	1.00-1.01	0.365
Cannabis use (yes)	−0.172	0.96	0.58-1.58	0.863
Sex at birth (female)	0.118	1.03	0.62-1.71	0.906
Duration of antipsychotic use (days)	−0.296	1.00	1.00-1.00	0.767

*reference category: high D2 affinity antagonist; significant p values are highlighted in bold prints

The greater relapse risk and shorter time to relapse observed in high D2 affinity antagonist users align with the dopamine supersensitivity hypothesis. This hypothesis states that long-term striatal D2 receptor blockade by antipsychotics may result in a compensatory upregulation of these receptors[20,36,37]. Discontinuation or dose reduction of antipsychotic drugs may consequently lead to enhanced dopamine-mediated signalling and subsequent psychotic exacerbation, referred to as "supersensitivity psychosis"[20,36,37]. Indeed, rodent studies showed that high affinity D2 antagonists, such as haloperidol and risperidone, induced dopamine supersensitivity[38], whereas the low affinity D2 antagonist olanzapine did not[39].

Partial D2 agonists may pose an exception to the dopamine supersensitivity hypothesis. Despite their high D2 affinity, they probably do not induce compensatory D2 receptor upregulation, due to their partial agonistic effect[20]. Animal studies have demonstrated that exposure to aripiprazole and brexpiprazole, in contrast to halo-

peridol, did not relate to increased D2 receptor density[19,38]. In fact, aripiprazole has even been suggested to prevent the development of dopamine supersensitivity[19].

Low D2 affinity antipsychotics are available in a broader range of dosages compared to high D2 affinity medications, allowing for a more gradual tapering trajectory and lower dopamine receptor occupancy with the lowest doses, thereby possibly reducing the likelihood of dopamine supersensitivity at the end of tapering. Animal studies confirm that low-dose antipsychotics do not seem to induce dopamine supersensitivity[40,41].

Aripiprazole stands out not only due to its partial D2 agonist properties, but also for its notably long half-life, which may be beneficial in tapering contexts. This drug has a half-life of approximately 75 hours, and the half-life of its active metabolite is around 94 hours. Such a long half-life may help reduce the risk of withdrawal and relapse symptoms compared to antipsychotics with shorter half-lives[42]. With other psychiatric medications, tapering protocols often involve switching from drugs with shorter half-lives to others with longer ones before gradually reducing the dose, in order to minimize withdrawal symptoms, as seen with the substitution of short-acting benzodiazepines with diazepam[43]. Similarly, for antidepressants with short half-lives, discontinuation symptoms are frequently reported[42], and substitution with a long-acting antidepressant, such as fluoxetine, is recommended[44]. Aripiprazole's long half-life, combined with its partial agonistic effects that seem to counter dopamine supersensitivity, may contribute to its lower relapse risk observed in our study. Positron emission tomography (PET) studies may clarify whether aripiprazole's partial agonism, extended half-life, or the combination of both, supports relapse prevention during tapering. Interestingly, all available partial agonists have similarly long half-lives and produce active metabolites with long-acting partial agonists effects[45]. While further research is needed to identify the ideal pharmacological profile for tapering, current evidence supports partial D2 agonists as preferable options.

Three considerations are important for interpreting our findings. First, since participants were not randomized by type of antipsychotic drug, there is a risk of bias by indication. However, participants using partial D2 agonists, and low and high affinity D2 antagonists were comparable in sociodemographic and clinical characteristics. For instance, baseline symptom severity was similar across the groups, with an average PANSS total score of 44.9 for high D2 affinity antagonist, 44.3 for low D2 affinity antagonist, and 44.2 for partial D2 agonist users (see Table 3). Although we do not have direct data on the severity of the initial psychosis, the dose at the start of tapering – often corresponding to the dose at remission – was included as a covariate and can serve as a proxy for illness severity. To reduce the potential bias by indication, we applied IPTW, a statistical method that adjusts for differences in clinical and sociodemographic characteristics, effectively serving as a statistical alternative for patient matching. While IPTW balances observed characteristics across the three D2 affinity groups, the findings may potentially still be influenced by unmeasured characteristics.

Second, there may be concerns regarding the limited range of tapering speeds in our study, as standard tapering trajectories were recommended as part of the study. Our results show that the average tapering speed of all participants was 0.133 mg/day olanzapine equivalents (range: 0.02-0.81), which corresponds to the discontinuation of 10 mg/day olanzapine over 75 days. This rate was nearly twice as fast as recommended by the HAMLETT tapering guide that participants and their clinicians received from the study team, which advises discontinuing 10 mg/day olanzapine in 140 days (see Table 1). Notably, 69.2% of participants tapered faster than the recommended trajectory, showing that there was a considerable range. Despite this substantial range, tapering speed was not a significant predictor of relapse.

It has been suggested that, when antipsychotics are tapered more gradually, the relapses are more evenly distributed over time[16]. This would mean that, with more gradual tapering and longer follow-up times, the association between tapering speed and risk of relapse decreases. This is further illustrated by a recent study on paliperidone discontinuation[46], which did not find a relationship between the rate of discontinuation (1-monthly versus 3-monthy long-acting injectable switch to placebo) and relapse. The authors concluded that the absolute levels of D2 receptor occupancy, rather than the rate of occupancy change, may be related to relapse. This implies that longer tapering trajectories may only extend the time to relapse by prolonging the period until sub-threshold levels of antipsychotic prophylaxis are reached[46]. However, this does not negate the risks associated with rapid tapering. Compared to abrupt discontinuation, a gradual tapering approach aiming for the lowest possible dose remains preferable[12,47]. Based on our current results, it might be unnecessary to adhere to an extremely slow tapering process, thereby prolonging exposure to antipsychotics.

Third, it is important to emphasize that the participants in this study were all in remission from a first psychotic episode, functioned relatively well, and received regular care in well-resourced facilities in the Netherlands that could provide close monitoring during the tapering trajectory. Generally, those who reach remission after a first psychotic episode have better long-term outcomes than those who do not[48], which limits the generalizability of our findings to those who are not able to reach remission. Furthermore, the relapse rate in our study (45.8%) is comparable to naturalistic antipsychotic maintenance cohorts (pooled prevalence of 43%, 1.5-2 years after first psychotic episode)[1], and even lower than other discontinuation trials (pooled prevalence of 57%, 18 months after first psychotic episode)[49]. This relatively low relapse rate could be a consequence of the frequency of monitoring and the early psychosis care in the Netherlands. For example, participants had contact with a clinical team member (i.e., a psychiatrist, psychologist or nurse) on average 3.6 times per month. Nearly all participants were recruited from early intervention services, which have demonstrated to reduce relapse rates and symptom levels, as well as improving occupational functioning[50].

In the present analyses, we were unable to differentiate between relapses and withdrawal psychosis. A rapid, short-lived (i.e., <6 weeks) and usually reversible psychosis occurring soon after antipsychotic dose reduction, discontinuation or switching is considered a withdrawal psychosis[51]. Withdrawal symptoms are not only a reflection of dopamine supersensitivity, but also of imbalances in

other neurotransmitter systems following dose reduction or discontinuation, including histamine, acetylcholine and serotonin. A recent pharmacovigilance study explored the relationship between neurotransmitter receptor affinities and the risk of reporting withdrawal symptoms, but did not find a significant association[52].

In our study, we took several steps to minimize the occurrence of withdrawal psychosis and to reduce potential bias from conflation between withdrawal and relapse[53]. For instance, our definition of relapse was based on the most recent guidelines[26], and included clinical judgement of treating clinicians as an additional source. Before tapering, we also informed clinicians, participants and their relatives about the potential for withdrawal symptoms. Nevertheless, future studies would greatly benefit from more detailed analyses that distinguish withdrawal from relapse, ideally employing standardized methods yet to be developed and validated.

It is also to be considered that we calculated the tapering speed as an average reduction in olanzapine equivalents mg/day over the entire trajectory, while the speed of the last steps and the shape of the trajectory may be important for the relapse risk as D2 receptor occupancy falls below the therapeutic threshold.

In conclusion, our study highlights several important considerations for clinicians, patients and relatives when tapering off antipsychotic medication after reaching remission from a first psychotic episode. A gradual tapering approach remains preferable, but adhering to an extremely slow tapering process may not be necessary. Particular caution is needed when tapering high D2 affinity antagonists, such as haloperidol or risperidone. For patients already stabilized on strong D2 antagonists, extra monitoring during tapering is warranted. It may be prudent to initiate treatment in first psychotic episode with a partial D2 agonist or a low D2 affinity antagonist, given their potentially more favorable relapse risk profile when considering dose reduction or discontinuation after remission.

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Effectiveness of clozapine augmentation with specific doses of other antipsychotics in schizophrenia: a meta-analysis from two nationwide cohorts

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Although clozapine is the most effective medication for treatment-resistant schizophrenia, response is inadequate in over half of people with that condition. There is limited guidance available on effective clozapine augmentation strategies. We studied the comparative effectiveness of specific doses of oral olanzapine, quetiapine, risperidone and aripiprazole augmentation of clozapine treatment on the risk of hospitalization due to a psychotic episode, as a marker for severe relapse, among patients with schizophrenia or schizoaffective disorder. In this population-based study, patients with one of those diagnoses receiving clozapine were identified from Finnish (years 1995-2017, N=14,053) and Swedish (years 2006-2021, N=8,743) nationwide registers. The risk of hospitalization due to a psychotic episode associated with periods of antipsychotic augmentation of clozapine treatment vs. same-dose clozapine monotherapy was assessed by a within-individual design, using each individual as his/her own control to eliminate selection bias, and analyzed with stratified Cox models. The two national cohorts were first analyzed separately; then results were combined using a random-effect meta-analysis. Secondary outcomes were somatic hospitalization, and hospitalization for psychosis or a somatic cause. The only augmentation associated with a significantly decreased risk of hospitalization due to psychosis in both countries was medium-dose (9 to <16.5 mg/day) aripiprazole combined with high-dose (≥330 mg/day) clozapine, and this combination was associated with the best outcome in the meta-analysis (adjusted hazard ratio, aHR=0.68, 95% CI: 0.62-0.75, p<0.0001). Among patients using medium-dose (180 to <330 mg/day) clozapine, medium-dose aripiprazole augmentation was the only treatment more effective than clozapine monotherapy after Bonferroni correction (aHR=0.79, 95% CI: 0.70-0.91, p=0.0006). The use of all high-dose augmentations was associated with an increased risk of hospitalization due to psychosis. Only aripiprazole augmentations were associated with a decreased risk of hospitalization for psychosis or a somatic cause, and the lowest risk was observed for medium-dose aripiprazole plus high-dose clozapine (aHR=0.70, 95% CI: 0.58-0.84, p=0.0001). This meta-analysis of two nationwide cohorts, totaling almost 23,000 patients using clozapine, indicates that medium-dose aripiprazole augmentation of clozapine treatment is associated with a 20-30% decreased risk of severe relapse compared with clozapine monotherapy within the same individuals, while augmentation with higher doses of aripiprazole (as well as with high doses of all other antipsychotics) is associated with an increased relapse risk.

Key words: Schizophrenia, clozapine, augmentation, relapse risk, dose of augmenting agents, aripiprazole, treatment-resistant schizophrenia

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Up to 40% of patients with schizophrenia do not respond to first-line antipsychotics, half of them since their first episode[1,2]. Among these individuals with treatment-resistant schizophrenia[3,4], clozapine is the most efficacious medication for reducing psychotic symptoms[5], psychiatric hospitalizations[6,7], health service costs[8], and all-cause mortality[9,10]. However, only 40-50% of these patients will have an adequate response to clozapine[11,12].

Non-response to clozapine is a major clinical challenge. Therefore, the search for effective clozapine augmentation strategies has received growing attention. Multiple meta-analyses of randomized controlled trials (RCTs) of clozapine augmentation have noted that the included studies were inadequately powered[13-17]. Therefore, there is a lack of clarity about which, if any, clozapine augmentation agent is efficacious[18-21].

One augmentation strategy supported by some evidence is the use of electroconvulsive therapy[15,22]. However, this option is not widely available, is difficult to implement on a long-term basis, and is not always acceptable to patients. An alternative strategy is to augment clozapine with another drug. In this context, combinations of other antipsychotics are commonly used in clinical care when clozapine is insufficiently effective[23,24]. There is some evidence that aripiprazole augmentation may be associated with improvement of negative symptoms and body weight[13].

However, although any putative clozapine augmentation may have a beneficial effect on symptoms in short-term RCTs[25], the most important issue for the well-being of patients is long-term effectiveness, i.e., relapse prevention and avoidance of severe adverse effects. It would not be feasible to conduct an RCT to investigate these outcomes, since this would require thousands of patient-years of observation.

This problem can be addressed by using large electronic databases built up in real-world settings. Thus far, only one such study has provided some data relevant to this issue[26], suggesting that aripiprazole plus clozapine is associated with a lower risk of psychiatric rehospitalization than clozapine monotherapy. However, the doses of antipsychotics were not investigated in that study.

This is an important issue, as the dose-response relationships seen with many antipsychotics are not linear. Beyond a certain dose, there is little – if any – additional benefit from further dose increases[27]. In contrast, the risk of several side effects continues to increase with higher doses[28,29]. Moreover, as antipsychotics show similar affinity profiles for many receptors, the combination of two

antipsychotics may further increase the likelihood of side effects[30].

The risk of additive side effects is a particular concern with clozapine, because of its broad receptor affinity profile[31]. Moreover, the trials used to investigate dose-response relationships for antipsychotics have generally excluded patients who did not respond to clozapine, so that it is not clear how relevant these findings are for clozapine augmentation.

This crucially important clinical issue of the optimal dose of agents used for clozapine augmentation has not been explored as yet. The aim of the current study was to investigate, in nationwide cohorts of patients with schizophrenia or schizoaffective disorder receiving clozapine, the comparative effectiveness of antipsychotic augmentation strategies for relapse prevention, using a within-individual design, with a special focus on exploring the optimal dose of augmenting agents.

METHODS

Study cohorts

The study population consisted of two nationwide register-based cohorts from Finland and Sweden, which were first analyzed separately and then meta-analyzed together.

The first cohort comprised all persons treated as inpatients for schizophrenia or schizoaffective disorder in Finland between 1972 and 2014, identified from the National Hospital Discharge register, which includes records of all hospital stays. Since 1996, schizophrenia and schizoaffective disorder were diagnosed according to the ICD-10 (codes F20 and F25, respectively). Beforehand, they were diagnosed according to the corresponding ICD-8 and ICD-9 codes (295*). Clozapine users were identified from the National Prescription Register, which covered the years from 1995 to 2017. Use of other medications was tracked through the same register. A lead-in period for previous prescription fills was necessary to find out if the patients were already using a specific medication. Therefore, the follow-up started on January 1, 1996.

The second cohort comprised all persons with a diagnosis of schizophrenia or schizoaffective disorder identified in Sweden between 1972 and 2021 from the National Patient Register (inpatient or specialized outpatient care) or the Micro-Data for Analysis of the Social Insurance System (MiDAS) register (sickness absence or disability pension). Since 1997, schizophrenia and schizoaffective disorder were diagnosed according to the ICD-10 (codes F20 and F25, respectively). Beforehand, they were diagnosed according to the corresponding ICD-8 and ICD-9 codes (295*). Clozapine users were identified from the National Prescribed Drug Register, which covered the years from 2006 to 2021. Use of other medications was tracked through the same register.

The data linkage was performed via a unique personal identification number, which is assigned to all residents of the two countries at birth or immigration. The linkage was done by the register maintainers, and the research team received pseudonymized data. The Finnish study was exempt from ethics committee approval under the national law. The research project was reviewed and approved by the institutions responsible for maintaining the registers: the Finnish National Institute for Health and Welfare (permission THL/1466/6.02.00/2013), the Social Insurance Institution of Finland (34/522/2013), and Statistics Finland (TK53-305-13). The Swedish project was approved by the Regional Ethical Review Board of the Karolinska Institutet (2007/762-31 and 2021-06441-02).

The follow-up started on the date of diagnosis or initiation of clozapine use, whichever came last. The follow-up ended at death (derived from Causes of Death register), emigration (only available for the Swedish cohort), or end of data linkage (December 31, 2017 for the Finnish cohort; December 31, 2021 for the Swedish one), whichever occurred first.

Exposure

Antipsychotic use was defined as Anatomical Therapeutic Chemical (ATC) code N05A, excluding lithium (N05AN01), and clozapine use as ATC code N05AH02. The most common four oral antipsychotics used to augment clozapine in the two cohorts (olanzapine, quetiapine, risperidone and aripiprazole) were chosen for this study, to ensure statistical power. Use of clozapine and these augmenting agents was modelled based on calculation of sliding averages of daily dose as defined daily doses (DDDs) according to the PRE2DUP method[32]. After formation of drug use periods by that method, these periods were split into dose categories of <0.6, 0.6 to <1.1, and ≥1.1 DDDs/day by a dose-modelling tool of PRE2DUP[33,34]. To ease interpretation of findings, the dose categories were then translated back to mg/day.

The reference category was clozapine monotherapy (referring to periods when this drug was used without any concomitant other antipsychotic) at the same dose as clozapine in the combination. Augmentations were combinations of one other antipsychotic with clozapine. A sensitivity analysis was conducted by using a 30-day omission period at the beginning of monotherapy and combination periods (to differentiate polypharmacy from switches).

Outcomes

The main outcome was hospitalization due to a psychotic episode (ICD-10 codes F20-F29). Secondary outcomes were hospitalization due to a somatic cause (A00-N99, excluding F00-F99) and the composite outcome of hospitalization due to psychosis or a somatic cause.

Statistical analysis

The analyses were conducted according to a within-individual design, in which each person acts as his/her own control to eliminate selection bias. This design automatically eliminates the impact of time-invariant factors, such as genetics and baseline severity of illness.

Time-varying factors were adjusted for in stratified Cox proportional-hazards models, including other medication use (antidepressants as N06A; mood stabilizers as carbamazepine N03AF01, valproic acid N03AG01, lamotrigine N03AX09, and lithium N05AN01; and benzodiazepines and related drugs as N05BA, N05CD and N05CF), time since cohort entry, and temporal order of use of antipsychotics and their combinations. The analyses were conducted separately in the Finnish and Swedish cohorts. The results were then combined using a random-effect meta-analysis.

Since there were a total of 36 dose categories for augmenting antipsychotics, the level of significance was set at 0.05/36 = 0.00138 with Bonferroni correction.

Data management and within-individual analyses were run with SAS 9.4, and meta-analysis with R Studio, metafor package (version 3.0-2). The results are reported as adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs).

RESULTS

Study cohorts

The overall study cohort consisted of 22,796 patients (14,053 in Finland and 8,743 in Sweden). A total of 13,614 patients (59.7%) used both clozapine monotherapy and clozapine plus another antipsychotic during the follow-up period, whose average duration was 12.1±6.5 years in Finland and 10.4±5.3 years in Sweden (see Table 1).

Table 1 Characteristics of the study cohorts, and clozapine and antipsychotic augmentation use

	Finnish cohort (N=14,053)	Swedish cohort (N=8,743)
Age (years) at cohort entry, mean±SD	39.1±13.3	45.5±12.6
Time (years) since diagnosis of psychosis, median (IQR)	6.4 (1.0-17.6)	11.9 (4.0-21.2)
Males, % (N)	58.2 (8,183)	60.0 (5,241)
Follow-up duration (years), mean±SD	12.1±6.5	10.4±5.3
Users of clozapine both as monotherapy and in combination during follow-up, % (N)	61.9 (8,704)	56.2 (4,910)
Users of clozapine both as monotherapy and in combination at the same dose during follow-up, % (N)*		
Low dose (<180 mg/day)	15.4 (2,165)	25.2 (2,207)
Medium dose (180 to <330 mg/day)	32.4 (4,559)	29.3 (2,558)
High dose (≥330 mg/day)	48.0 (6,751)	41.5 (3,627)
Most common antipsychotic augmentations, % (N)		
Low-dose clozapine combined with:		
Aripiprazole (9 to <16.5 mg/day)	5.2 (731)	8.9 (775)
Aripiprazole (≥16.5 mg/day)	5.3 (747)	7.0 (615)
Aripiprazole (<9 mg/day)	1.7 (237)	10.0 (871)
Olanzapine (≥11 mg/day)	3.4 (481)	6.1 (530)
Medium-dose clozapine combined with:		
Aripiprazole (9 to <16.5 mg/day)	9.5 (1,330)	10.9 (954)
Aripiprazole (≥16.5 mg/day)	9.7 (1,360)	8.2 (716)
Olanzapine (≥11 mg/day)	6.0 (837)	5.5 (483)
Quetiapine (<240 mg/day)	7.1 (991)	3.0 (263)
High-dose clozapine combined with:		
Aripiprazole (≥16.5 mg/day)	11.7 (1,648)	11.9 (1,042)
Aripiprazole (9 to <16.5 mg/day)	11.0 (1,551)	11.6 (1,013)
Olanzapine (≥11 mg/day)	7.2 (1,005)	7.0 (616)
Quetiapine (<240 mg/day)	8.8 (1,241)	3.2 (278)

*The same patient may have used multiple dose categories during the follow-up. IQR – interquartile range.

Hospitalization due to psychosis

During the follow-up period, a total of 13,684 out of 22,796 patients (60.0%) experienced a psychotic relapse leading to hospitalization (9,243 in Finland and 4,441 in Sweden). The only augmentation associated with a significantly decreased risk of hospitalization in both countries, compared to same-dose clozapine monotherapy, was medium-dose (9 to <16.5 mg/day) aripiprazole combined with high-dose (≥330 mg/day) clozapine (aHR=0.70, 95% CI: 0.62-0.78 in Finland; aHR=0.66, 95% CI: 0.57-0.77 in Sweden) (see Table 2). This combination was also associated with the best outcome in the meta-analysis (aHR=0.68, 95% CI: 0.62-0.75, p<0.0001) (see Figure 1).

Medium-dose aripiprazole augmentation was the only combination with high-dose clozapine associated with a significantly beneficial outcome when Bonferroni correction was applied. It was also the most frequently used combination in both countries (2,311 patient-years in Finland, and 1,302 patient-years in Sweden) (see Table 2).

Among patients using medium-dose (180 to <330 mg/day) clozapine, medium-dose aripiprazole augmentation was the only treatment significantly more effective than clozapine monotherapy (aHR =0.79, 95% CI: 0.70-0.91, p=0.0006) when Bonferroni correction was applied (see Figure 1).

The use of all high-dose augmentations was associated with an increased risk of hospitalization due to psychosis. The worst outcomes, compared with clozapine monotherapy, were observed for high-dose (≥5.5 mg/day) risperidone combined with medium-dose clozapine (aHR=1.95, 95% CI: 1.27-3.00, p=0.0023) and high-dose clozapine (aHR=1.77, 95% CI: 1.35-2.31, p<0.0001) (see Figure 1).

The results from sensitivity analyses using a 30-day omission period at the beginning of monotherapy and combination periods were in line with those of the primary analysis, although CIs were wider due to lower statistical power (because of frequent changes

Table 2 Risk of hospitalization due to psychosis associated with clozapine (CLZ) augmentation in three dose categories, compared with same-dose clozapine monotherapy, in the Finnish and Swedish cohorts

	Dose in DDDs/day		Dose in mg/day		Finnish cohort				Swedish cohort			
Combination	CLZ	Augmenting agent	CLZ	Augmenting agent	Events	Users	PY	aHR (95% CI)	Events	Users	PY	aHR (95% CI)
CLZ - olanzapine	<0.6	<0.6	<180	<6	38	193	85	1.02 (0.67-1.54)	17	327	133	0.52 (0.30-0.91)
	<0.6	0.6 to <1.1	<180	6 to <11	44	331	167	1.05 (0.72-1.53)	22	354	176	0.96 (0.58-1.59)
	<0.6	≥1.1	<180	≥11	93	481	298	0.84 (0.65-1.09)	73	530	203	1.39 (1.01-1.91)
	0.6 to <1.1	<0.6	180 to <330	<6	42	283	159	0.73 (0.51-1.06)	18	280	115	1.08 (0.62-1.89)
	0.6 to <1.1	0.6 to <1.1	180 to <330	6 to <11	75	481	356	0.90 (0.70-1.17)	22	363	218	0.58 (0.34-1.00)
	0.6 to <1.1	≥1.1	180 to <330	≥11	221	837	565	1.14 (0.96-1.36)	64	483	240	0.92 (0.66-1.27)
	≥1.1	<0.6	≥330	<6	97	372	257	0.71 (0.55-0.91)	32	271	197	0.68 (0.44-1.05)
	≥1.1	0.6 to <1.1	≥330	6 to <11	178	577	573	0.85 (0.70-1.02)	85	393	328	0.82 (0.63-1.07)
	≥1.1	≥1.1	≥330	≥11	528	1,005	1,154	1.15 (1.03-1.30)	245	616	407	1.31 (1.10-1.56)
CLZ - quetiapine	<0.6	<0.6	<180	<240	131	606	313	1.51 (1.19-1.92)	33	344	219	0.90 (0.58-1.42)
	<0.6	0.6 to <1.1	<180	240 to <440	50	272	173	1.03 (0.72-1.46)	23	173	75	0.97 (0.52-1.79)
	<0.6	≥1.1	<180	≥440	84	300	143	1.39 (1.05-1.84)	23	192	121	1.08 (0.64-1.83)
	0.6 to <1.1	<0.6	180 to <330	<240	239	991	829	1.09 (0.92-1.28)	22	263	149	0.97 (0.59-1.60)
	0.6 to <1.1	0.6 to <1.1	180 to <330	240 to <440	89	496	403	0.92 (0.72-1.18)	17	163	84	1.38 (0.80-2.38)
	0.6 to <1.1	≥1.1	180 to <330	≥440	113	545	369	1.20 (0.95-1.51)	33	187	132	1.36 (0.84-2.18)
	≥1.1	<0.6	≥330	<240	458	1,241	1,413	0.94 (0.83-1.06)	75	278	298	0.91 (0.68-1.23)
	≥1.1	0.6 to <1.1	≥330	240 to <440	370	705	726	1.02 (0.89-1.17)	34	212	155	0.60 (0.39-0.91)
	≥1.1	≥1.1	≥330	≥440	444	746	890	1.22 (1.07-1.38)	99	253	165	1.47 (1.11-1.95)
CLZ - risperidone	<0.6	<0.6	<180	<3	72	258	133	1.37 (1.02-1.83)	19	321	300	0.68 (0.39-1.18)
	<0.6	0.6 to <1.1	<180	3 to <5.5	25	155	72	0.81 (0.51-1.28)	13	173	75	0.69 (0.33-1.47)
	<0.6	≥1.1	<180	≥5.5	23	90	33	1.36 (0.82-2.26)	15	114	27	2.12 (1.03-4.37)
	0.6 to <1.1	<0.6	180 to <330	<3	103	460	478	0.88 (0.70-1.11)	29	316	345	0.80 (0.50-1.31)
	0.6 to <1.1	0.6 to <1.1	180 to <330	3 to <5.5	107	312	244	1.41 (1.09-1.84)	23	168	138	1.79 (1.01-3.18)
	0.6 to <1.1	≥1.1	180 to <330	≥5.5	27	171	66	1.80 (1.12-2.90)	6	107	44	2.79 (1.02-7.63)
	≥1.1	<0.6	≥330	<3	323	620	926	0.99 (0.85-1.16)	117	335	487	0.83 (0.65-1.06)
	≥1.1	0.6 to <1.1	≥330	3 to <5.5	226	463	500	1.16 (0.98-1.37)	61	240	184	1.33 (0.96-1.86)
	≥1.1	≥1.1	≥330	≥5.5	137	262	265	1.60 (1.27-2.00)	63	240	50	2.12 (1.46-3.09)
CLZ - aripiprazole	<0.6	<0.6	<180	<9	20	237	144	0.69 (0.42-1.14)	77	871	588	0.80 (0.59-1.08)
	<0.6	0.6 to <1.1	<180	9 to <16.5	115	731	573	0.80 (0.62-1.03)	58	775	753	0.55 (0.39-0.76)
	<0.6	≥1.1	<180	≥16.5	145	747	443	0.97 (0.77-1.21)	101	615	384	1.43 (1.08-1.90)

Table 2 Risk of hospitalization due to psychosis associated with clozapine (CLZ) augmentation in three dose categories, compared with same-dose clozapine monotherapy, in the Finnish and Swedish cohorts *(continued)*

Combination	Dose in DDDs/day		Dose in mg/day		Finnish cohort				Swedish cohort			
	CLZ	Augmenting agent	CLZ	Augmenting agent	Events	Users	PY	aHR (95% CI)	Events	Users	PY	aHR (95% CI)
	0.6 to <1.1	<0.6	180 to <330	<9	49	398	368	0.86 (0.61-1.21)	70	818	553	0.89 (0.65-1.20)
	0.6 to <1.1	0.6 to <1.1	180 to <330	9 to <16.5	225	1,330	1,583	0.77 (0.65-0.91)	127	954	1,087	0.85 (0.68-1.06)
	0.6 to <1.1	≥1.1	180 to <330	≥16.5	369	1,360	1,270	1.13 (0.98-1.29)	135	716	549	1.73 (1.38-2.18)
	≥1.1	<0.6	≥330	<9	98	443	392	0.82 (0.64-1.04)	108	831	564	0.66 (0.52-0.84)
	≥1.1	**0.6 to <1.1**	**≥330**	**9 to <16.5**	**517**	**1,551**	**2,311**	**0.70 (0.62-0.78)**	**315**	**1,013**	**1,302**	**0.66 (0.57-0.77)**
	≥1.1	≥1.1	≥330	≥16.5	885	1,648	2,244	1.13 (1.03-1.24)	556	1,042	835	1.76 (1.54-2.03)

Data concerning the only augmentation associated with a significantly decreased risk of hospitalization due to psychosis in both countries are highlighted in bold prints. DDD – defined daily dose, PY – person-years, aHR – adjusted hazard ratio.

in dose categories due to titration) (see supplementary information).

Somatic hospitalization

During the follow-up period, 52.6% (N=7,393) of patients in the Finnish cohort and 41.3% (N=3,611) of those in the Swedish cohort experienced a somatic hospitalization. The lowest point estimates were observed for low-dose clozapine plus low-dose risperidone (aHR=0.62, 95% CI: 0.32-1.20), and high-dose clozapine plus medium-dose aripiprazole (aHR=0.66, 95% CI: 0.30-1.44), but these findings did not reach statistical significance (see also supplementary information).

The high-dose clozapine plus medium-dose quetiapine combination was associated with a decreased risk (aHR=0.73, 95% CI: 0.55-0.96) of somatic hospitalization. The medium-dose clozapine plus high-dose olanzapine (aHR=1.45, 95% CI: 1.10-1.92), the high-dose clozapine plus high-dose aripiprazole (aHR=1.28, 95% CI: 1.09-1.49), and the high-dose clozapine plus high-dose olanzapine (aHR=1.47, 95% CI: 1.19-1.81) combinations were associated with an increased risk of somatic hospitalization. None of these findings – except the last one – survived Bonferroni correction (see also supplementary information).

Hospitalization due to either psychosis or a somatic cause

The results concerning the composite outcome of hospitalization due to psychosis or a somatic cause in the meta-analysis are shown in Figure 2, while those concerning the two cohorts are presented in the supplementary information.

This composite outcome was observed in 80.9% (N=11,375) of Finnish patients and 71.7% (N=6,267) of the Swedish cohort. Only aripiprazole augmentations of clozapine were associated with a decreased risk of this outcome, and the lowest risk was observed for medium-dose aripiprazole plus high-dose clozapine (aHR=0.70, 95% CI: 0.58-0.84, p=0.0001) (see Figure 2).

Hospitalization risk during clozapine monotherapy

In the meta-analysis, medium-dose clozapine monotherapy was associated with a lower risk of hospitalization due to psychosis than low-dose monotherapy (aHR=0.75, 95% CI: 0.62-0.91), whereas high-dose clozapine monotherapy was not (aHR=1.03, 95% CI: 0.86-1.23).

The risk of somatic hospitalization did not differ significantly among dose categories of clozapine monotherapy (medium dose: aHR=0.93, 95% CI: 0.85-1.01; high dose: aHR=1.37, 95% CI: 0.70-2.70, compared with low-dose). The results for the composite hospitalization outcome were in line with those for hospitalization due to psychosis, as medium-dose (aHR=0.80, 95% CI: 0.74-0.87), but not high-dose (aHR=1.10, 95% CI: 0.82-1.48), clozapine was

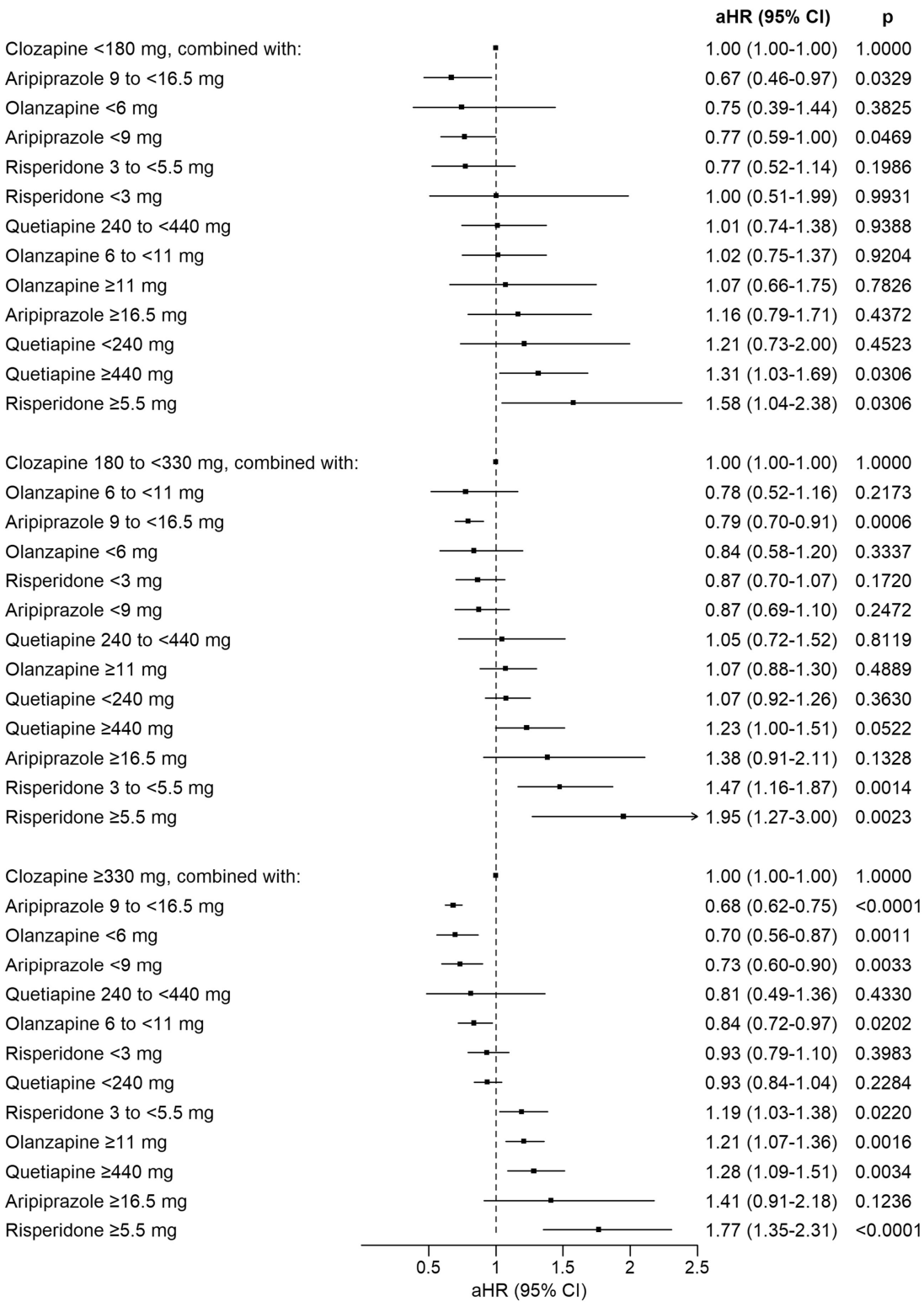

Figure 1 Risk of hospitalization due to psychosis associated with clozapine augmentation in three dose categories, compared with same-dose clozapine monotherapy: meta-analysis of the Finnish and Swedish cohorts. aHR – adjusted hazard ratio.

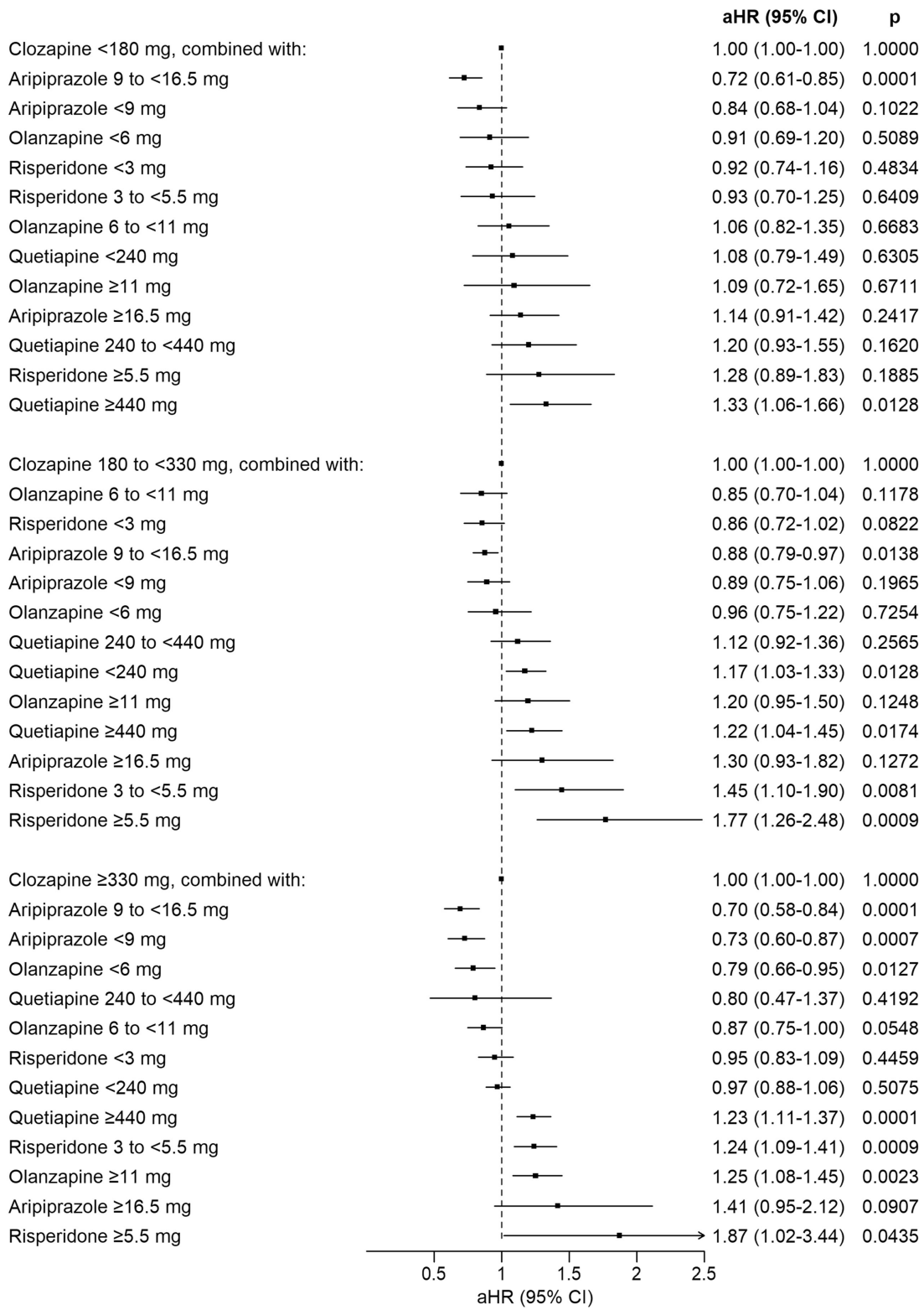

Figure 2 Risk of hospitalization due to psychosis or a somatic cause associated with clozapine augmentation in three dose categories, compared with same-dose clozapine monotherapy: meta-analysis of the Finnish and Swedish cohorts. aHR – adjusted hazard ratio.

associated with a lower risk of this outcome than low-dose monotherapy.

DISCUSSION

The results of this large database study showed consistently in both Finnish and Swedish nationwide cohorts that medium-dose (9 to <16.5 mg/day) aripiprazole augmentation of clozapine was associated with a substantially decreased risk of severe psychotic relapse leading to hospitalization when compared with same-dose clozapine monotherapy within the same individuals.

In the meta-analysis, the relapse risk was 32% lower with medium-dose aripiprazole augmentation of the most commonly used clozapine dose (≥330 mg/day). Since the overall risk of relapse in our study population was 60%, a risk decrease of 20-30% would correspond roughly to 10-20% decrease in the absolute risk. This finding suggests that the medium-dose aripiprazole combination with high-dose clozapine treatment is associated with a considerably decreased rate of hospitalization due to a psychotic episode.

One previous Finnish study provided some data on the real-world effectiveness of clozapine augmentation with other antipsychotics in relapse prevention, but without dose analysis[26]. The results from that study indicated that aripiprazole augmentation in general was associated with a 14% decreased risk of severe psychotic relapse leading to hospitalization. In the present study, we covered three more follow-up years in the Finnish cohort, provided results also from a corresponding Swedish cohort, stratified results by antipsychotic dose, and conducted meta-analyses combining the results from the two nationwide cohorts to ensure statistical power and increase the generalizability of findings. When stratified by clozapine dose, our results showed that, while the combination of medium-dose aripiprazole plus high-dose clozapine was associated with a 32% decreased risk of severe psychotic relapse, a higher aripiprazole dose combined with high-dose clozapine was associated with a 41% increased risk.

These results underline the importance of carefully selecting the dose of the augmenting antipsychotic, and suggest that, if the standard dose of aripiprazole does not help, it is probably not useful to increase that dose. The same was true for all other antipsychotic augmentations, suggesting that high-dose antipsychotic augmentation of clozapine is very unlikely to decrease the risk of relapse.

Even though decreasing the risk of psychotic relapse is important, the other side of the coin is tolerability. We used the risk of somatic hospitalization as a marker reflecting the risk of putative severe adverse effects. Our results showed that the most common combination – high-dose clozapine plus medium-dose aripiprazole – was associated with a non-significantly decreased risk of somatic hospitalization, and also with the lowest risk of the composite outcome of hospitalization due to psychosis or a somatic cause, when compared with clozapine monotherapy within the same dose range.

It is striking that we did not find a clear benefit from augmentation with antipsychotics other than aripiprazole. This finding could reflect the fact that aripiprazole is a dopamine D2 partial agonist, whilst the other drugs, including clozapine, are all D2 antagonists[31,34]. This explanation is consistent with our finding that high-dose aripiprazole was not beneficial, as this drug shows a D2 receptor occupancy >90% at 15 mg/day, and higher doses result in little change in D2 occupancy[35,36] or efficacy[27], while parkinsonism[28] and akathisia[29] may emerge at these higher doses. Relatedly, antipsychotics doses above 5 mg/day risperidone equivalents start to become less effective for relapse prevention[37].

It has been proposed that some cases of treatment-resistant schizophrenia are due to D2 receptor supersensitivity secondary to long-term treatment with D2 antagonists, and that D2 partial agonism might counteract this effect[38]. An additional consideration is that aripiprazole may reduce some side effects of clozapine, such as sedation and weight gain[13,39,40], which may also contribute to its benefits as an augmentation strategy.

Randomized controlled trials, mirror-image investigations and observational studies (including some using nationwide databases) have shown that, in head-to-head comparisons with oral antipsychotics, the use of long-acting injectable antipsychotics (LAIs) is associated with a substantially lower risk of severe relapse leading to hospitalization[41,42]. On the basis of this evidence, it is possible that aripiprazole LAI augmentation of clozapine might be even more effective than oral aripiprazole augmentation. Although the total number of patients in our study was almost 23,000, we did not have enough patients with this combination for statistical analysis, since the current regulations of the European Medicines Agency (EMA) warn against the concomitant use of clozapine and LAIs[43].

In interpreting the results of this study, its strengths and potential limitations need to be considered. Strengths include the use of unselected, comprehensive data from nationwide registers, providing consistent results from two different countries. Moreover, we analyzed augmentations by dose categories, which provides crucial information for clinical practice. Although our cohorts included almost 23,000 patients, there was still some lack of statistical power for somatic hospitalizations, because there were so many drug combinations.

Lack of randomization is an inherent limitation of observational studies, and selection bias is potentially a major problem. However, we used a within-individual analysis, which eliminates selection bias relating to all time-invariant factors, such as genetics, sex, initial severity of the illness, personal history before the start of follow-up, and other factors that can be related to antipsychotic combination treatment choice[24]. Concerning factors changing over time, we adjusted for the time since cohort entry, the order of the treatment periods, and the concomitant use of antidepressants and benzodiazepines.

We did not have information on fluctuation of the symptom severity over time. Since it is logical to assume that augmenting treatments are started when the symptoms get worse, we may assume that, if the temporal fluctuation of illness severity had been controlled for, the superiority of aripiprazole augmentation over clozapine monotherapy would have been even more distinct.

Clozapine levels are a more accurate predictor of treatment response than clozapine dose[44]. However, as clozapine levels were

not available, we were only able to use clozapine dose in the analysis. We were also only able to include somatic hospitalization as a measure of adverse effects of treatment. We did not have data on adverse drug reactions that were not associated with hospitalizations and, as such, are not able to comment on this feature, which should be monitored when combining aripiprazole with clozapine[45]. Finally, no data on smoking status were available, while clozapine doses needed to achieve the same blood levels are higher in smokers[46,47].

In conclusion, this meta-analysis from two nationwide cohorts provides the first evidence on the specific antipsychotic doses in the augmentation of clozapine treatment that are effective for relapse prevention. Our results suggest that augmenting high-dose clozapine with medium-dose aripiprazole is associated with up to 30% decreased risk of severe relapse leading to rehospitalization, while augmentation with higher aripiprazole doses, or high doses of other antipsychotics, actually increases the risk of rehospitalization.

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Distinct cognitive trajectories in the early course of psychosis are associated with clinical and functional outcomes longitudinally

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Cognitive dysfunction is a core dimension in psychotic disorders and among the strongest predictors of disability and poor quality of life. Cognitive impairments are highly heterogeneous, and cross-sectional studies have consistently found evidence of distinct cognitive profiles both within diagnoses and transdiagnostically. Findings regarding the course of cognitive impairments over time have been mixed. We hypothesized that subgroups of patients in the early course of psychosis show distinct cognitive trajectories that can be identified using data-driven methods, and that these subgroups differ on clinical and functional outcomes over time. Persons with schizophrenia-spectrum disorders or mood disorders with psychosis in the early course of illness (N=127) were assessed using clinical, functional and cognitive measures at three timepoints: baseline, 8 and 16 months. Group-based trajectory modeling was used to identify cognitive subgroups, which were then compared on clinical and functional measures using multilevel models. We identified three distinct cognitive subgroups: an Impaired group, an Average group, and a High-Functioning group. Cognition was stable over the follow-up period in the Impaired and High-Functioning groups, whereas the Average group showed cognitive improvement. Groups did not differ in terms of diagnostic distribution, baseline clinical symptoms, and most baseline functional and demographic measures. However, over the follow-up, group membership predicted changes in negative symptoms, social functioning, and patient-reported outcomes, with the Impaired group showing the most severe illness course. We conclude that patients in the early course of psychosis show distinct cognitive trajectories that predict future symptoms and social functioning, despite presenting no clinical differences at baseline. These findings have implications for understanding biology-cognition associations, which may be related to heterogeneity; developing predictive models for clinical and functional outcomes; and personalizing treatment to support patients' cognitive, clinical and functional needs towards improving illness course.

Key words: Cognitive impairment, psychosis, schizophrenia-spectrum disorders, mood disorders with psychosis, follow-up, trajectory, early psychosis, negative symptoms, social functioning, patient-reported outcomes

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Psychotic disorders – including schizophrenia-spectrum disorders and mood disorders with psychosis – are a major source of suffering for patients and carers, and a leading cause of disability worldwide[1]. These disorders often have their onset in adolescence or early adulthood, causing significant disruption in multiple domains such as school, work and relationships, which may have deleterious effects during this dynamic developmental stage and beyond. Cognitive impairment is a hallmark dimension of psychosis and a leading cause of poor functioning and reduced quality of life in this population[2-4]. Unfortunately, there are currently no first-line interventions with a significant replicated impact on this domain.

At the group level, evidence suggests that cognitive impairments are present at the time of illness onset, and that early and possibly ongoing illness-related changes in cognition, or "neuroprogression", occur from the early phases (and perhaps prior to onset) into chronicity[5]. However, findings regarding the timing and course of neuroprogressive changes in cognition are mixed. For example, some studies suggest that cognitive impairment in psychotic disorders is widespread by illness onset[6-11], whereas others report more selective or attenuated impairments[12]. Through the early course of psychosis, some reports show continuing cognitive decline[13,14], some others report no change[15-17], and still others show improvement in some cognitive domains[15].

One possible reason for these inconsistencies may be that the severity and course of cognitive impairments is highly heterogeneous in people with psychotic disorders. Studies using data-driven clustering approaches to characterize cross-sectional cognitive impairments in schizophrenia-spectrum, affective, or transdiagnostic psychosis consistently identify groups with distinct cognitive profiles[4,18-21]. Cognitive subgroups have also been found to differ in associated features, including gray matter volume, resting state connectivity, and community functioning[19,22-24].

Fluid cognition, or the ability to use cognitive skills to solve problems and perform cognitive tasks in the moment without reliance on prior rote knowledge (e.g., working memory, processing speed), appears to be especially impaired in both schizophrenia-spectrum disorders and mood disorders with psychosis, relative to crystallized cognition, which relies more heavily on prior knowledge or learning (e.g., defining the meanings of words)[25]. Fluid cognition has been linked to psychosocial functioning, substance use, and self-reported perceived mental health[26], as well as to biomarkers including white matter integrity[27] and genetic abnormalities in schizophrenia[28].

In schizophrenia-spectrum disorders, there is evidence of premorbid cognitive impairments in both crystallized and fluid cognition. However, measures of fluid cognition appear to worsen significantly after illness onset, whereas crystallized cognition appears to be more stable[29,30]. In mood disorders with psychosis, there is not strong evidence of premorbid cognitive impairments, but post-onset fluid cognition is impaired relative to controls[8,31,32], and may be globally and significantly impaired in a subset of individuals[18,19]. Thus, fluid cognition may be vulnerable to illness-related neuroprogressive decline, and change trajectories of fluid cognition may be more strongly associated with objective and subjective clinical symptoms and community functioning.

In this study, we aimed to map cognitive trajectories longitu-

dinally in people in the early course of psychosis. Specifically, we aimed to identify subgroups of patients who show distinct patterns of cognitive functioning, and to examine cognitive course over time and in association with clinical and functional illness course. We hypothesized that: a) group-based trajectory modeling would reveal distinct cognitive subgroups transdiagnostically, and b) emergent subgroups would differ on clinical and functional outcomes longitudinally. We also aimed to explore baseline predictors of cognitive subgroup membership, with the ultimate goal of improving prediction of clinical and functional illness course.

METHODS

Participants

Patients meeting DSM-5 criteria for schizophrenia-spectrum disorders (schizophrenia, schizophreniform disorder, schizoaffective disorder, or psychosis not otherwise specified) or mood disorders (bipolar disorder or major depression) with psychotic features, as ascertained by the Structured Clinical Interview for DSM-5 - Research Version (SCID-5-RV)[33], were recruited at McLean Hospital and Brigham and Women's Hospital via flyers and the Mass General Brigham website. Those fulfilling a set of pre-defined criteria specified below (N=48 with schizophrenia-spectrum disorders and N=79 with psychotic mood disorders) were included in the study. All participants were outpatients at the time of recruitment, and provided their informed consent to participate.

Inclusion criteria were onset of illness within 6.5 years, determined through the SCID-5-RV and all available collateral data (e.g., medical records), and age 18-35 at the time of consent. Exclusion criteria were DSM-5 diagnosis of substance-induced psychosis or psychotic disorder due to a general medical condition, head injury with medical sequelae, current severe substance use disorder based on SCID-5-RV interview, and IQ less than 70 based on Wechsler Abbreviated Scale of Intelligence, 2nd edition (WASI-II).

All procedures were approved by the Mass General Brigham Human Research Committee and Institutional Review Board, and complied with the regulations set forth by the Declaration of Helsinki.

Assessment tools

Cognition was evaluated using the National Institutes of Health (NIH) Toolbox Cognition Battery[34], which assesses multiple domains. The Toolbox tasks are administered via iPad, and scores are calculated by the scoring software, including individual subtest scores, Fluid Cognition Composite score, Crystallized Cognition Composite score, and Total Composite score. Tests include the Dimensional Change Card Sort, Flanker Inhibitory Control and Attention, Picture Sequence Memory, List Sorting Working Memory, and Pattern Comparison Processing Speed tests (fluid cognition), and the Picture Vocabulary and Oral Reading Recognition tests (crystallized cognition). Fully corrected t-scores accounting for race, ethnicity, age, level of education, and sex were used in the analyses. IQ was estimated using the Vocabulary and Matrix Reasoning subtests of the WASI-II. Raw scores were converted to standard scores based on age, with a mean of 100 and a standard deviation (SD) of 15.

State clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS)[35], the Brief Negative Symptom Scale (BNSS)[36], the Young Mania Rating Scale (YMRS)[37], and the Montgomery-Åsberg Depression Rating Scale (MADRS)[38], administered by trained researchers. The PANSS yields Positive, Negative, General, and Total scores. The BNSS yields a Total score and several subscale scores (Anhedonia, Lack of Normal Distress, Asociality, Avolition, Blunted Affect, and Alogia). The YMRS and the MADRS yield Total scores.

Functioning was assessed using the Mental Illness Research Education and Clinical Center (MIRECC) Global Assessment of Functioning (GAF)[39], which yields Social, Occupational, and Symptom subscale scores. The NIH Toolbox Emotion domain tasks[40] were administered to assess participant-reported Psychological Well-Being, Social Satisfaction, and Negative Affect. As with cognition, these questionnaires were administered via iPad.

Procedures

Baseline assessments included collection of information on demographics, medical and psychiatric history, and Hollingshead parental socioeconomic status, in addition to the administration of the above-mentioned neuropsychological tests, and clinical and functional scales, consistent with the Human Connectome Project for Early Psychosis[41], of which this project is an extension. A magnetic resonance imaging scan was also performed. Current antipsychotic treatment was assessed by calculating chlorpromazine equivalents (in mg/day) through the defined daily dose (DDD) method[42]. The same procedures were repeated at 8- and 16-month visits.

Statistical analysis

Group-based trajectory modeling[43] was used to identify groups of participants following similar cognitive trajectories based on the NIH Toolbox Fluid Cognition Composite scores. Modelling was performed in Stata/BE 17.0 (StataCorp, College Station, TX, USA) using the plugin "Traj", a latent class growth analysis aimed to fit finite mixture models to longitudinal data[44]. This analysis allows specification of the data structure, number of groups to be included, and the shape of each group trajectory (linear, quadratic, cubic, and quartic). As the cognition data were normally distributed, the censored normal option was chosen.

Model fit was tested at varying group numbers. After the optimal number of groups was established, additional models were run reducing the polynomial orders until the highest order polynomial for each group was significant. Because the Traj command uses the maximum likelihood method for parameter estimation, all available data are included in the models.

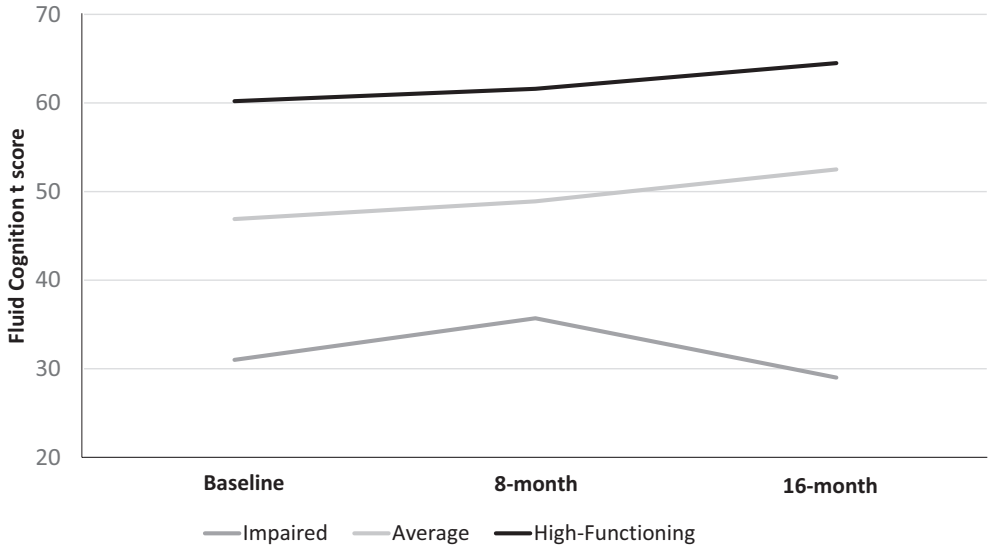

Figure 1 Trajectory plots of NIH Toolbox Fluid Cognition Composite fully-corrected t-scores by emergent cognitive subgroups across the follow-up period.

Models were generated and model fit was evaluated using Bayesian information criteria (BIC) and by calculating the Bayes factor. This is a method of model comparison that computes a ratio of the probability of each of two models being correct[45]. Here, Bayes factor was computed by subtracting the model with more groups from the just-previous model using the formula $e^{(BIC2-BIC1)}$. Thus, numbers greater than 1 favor the current model, while those lower than 1 favor the previous model.

Emergent trajectory groups were then compared on baseline demographic, cognitive, clinical, diagnostic and functioning measures using ANOVA or chi-square, as appropriate. Repeated measures ANOVAs were used to examine cognitive change over the follow-up period. Multilevel models predicting clinical and functional outcomes by trajectory group, timepoint, and the group x timepoint interaction were run to examine clinical and functional outcomes. For significant omnibus tests, post-hoc comparisons were conducted with Bonferroni correction. Lastly, time invariant covariates were modeled as baseline predictors of cognitive group membership assignment.

RESULTS

Model selection and trajectory analysis

Trajectory models were generated and model fit was evaluated using BIC and Bayes factor as described above. Our final model included three groups with one quadratic and two linear polynomials.

Trajectory analysis classified the majority of patients into an Average group (N=83; 65.3%), followed by an Impaired group (N=26; 20.5%) and a High-Functioning group (N=18; 14.2%) (see Figure 1). These groups differed significantly from each other on the NIH Toolbox Fluid Cognition Composite at baseline (F=153.1, p<0.0001), 8-month (F=33.4, p<0.0001) and 16-month (F=43.7, p<0.0001) timepoints (see Table 1). Variability was lower than would be expected based on t-score standardization (i.e., mean=50, SD=10), suggesting reduced heterogeneity within trajectory groups relative to the general population (SDs by group were 6.0, 5.7 and 5.0, respectively).

Trajectory groups did not differ at baseline on age, sex, race or education. However, groups did differ on parental socioeconomic status, which was significantly lower in the Impaired than in the Average group, and on estimated IQ, which was significantly lower in the Impaired than in the High-Functioning group (see Table 2).

Cognitive trajectories for the Average and High-Functioning groups were linear over the follow-up period, whereas the cognitive trajectory of the Impaired group showed a non-linear, quadratic pattern, with a slight increase at 8 months followed by a slight decrease at 16 months (see Figure 1). In terms of within-trajectory cognitive change over time, repeated measures ANOVAs by trajectory group showed no effect of timepoint on cognition for the High-Functioning and Impaired groups (F=1.45, p=0.28, and F=1.37, p=0.29, respectively). The Average group did show a significant main effect of time (F=4.19, p=0.02) in the direction of cognitive improvement.

Table 1 NIH Toolbox Fluid Cognition Composite scores (mean±SD) at each timepoint in cognitive trajectory subgroups

	Impaired (N=26)	Average (N=83)	High-Functioning (N=18)	Statistical test
Baseline	31.0±5.7	47.1±5.8	61.5±5.0	F=153.1, p<0.0001
8-month	35.7±4.1	48.9±6.3	61.6±8.6	F=33.4, p<0.0001
16-month	29.0±7.3	52.7±6.7	64.5±3.3	F=43.7, p<0.0001

Table 2 Baseline demographic characteristics in cognitive trajectory subgroups

	Impaired (N=26)	Average (N=83)	High-Functioning (N=18)	Statistical test
Age (years), mean±SD	23.6±3.5	23.8±3.8	24.6±4.2	F=0.36, NS
Sex (% female)	46.1	54.2	38.9	X^2=1.62, NS
Race (% Caucasian)	69.2	75.9	72.2	X^2=0.44, NS
Education (years), mean±SD	14.0±1.9	15.1±2.0	15.0±3.3	F=2.40, NS
Parental Hollingshead SES, mean±SD	46.5±14.3	54.8±10.3	53.3±11.1	F=4.03, p<0.05, Average > Impaired
WASI-II Full Scale IQ, mean±SD	105.7±14.2	111.2±11.1	118.2±13.4	F=5.63, p<0.01, High-Functioning > Impaired

SES – socioeconomic status, WASI-II – Wechsler Abbreviated Scale of Intelligence, 2nd edition, NS – not significant

Clinical and functional outcomes

Groups did not differ significantly on any clinical measures at baseline, while they did differ on MIRECC GAF Social Functioning, with a significantly lower score in the Impaired than in the High-Functioning group. Groups did not differ on any other measures of functioning or on patient-reported measures of Psychological Well-Being, Social Satisfaction, or Negative Affect at baseline (see Table 3).

Over the follow-up, however, groups differed significantly on several clinical and functional measures. Multilevel models showed that group membership was a significant predictor of BNSS Total (B=–4.69, p=0.001), PANSS Negative (B=–1.28, p=0.03), GAF Occupational (B=6.95, p=0.009) and Social Functioning (B= 5.54, p=0.04), and patient-reported Psychological Well-Being (B= 2.90, p=0.01) and Negative Affect (B=–3.39, p=0.005). Groups did not differ on measures of mania, depression, positive or general symptoms of psychosis, GAF Symptoms, or patient-reported Social Satisfaction.

Post-hoc comparisons showed that, at the 8-month follow-up, the High-Functioning group differed significantly from the Impaired group on GAF Occupational and Social Functioning (p= 0.02 and p=0.03, respectively) and self-reported Negative Affect (p= 0.002). The Average group did not differ from the other groups at

Table 3 Baseline clinical and functional measures in cognitive trajectory subgroups

	Impaired (N=26)	Average (N=83)	High-Functioning (N=18)	Statistical test
Duration of illness (years), mean±SD	2.2±1.7	2.4±1.8	2.7±1.7	F=0.43, NS
Chlorpromazine equivalents (mg/day), mean±SD	239.8±337.8	178.4±178.2	136.8±177.0	F=1.25, NS
Diagnosis (% schizophrenia-spectrum disorders)	46.1	37.3	27.7	X^2=1.54, NS
PANSS Total, mean±SD	48.1±11.8	43.4±10.2	44.6±12.3	F=1.78, NS
PANNS Positive, mean±SD	10.0±3.9	9.4±3.5	9.7±3.4	F=0.23, NS
PANSS Negative, mean±SD	12.6±5.6	11.1±4.6	11.4±3.3	F=0.89, NS
PANSS General, mean±SD	25.6±6.8	23.1±5.7	23.1±6.8	F=1.61, NS
BNSS Total, mean±SD	15.8±9.4	13.7±7.9	12.3±8.6	F=0.89, NS
YMRS Total, mean±SD	6.4±8.3	4.9±5.7	4.3±5.3	F=0.66, NS
MADRS Total, mean±SD	11.6±8.3	11.5±11.2	10.8±9.3	F=0.04, NS
GAF Symptoms, mean±SD	67.6±15.2	66.6±18.5	70.5±25.0	F=0.30, NS
GAF Occupational, mean±SD	57.9±24.6	68.6±22.1	72.9±23.7	F=2.76, NS
GAF Social, mean±SD	71.0±17.7	76.7±14.3	82.9±10.6	F=3.48, p<0.05, Impaired < High-Functioning
Psychological Well-Being, mean±SD	40.4±7.0	41.7±9.3	43.6±10.6	F=0.63, NS
Social Satisfaction, mean±SD	40.3±9.7	42.6±9.2	43.1±7.6	F=0.73, NS
Negative Affect, mean±SD	58.5±9.3	58.0±10.0	56.5±11.5	F=0.22, NS

PANSS – Positive and Negative Syndrome Scale, BNSS – Brief Negative Symptom Scale, YMRS – Young Mania Rating Scale, MADRS – Montgomery-Åsberg Depression Rating Scale, GAF – Mental Illness Research Education and Clinical Center (MIRECC) Global Assessment of Functioning, NS – not significant

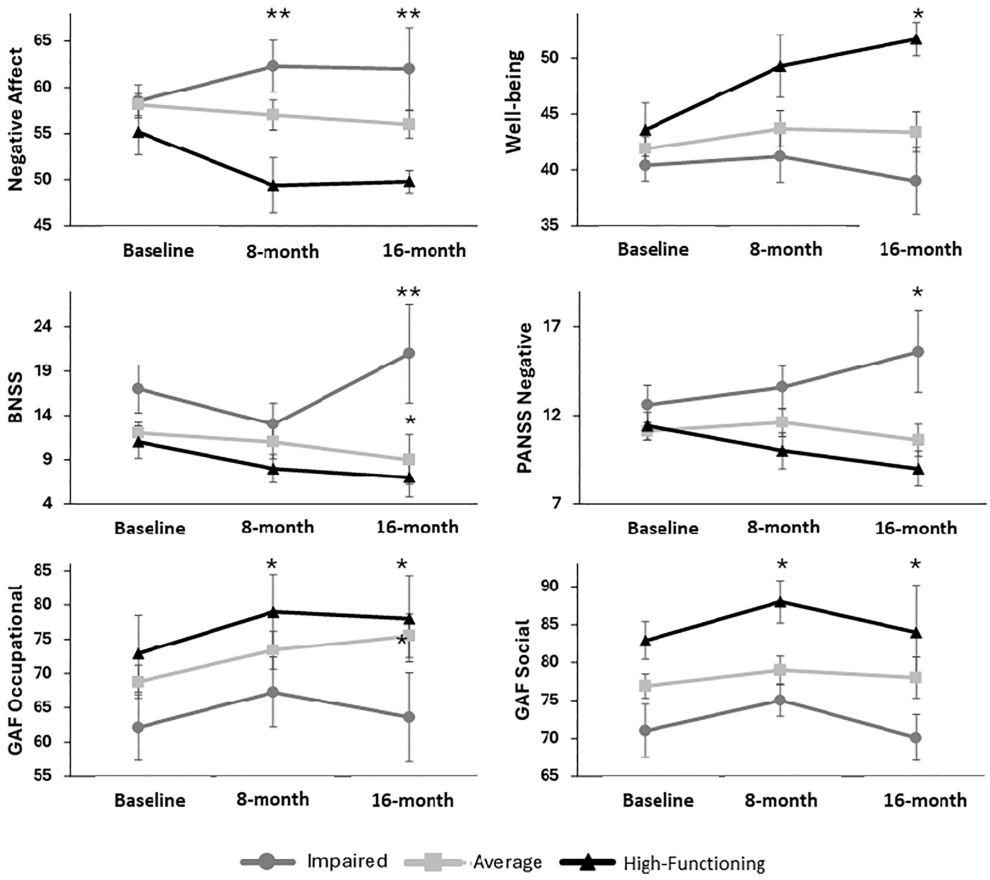

Figure 2 Clinical and functional outcomes by cognitive trajectory subgroups. *p<0.05, **p<0.01, BNSS – Brief Negative Symptom Scale, PANSS – Positive and Negative Syndrome Scale, GAF – Mental Illness Research Education and Clinical Center (MIRECC) Global Assessment of Functioning.

the 8-month follow-up (see Figure 2).

At the 16-month follow-up, the High-Functioning group differed significantly from the Impaired group on PANSS Negative (p=0.03), BNSS Total (p=0.009), GAF Social and Occupational Functioning (p=0.04 and p=0.01, respectively), and self-reported Negative Affect (p=0.004) and Psychological Well-Being (p=0.01). Additionally, the Average group differed significantly from the Impaired group on the BNSS Total (p=0.01) and GAF Occupational Functioning (p=0.02) (see Figure 2).

While not statistically significant, chlorpromazine equivalents at the 16-month follow-up were nearly three times higher in the Impaired than in the High-Functioning group (201.8±205.7 and 71.3±123.1 mg/day, respectively). Linear regressions predicting negative symptoms, functioning, and self-reported Well-Being and Negative Affect at follow-up by trajectory group controlling for medication showed no significant effect of chlorpromazine equivalents on any of the outcomes at either 8 or 16 months.

Predictors of group assignment

Time invariant variables were added to the trajectory model to evaluate possible baseline predictors of group assignment relative to the reference group, which was the Impaired group. Demographic variables (age, sex assigned at birth, education, and parental socioeconomic status) were included and presented as estimates of the risk for each group relative to the Impaired group. Higher education in years was significantly associated with classification into the High-Functioning group (parameter estimate = –4.94, p=0.03), and approached significance for the Average group (parameter estimate = –4.00, p=0.07). No other demographic variable was predictive of group membership.

DISCUSSION

Using group-based trajectory analysis, we identified three distinct cognitive subgroups in people with early psychosis: a High-Functioning group performing approximately one SD above the normative mean, an Average group performing within the normative range, and an Impaired group performing approximately two SDs below the mean. There was no evidence of cognitive change over time in the High-Functioning or Impaired groups, whereas cognition improved significantly in the Average group over the follow-up period, consistent with a recent report in early psychosis of cognitive stability in most measures and cognitive gains in select

others[46].

At baseline, groups did not differ on clinical symptoms, Symptom and Occupational GAF measures, or patient-reported measures. However, significant differences between groups in negative symptoms, social and occupational functioning, and self-reported psychological well-being and negative affect emerged over time, with the Impaired group showing the most unfavorable clinical, functional and patient-reported outcomes at follow-up. These data suggest that cognitive subtyping was able to identify groups of participants who, despite being clinically indistinguishable at baseline, experienced different clinical and functional courses of illness. Findings that progressive brain changes through early psychosis and into chronicity are associated with both cognitive impairment and negative symptoms[47] suggest that these domains may be linked by similar underlying neuroprogressive pathophysiology.

Groups did differ at baseline on parental socioeconomic status and estimated IQ, with the Impaired group showing the lowest scores on both measures. This is consistent with previous reports linking parental and neighborhood socioeconomic status with executive functioning and associated brain activation, as well as with psychosocial outcomes longitudinally[48,49].

In terms of IQ, the High-Functioning group scored significantly higher than the Impaired group, with the Average group intermediate in performance. It should be noted that, in our sample, all three groups scored in the average to above average range on IQ. This suggests that the Impaired group's cognitive functioning on the NIH Toolbox assessment was significantly lower than would be predicted based on IQ, which may indicate cognitive decline premorbidly or at the time of onset. In contrast, the High-Functioning group was approximately one SD above the mean on both IQ and fluid cognition.

These findings are consistent with previous reports using cluster analysis to identify groups of people with schizophrenia-spectrum disorders with similar cognitive trajectories based on current cognitive functioning and estimated premorbid IQ. Those reports identified three groups from premorbid to illness stages (no impairment, adolescent decline, and persistent impairment[50,51]), which differed on clinical and functional outcomes and polygenic risk scores[50], suggesting that cognitive subtypes based on IQ are associated with both clinically and biologically relevant outcomes.

Given the relative stability of cognition over time and the associations between subgroup membership and future clinical and functional outcomes, baseline cognitive subgroups may represent important predictors of illness course. In terms of predictors of group assignment, we found that only years of education predicted membership in the High-Functioning group compared to the Impaired group. Thus, baseline cognition may be sufficient to identify patients early in the course of illness who may be at risk for poor outcomes and may benefit from additional therapeutic supports.

For example, numerous studies have shown that cognitive remediation is effective at driving cognitive improvements in people with schizophrenia-spectrum disorders or mood disorders with psychosis[52-56], and could be offered to patients experiencing significant cognitive impairments. Similarly, newer antipsychotic medications that may have pro-cognitive effects might be considered for people experiencing significant cognitive challenges. Lastly, extending cognitive health services to help-seeking youth at clinical high risk for psychosis experiencing cognitive impairments may be warranted, as youth who go on to transition to psychosis exhibit the most significant impairments in cognition premorbidly[57].

Some limitations of this study should be taken into consideration. First, our follow-up duration was relatively short. Cognitive changes over longer follow-up periods that include frequent assessments (i.e., less than one year apart) may help to better clarify the longer-term trajectories of cognition and associated clinical and functional course of illness, and may reveal non-linear trends over time. Based on the WASI-II, our participants presented with higher-than-average estimated IQ scores, suggesting that our sample may not be representative of other samples of people with psychosis[58-60], which may limit generalizability of the findings. Additionally, the relatively high IQ scores in our sample may have biased emergent clusters, and may in part explain our finding that most participants were assigned to Average or High-Functioning groups. Lastly, we cannot completely tease out possible medication effects, although the inclusion of chlorpromazine equivalents in the regression models did not change the model fits, and they were not a significant independent predictor of any outcomes.

To our knowledge, this is the first study to use group-based trajectory modelling to estimate cognitive change longitudinally in early psychosis and examine associations with clinical and functional outcomes. These findings have implications for addressing major challenges in understanding biology-cognition associations, developing predictive models for clinical and functional outcomes, and personalizing treatment to support patients' cognitive, clinical and functional recovery early in illness, when interventions may be maximally effective.

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Recent advances in the conceptualization and evidence supporting the HiTOP approach

The Hierarchical Taxonomy of Psychopathology (HiTOP) endeavor has been underway for less than a decade, yet is showing signs of having a major impact on numerous areas of research and practice in mental health.

Broadly speaking, HiTOP is a consortium of hundreds of investigators interested in articulating an empirical alternative to traditional psychiatric nosologies. These nosologies are framed by assumptions that may or may not comport with empirical observations. Primarily, they articulate categories of mental disorder, regardless of the evidence (or lack thereof) that mental disorders are categorical in nature.

The perspective taken by the HiTOP consortium draws on two robust systematic observations about the nature of human variation in psychopathological tendencies[1,2]. First, these tendencies are generally better modeled as dimensions as opposed to categories. An extensive literature shows that, when formal models of psychopathological variation are compared, dimensional models tend to fit better than categorical ones. Second, continuous dimensions of psychopathology delineate a hierarchy of constructs in a reasonably reliable manner. Based on evidence, psychopathology is not well modeled as hundreds of categories. Rather, dimensions of psychopathological experiences are organized into constructs that vary in their breadth (e.g., a broad internalizing spectrum, encompassing diverse forms of emotional dysregulation) vs. specificity (e.g., anhedonia).

Here I emphasize two areas in which the consortium has been particularly active recently: a) clinical utility and interfacing with medicine, and b) neuroscientific utility. In selecting these areas, I do not mean to omit or slight the numerous other areas in which the HiTOP consortium has been active in the professional literature. Rather, I emphasize these areas because they strike me as having specific relevance to the scope of *World Psychiatry*.

Clinical utility is an area of research and scholarship that arguably has great potential to impact the lives of our patients most immediately. Many front-line practitioners are understandably frustrated by the limitations of traditional nosologies, because their patients do not fit neatly into ordinary categorical rubrics. Real life patients tend to present with a mix of symptoms from putatively distinct psychiatric categories, frustrating efforts at effective case conceptualization and development of corresponding treatment plans. Transitioning to more effective approaches to modeling psychopathology will be easier if practitioners can readily perceive the value of dimensional alternatives to traditional nosologies.

Along these lines, Balling et al[4] conducted a study involving 143 active clinicians, with the aim of gauging the clinical utility of the HiTOP and DSM approaches to making diagnostic ratings of clinical vignettes. Each clinician in the study made diagnostic ratings using both systems and was asked about the clinical utility of the systems after making the ratings. Participants favored HiTOP (compared with DSM) for overall clinical utility, as well as for specific areas of utility (e.g., formulating an effective approach to intervention). These findings suggest that clinicians readily perceive the utility of the HiTOP approach to diagnostic formulation. The HiTOP consortium is very active in cultivating a network of clinicians and providing specific clinical tools and workshops (see www.hitop-system.org/the-clinical-network).

Looking toward the future, many psychiatric researchers and practitioners are heavily investing in the prospect of neuroscientific technologies to place mental disorder research and intervention on surer scientific footing. Remarkable technologies exist for imaging the human brain non-invasively, and the hope is that neuroscience can provide a mechanistic understanding of mental disorder that transcends the epistemic limitations of patients' verbal reports of their experiences.

Various ways forward can be articulated at the interface of neuroscience and psychiatric disorder. For example, it might be possible to delineate neural "circuitry" in infrahuman species with a high degree of experimental precision and draw on that knowledge to articulate ways that homologous circuitry may go awry in humans. Nevertheless, bringing that "bench level" understanding to the "bedside" requires a model-based view of human phenotypes. For example, a specific "circuit" in rodents and corresponding behavioral observations may be somewhat distant from the experience of delusions of religious persecution in humans.

Along these lines, neuroscientists active in the HiTOP consortium have emphasized the importance of behavioral phenotyping in humans as a key tether in the search for neurobiological substrates of human psychopathology[5,6]. For example, a specific neurobiological observation (e.g., individual differences in a specific event-related potential, or connectivity in a specific circuit delineated via resting state functional magnetic resonance imaging) could be associated with a highly specific psychopathological phenotype (e.g., somatic delusions) and/or a broad range of phenomena (e.g., diverse forms of thought problems, ranging from delusional beliefs to eccentric interests to hebephrenic behaviors)[7].

The dimensional-hierarchical approach delineated in HiTOP provides a phenotypic tether for neuroscientific inquiry of this type. Instead of being limited to cataloguing piecemeal bivariate associations between putative categories and specific neurobiological paradigms, the HiTOP approach emphasizes the importance of multivariate research that ties together breadth of phenotypic assessment with diverse neurobiological approaches. Relatedly, many areas of clinical medicine are fundamentally dimensional in their approach to diagnostic formulation, yet are stymied by reliance on psychiatric categories (e.g., oncology)[8]. There is therefore much promise in linking the HiTOP approach with clinical medicine.

To summarize, the HiTOP consortium has grown from a modest cadre of investigators interested in modeling psychopathology empirically, to a group of hundreds of clinicians and investiga-

tors working together to articulate a coherent vision that ties together basic research and clinical application. The consortium is eager to grow, and new members are always welcome (see www.hitop-system.org). Moreover, the future is in the hands of younger generations of clinicians and researchers; hence, the HiTOP consortium places a strong emphasis on generativity (see www.hitop-system.org/trainees). Importantly, consortium members have also carefully articulated a principled approach to updating the HiTOP model as evidence accumulates[9], hoping that such guardrails can help to moderate the stressors associated with the continuous evolution of knowledge in mental health research and practice.

Of course, HiTOP is but one of several promising alternatives to traditional psychiatric categories. Ultimately, openness and unbounded conversations among diverse groups of scholars in mental health is the key to progress. Hopefully, this brief update can serve to promote constructive and wide-ranging discourse that improves the lives of our patients worldwide.

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Screening, assessment and management of gaming disorder: recent evidence and future directions

Video gaming is a thriving billion-dollar industry and among the most popular leisure and entertainment activities in the world. The mass appeal of digital games as a consumer product can be attributed to their low cost and convenience, few restrictions or barriers to entry, and seamless integration with most digital devices and platforms in the modern technological landscape. Psychologically, games are desirable because they provide excitement, relaxation, amusement, a sense of achievement, and an escape from reality. Games also provide opportunities for socializing and cultural participation (e.g., esports), which can further support and normalize gaming as a dominant routine and lifestyle choice.

Although gaming can have personal and social benefits, there is increasing public health awareness of the negative consequences of excessive gaming, including harmful effects on mental and physical health, academic and work performance, and interpersonal relationships. There is also growing research on game design properties[1] supporting the notion that games are not always fun and transient entertainment; they can be highly sophisticated products designed to encourage persistent engagement and preoccupation. Certain games employ financial elements (e.g., microtransactions and "loot boxes") to strengthen players' commitment to the game and its ecosystem, which can pose risks related to overspending and gambling-like behaviors.

The study of problematic gaming as an issue of clinical and public health relevance has made significant advances in recent years[2]. An important step forward has been the World Health Organization (WHO)'s formal inclusion of "hazardous gaming" and "gaming disorder" categories in the ICD-11. Notably, gaming disorder was not included in the DSM-5-TR, but the disorder is under consideration for the next edition of that diagnostic system.

Gaming disorder is defined by impaired control over gaming behavior, increasing priority given to this behavior so that it takes precedence over other life interests and daily activities, continuation of the behavior despite negative consequences, and consequent significant distress or impairment in important areas of functioning. A Delphi study of international experts has confirmed that these criteria have high diagnostic and clinical validity and prognostic value[3].

The clinical descriptions of gaming disorder in the ICD and DSM systems have been influential in guiding research and clinical programs in the rapidly growing field of behavioral addictions, and have bolstered the field's credibility alongside other addictions and health science in general. The formalization of gaming disorder has also paved the way for research into other digital technologies that can be harmful and addictive, including social media and smartphone use in general.

An important objective in research on gaming disorder has been determining the nature and scale of gaming-related problems in vulnerable populations (e.g., adolescents) as well as the general population. Epidemiological research has reported trends of increasing gaming and related screen time, particularly noting a sharp rise during the COVID-19 pandemic[4]. Reviews and meta-analyses have estimated that the prevalence of gaming disorder is about 1 to 3%, and the condition is more common among young males[5], with higher rates reported in East Asian nations.

Identifying and monitoring gaming disorder is challenging for several reasons, including the covert and highly time-consuming nature of gaming. Individuals with gaming disorder can be difficult to reach because they spend most of their time playing games privately and have become disengaged from school, work, or community institutions. The constant mental and physical demands of habitual gaming preclude normal engagement in, or "multi-tasking" with, other activities. Gaming is often more hidden than activities such as drinking or smoking.

Conducting research into this area is difficult, particularly when one tries to target highly committed gamers. For example, in studies with an interest to target people at higher risk, researchers have often relied on the goodwill of online gaming communities to opt in to surveys, which has potentially biased the findings. At the tertiary or treatment-seeking level, researchers often find that affected individuals rarely engage with health systems to address gaming-related issues. Help-seeking usually occurs under pressure from a partner or family, which makes it difficult to effectively track the progression and recovery rates of the disorder. A further issue is that of comorbidity. Gaming disorder may receive less attention when it co-occurs with other conditions, particularly in the case of autism spectrum disorder and attention-deficit/hyperactivity disorder (ADHD), where habitual gaming may be seen as intractable or a necessary coping strategy.

Another challenge has been that the literature on gaming disorder has a history of inconsistent screening and assessment. Early approaches to measurement commonly involved adaptations of problem gambling or substance use symptom checklists, prior to the field developing its own more specific measures. There has been a "silo effect" in psychometric validation studies, where research teams have developed and evaluated their own tool rather than gather and pool data on select tools.

More than 50 tools or composite measures for gaming disorder have been created in the past two decades[6]. These tools have been developed in treatment centers where they have been used primarily for management of the center's caseload and trials and rarely adopted elsewhere. The WHO is developing a screening and diagnostic tool for gaming disorder to provide a "gold standard" which may unify assessment practices[7].

On a more positive note, the evidence on treatment of gaming disorder is steadily developing in the context of increasing global demand for interventions. Psychotherapeutic approaches, particularly cognitive-behavioral therapy (CBT), have the most empirical evidence, but there are few high-quality studies[8]. A randomized controlled trial evaluated manualized CBT for gaming disorder, and reported that most patients (69%) showed remission, compared with 24% of the waitlist control[9].

Treatment studies have also examined motivational interviewing and counseling, family therapy, and psychosocial rehabilitation. Medication trials have evaluated drugs for depression (bupropion, escitalopram) or ADHD (methylphenidate, atomoxetine) and have shown less effectiveness than CBT. The treatment literature has been generally limited by small samples, lack of randomization and follow-up measures, and lack of control for psychiatric comorbidities.

There are several priority areas for future research. The field would benefit from greater consistency in measuring gaming-related problems across the continuum. There is a need for high-quality population and platform user studies using innovative sampling strategies to understand the onset and progression of gaming disorder, as well as the risk factors and vulnerabilities that influence its severity. The field could consider more sensitive technological measures embedded in game software that detect the escalation of gaming behavior. Studies should evaluate game design features that drive excessive play and spending.

Interventions for gaming disorder are hindered by poor engagement by the predominantly young male gamer population. Psychological treatment providers should consider co-designing interventions with gamers and other stakeholders to optimize their content and delivery. Given the broad continuum of problem gaming, there is a need for stepped care approaches that can flexibly match the intensity of treatment to the needs and profile of the individual gamer. Just as digital games become more sophisticated, it is imperative that the field of gaming disorder innovates its research and clinical practices to address this globally prevalent condition.

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International developments in the provision of recovery-oriented care in forensic mental health services

Forensic mental health services are tasked with providing care to some of the most clinically complex and marginalized persons in society. Indeed, forensic service users are often doubly stigmatized, owing to their status as persons with mental illness and the fact that they have offended, which results in complex and multilayered challenges to recovery.

The last decade has seen growing recognition that patient recovery and rehabilitation are integral aspects of forensic psychiatric practice. This is reflected in the expanding literature on "secure recovery", referring to the application of general mental health recovery principles to forensic settings. This includes a growing knowledge of staff and patient perceptions of recovery-oriented

care in forensic settings, as well as an increasing experience in the identification and measurement of core elements of recovery in these settings[1].

Five key elements of people's experiences of recovery in mental illness have been described in the literature: Connectedness, Hope and optimism about the future, Identity, Meaning in life, and Empowerment (CHIME)[2]. This CHIME framework has been recently extended to reflect the experiences of forensic service users, based on a systematic review and thematic synthesis of the relevant literature[1]. The result has been a robust conceptual framework to guide recovery-oriented practices in forensic mental health services (the "CHIME-S"). It has been documented that recovery in forensic mental health encompasses the same CHIME elements, but with the added domain of safety and security (the "S" in CHIME-S).

In developing the CHIME-S framework, the centrality of therapeutic relationships with clinical staff in patient recovery, especially considering the long lengths of stay that characterize forensic hospitalizations, emerged clearly. This literature also highlighted the importance of therapeutic opportunities to elaborate the impacts of previous trauma, victimization and offending in the course of developing a new identity that is separate from that of the "offender-patient". The ultimate goal of regaining one's freedom, independence and autonomy was particularly salient among forensic service users, as were the perceived barriers to recovery in forensic care (e.g., feelings of disconnectedness, hopelessness, stigma and disempowerment).

Perhaps the greatest challenge encountered when bringing a recovery framework into forensic settings is a perceived tension between core recovery principles, such as promoting autonomy and patient empowerment, and the security and legal obligations encompassed by forensic services[3]. This tension can result in skepticism about whether true recovery is possible in the context of secure hospital settings where liberty and autonomous decision-making are significantly curtailed.

However, in the context of forensic care, security and therapy can be synergistic rather than competing aspects. On a day-to-day basis, this can be reflected in clinical practices that strive to deliver compulsory care respectfully and therapeutically, while preserving as much patient choice and control as possible. Further, shared decision-making models around the assessment and formulation of violence risk are important vehicles through which patient voice and engagement can be promoted. New tools that require both patient and staff perspective on clinical progress and risk understanding, such as the Early Recognition Method (ERM)[4] and DUNDRUM 3 and 4[5], are examples of structured approaches that give space to patient voice and shared vision during the process of secure recovery.

Interestingly, though, secure recovery conflicts with human rights arguments that all forms of coercion must be abolished, including detention in hospitals. This is despite the growing evidence that people can and do recover in situations of security, particularly so if care is oriented towards values of respect, inclusion, maximizing voice, and building positive therapeutic alliances[1]. Secure recovery envisages a "whole of life" concept of service delivery, including understanding people's life history, their respectful involvement in their care, and assisting them in being fully involved as family members, workers, and members of society.

It is also increasingly clear that secure recovery cannot fully come to fruition in the absence of cultural considerations and the incorporation of one's cultural identity into forensic assessment, formulation and treatment. There is an increasing awareness of the inequities afflicting many persons who receive forensic care, and how such inequities complicate their recovery efforts. Forensic mental health services are now increasingly urged to take a position of advocacy addressing these inequities[6], an urgency that is amplified by the fact that many forensic services internationally comprise an over-representation of Black, Indigenous and other racialized groups. In spite of this, the integration of culturally-responsive assessment and treatment frameworks in forensic service delivery is often lacking, and there is an absence of literature to guide forensic services in the provision of equitable, diverse and inclusive practices for patients, families and staff[6].

Promoting cultural responsiveness to the needs of patients requires strong family engagement and regular opportunities to share knowledge and experiences. Shared decision-making models will facilitate a mutual understanding – between the patient, his/her loved ones, and the clinical team – of the person's particular pathway to risk, and will help to co-develop an understanding of clinical and personal pathways to safety. Without patient and family involvement and cooperation, relevant information for treatment and risk management planning is more likely to go unreported[4], while respectful and collaborative clinician-patient relationships can promote open communication of risk and safety concerns from both patients and family members. Further, forensic patients continue to experience significantly poorer health and safety outcomes compared to non-forensic service users across a number of indicators, including premature mortality, obesity, and violent victimization[7], which are often ignored.

The rapidly increasing body of research on secure recovery reflects a change in forensic clinical practices internationally to align care with recovery-oriented principles. There is also a notable consistency across studies concerning the core elements of secure recovery, and their intersection with recovery principles in general mental health services. There is a perceived need to describe and develop high functioning systems of care that can represent exemplars of practice. However, research describing outcomes of forensic care has proven difficult, and evidence on the effectiveness of "treatment as usual" (TAU) is hampered by a lack of consistency across services in setting quality standards and guidelines for TAU[8].

Forensic mental health services are high cost, and provide care to persons seen as presenting a high risk of harm to self and others. This demands that care be personalized, carefully delivered, and guided by demonstrable quality standards to ensure continuously improving outcomes for patients[8]. One key component of this is to develop and propagate a well-articulated model of care (MOC) that outlines best practices for patients at different stages of recovery. The MOC describes key functions that the service must de-

liver, including goals, pathways and processes of care, therapeutic programming, and service measurement and evaluation. Several forensic services around the world have developed such a MOC and employ it in all components of service design and delivery.

Evidence of MOC success can be collected through measurable performance indicators at the organizational (e.g., sustainable admission and discharge rates; rates of violence, restrictive practices, and absconding) and individual (e.g., symptomatic and personal recovery) levels[9]. It is from these developments that the aspiration to excellence in forensic care provision can emerge, including the systematic implementation and evaluation of secure recovery-oriented care, and strategies that deliver on improving "real world" outcomes for patients – including personal, symptomatic and functional recovery – and the resumption of autonomy and responsibility in the community.

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Antisocial personality disorder: current evidence and challenges

Antisocial personality disorder (ASPD) is characterized by a pattern of socially irresponsible, exploitative and guiltless behaviors that affects all important life domains[1]. Behaviors can include criminal acts, failure to sustain consistent employment, manipulation of others for personal gain, deliberate deception, and disturbed relationships. Other attributes include a lack of empathy for others, impulsivity and aggression, and failure to follow a life plan.

Antisociality occurs along a spectrum ranging from relatively minor acts at one end (e.g., lying) to serious acts of violence at the other. Formal diagnostic criteria were introduced in 1980, strongly influenced by the work of L. Robins, who carefully charted the course of former child guidance clinic patients[2,3]. The DSM criteria have since been refined, but remain true to Robins' vision of a chronic behavioral disorder with a childhood onset[4].

Surveys in the US and UK show that 2-5% of the general adult population meets criteria for lifetime ASPD[5]. Risk factors include male sex, younger age, urban residence, and lower educational achievement. The disorder is often associated with substance use disorders, mood/anxiety disorders, learning disorders, or attention-deficit/hyperactivity disorder (ADHD). Rates of suicide attempts and completed suicide are elevated.

Robins and others have documented the early onset of ASPD[3,6]. If symptoms are sufficiently severe, a child may warrant the diagnosis of conduct disorder. This diagnosis converts to ASPD if antisocial symptoms persist past age 18. The severity of ASPD is greater early in its course, but tends to lessen with advancing age[6]. Improvement often follows many years of behavioral symptoms that stunt the person's educational and work achievement and contribute to his/her unstable relationships and impoverished home life.

ASPD is thought to result from the interplay of genes and environment[7]. Family, twin and adoption studies suggest a heritable component, yet how the disorder is transmitted is unclear even as newer genetic methods are being applied. Some experts have suggested that ASPD may result from the consequences of a neurodevelopmental insult, chronic central nervous system underarousal, or deficient cognitive processing, while others have pointed to childhood maltreatment, poor parenting, and disturbed peer relationships as potential contributors. Roles have been proposed for serotonin, dopamine and testosterone. Structural and functional brain imaging studies have shown anomalies in frontal and temporal cortices, regions that mediate emotions and behavior.

The patient's history is the most important basis for diagnosing ASPD[8]. While the patient is the best source of information, family members are often more accurate in describing antisocial behavior than the patient, who may have little motivation to be truthful. Records of previous clinic or hospital visits can provide additional diagnostic clues. The patient interview should be wide-ranging and include a full assessment of the personal, social, medical and family history.

Psychological testing is not diagnostic, but can be helpful if informants are unavailable[8]. The Minnesota Multiphasic Personality Inventory yields a broad profile of personality functioning, and a certain pattern of results is suggestive of antisociality (i.e., the "4-9 profile"). The Psychopathic Checklist-Revised can be used to measure the severity of the individual's psychopathic traits, which might be particularly important in forensic settings. ASPD can be assessed using a structured diagnostic interview (e.g., Alcohol Use Disorder and Associated Disabilities Interview Schedule-5; Structured Clinical Interview for DSM-IV Personality Disorders), but these instruments are not commonly utilized in clinical practice. Because some antisocial persons have specific learning disorders, cognitive and intellectual testing can be useful.

The medical history is important to assess. People with ASPD tend to engage in impulsive and/or risky behaviors that put them at risk for sexually transmitted diseases and injuries from accidents and other physical trauma. Antisocial persons are at increased risk for suicide and should be asked about suicidal thoughts and past suicidal behaviors.

Laboratory tests are unnecessary unless they are prompted by the medical history or presenting symptoms, for example blood alcohol level, urine drug screen, or liver enzymes for those who mis-

use alcohol or drugs. Likewise, structural or functional brain imaging is unnecessary in the absence of localizing neurological signs.

The differential diagnosis of ASPD includes other personality disorders (e.g., narcissistic, borderline), substance use disorders, psychotic and mood disorders, intermittent explosive disorder, and medical conditions that might cause violent outbursts (e.g., partial complex seizures) or personality changes. The DSM-5 Z-code diagnosis "adult antisocial behavior" is used in persons who meet adult ASPD criteria but have no history of conduct disorder prior to age 15[4].

The treatment needs of persons with ASPD should be addressed in outpatient settings. There is usually little reason to psychiatrically hospitalize these persons, and they can be disruptive to the ward milieu. Exceptions include crisis stabilization for recent or imminent suicidal behavior, recent or threatened violence or assaultive acts, and/or medical monitoring of alcohol or drug withdrawal[7].

While the disorder is often thought untreatable, this conclusion is premature because of the lack of relevant treatment research[9]. No medication is currently approved to treat ASPD, nor are any routinely used. Medications are sometimes used "off-label" to treat the antisocial patient's aggression and irritability, including lithium and other mood stabilizers, antidepressants, and atypical antipsychotics. Response is variable. Improvement might only mean that the individual has fewer outbursts or has a "longer fuse" giving him/her more time to reflect before acting out. There is no guarantee that the antisocial person will agree to take medication if prescribed.

Medications can be used to treat the patient's co-occurring disorders, for example antidepressants to address comorbid mood and anxiety disorders, or lithium to treat comorbid bipolar disorder. Because benzodiazepines can be disinhibiting and are habit-forming, their use is not recommended. Stimulant medications for comorbid ADHD should be avoided as well. Instead, non-addicting alternatives such as bupropion, clonidine or atomoxetine could be considered. Those who misuse drugs or alcohol should be referred to evidence-based treatment programs. Successful treatment of the person's co-occurring disorders has the potential to reduce the overall severity of his/her antisocial behavior.

Several psychosocial treatments have been studied in patient samples comprising persons with ASPD, including cognitive-behavioral therapy, mentalization-based treatment, contingency management, psychoeducation, skills training, and motivational interviewing. Taken together, these studies suggest that significant positive changes can occur in people with ASPD, warranting further research. Moreover, there is no evidence that the above treatments make ASPD people worse.

In summary, ASPD is common and problematic. It begins early and is typically chronic and lifelong, with a trend toward improvement with advancing age. It likely results from the interplay of genes and environment. Diagnosis rests on the patient's history of recurrent behavioral problems, because there are no diagnostic tests. Treatment is vexing and unsatisfying. Research is needed to identify the genetic roots and underlying neurobiology of the disorder. Treatment research should include studies of medications to target anger, irritability and other antisocial symptoms, while psychotherapy should target interpersonal, social and cognitive aspects of the disorder.

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Improving care for mental health, neurological and substance use conditions by enhancing pre-service education for doctors and nurses: a new WHO guide

Recent efforts to reduce the enormous treatment gap and significant mental health care workforce shortages have focused on training primary care staff to recognize and provide care for people with mental health, neurological and substance use (MNS) conditions[1]. In-service (or on-the-job) training is a useful and evidence-based approach for upskilling doctors and nurses to manage these conditions[2]. However, an additional and more sustainable approach is to strengthen competency-based mental health care education for health care providers before they enter the workforce[3]. Here we argue for a stronger emphasis on pre-service university education for doctors and nurses in the areas of mental health, brain health and substance use, and outline the work that the World Health Organization (WHO) is undertaking to promote this approach.

Both pre-service education and in-service training are necessary to secure a competent workforce to provide care for people with MNS conditions. Pre-service education equips health care providers with basic professional attitudes, knowledge and skills during their undergraduate or first-degree training. It sets the foundations for clinical practice and provides an important reference point for follow-up in-service, post-graduate and continuous education.

Strengthening the focus on MNS care in the pre-service education of doctors and nurses is especially valuable because it ensures that primary health care providers accept responsibility for MNS care from the earliest stages in their careers[4]. Universities can, through relevant assessment, ensure the competence of their graduates before they enter the workforce. And, because new graduates will be better equipped to provide care for people with MNS conditions, there will be a reduced need to rely on in-service training[5]. Importantly, good-quality pre-service education can help to reduce stigma related to MNS conditions among health care providers[6].

Nonetheless, pre-service education in MNS care is currently often inadequate, despite its strategic value. Commonly cited obstacles to embedding MNS care into pre-service education for medical and nursing students include time constraints, too few trained educators and clinical sites available, lack of endorsement from decision-makers, and faculty staff resistance due to increased workload or territorialism[3].

The pre-service education on providing care for people with MNS conditions that is available for medical and nursing undergraduates varies widely in quality. It is typically brief and theoretical, and so insufficiently geared to the tasks that doctors and nurses can be expected to do[7]. For example, students may learn about prescribing psychotropic medicines, but may be insufficiently trained in promoting human rights and providing non-pharmacological management and support (e.g., psychoeducation, stress management, psychosocial support). Too often, clinical internships are placed in specialized care settings, such as psychiatric hospitals, which do not adequately reflect the MNS needs that medical or nursing students are likely to encounter after graduation.

The result is that medical and nursing graduates regularly fail to achieve the competencies they need to adequately identify, support and refer people experiencing emotional distress, MNS conditions and social difficulties. Common conditions such as depression, anxiety and substance use disorders go unnoticed or are poorly managed by primary health care providers. Person-centred, rights-based, recovery-oriented care is rare.

There is an urgent need to advance competency-based pre-service education programmes to equip future doctors and nurses in preventing, promoting, and providing care for people with MNS conditions, and so better prepare them for any subsequent post-graduate education and in-service work. This will in turn improve the extent and quality of care for people living with MNS conditions globally.

The WHO's Mental Health Gap Action Programme (mhGAP) provides evidence-based guidance and tools for integrating priority MNS conditions into general health care settings. While it is most often used as a clinical tool or as the basis for in-service training, we encourage educators and decision-makers to also use the mhGAP Intervention Guide[8] as a key tool for enhancing pre-service education[4]. Experience from around the world shows that mhGAP-based pre-service training can be implemented in diverse settings and programmes[3].

To advance the necessary reform to pre-service education, WHO has worked to identify the core competencies that doctors and nurses need to provide quality MNS care, and how these can be embedded in medical and nursing undergraduate curricula. In partnership with other international organizations, we have published a practical guide for health care workforce decision-makers and educators[9]. Using a competency-based approach that is associated with better learner engagement and preparedness for practice, the guide provides an overview of the key activities and considerations needed to integrate mental health care competencies into a university's teaching processes for professionals non-specialized in providing care for MNS conditions.

The new guide defines each core competency – and the attitudes, knowledge and skills required to achieve it – that doctors and nurses working in general health care need to support people experiencing MNS conditions. It provides examples of the learning content, teaching methods and assessments to include in undergraduate curricula. And it offers guidance to further support programme implementation, for example on training educators, securing the support and endorsement of faculty, administrators, accreditors and regulatory bodies, and monitoring and evaluation.

Moving forward, the WHO aims to mobilize action to apply this guide and support countries to scale up pre-service education for

MNS care globally. We encourage all stakeholders to participate in this process by advocating for MNS care competencies to be embedded in medical and nursing education and actively working to enable curricular change and sustainable workforce development.

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The International Consortium on Paranoia Research: an introduction

Paranoia is defined as distressing and unfounded beliefs that others intend to cause harm[1]. While traditionally associated with schizophrenia, prominent paranoia can be present in several other clinical conditions, and milder paranoid thoughts are highly prevalent in the general population, indicating that paranoia spans the continuum from healthy to pathological.

Over the last 25 years, research has consistently demonstrated that, across this continuum, paranoia is associated with a wide range of negative impacts on mental health and social functioning, including increased anxiety, depression, stress and loneliness, and decreased social support, prosocial behaviors and interpersonal relationships[2,3]. Thus, paranoia is increasingly recognized as a significant clinical and global health challenge that requires coordinated research efforts.

The International Consortium on Paranoia Research was founded in 2022 with three primary goals: a) to provide a springboard for advancing understanding of paranoia, including its mechanisms, consequences and treatment, by fostering collaboration between international researchers and clinicians; b) to identify gaps in knowledge regarding paranoia and pave avenues for novel research; and c) to promote paranoia as an important topic, and increase global access to research findings. Inaugural meetings of the Consortium focused on identifying open questions and research priorities. These topics follow the broad themes of phenomenology, measurement, mechanisms, intervention, and cultural impact.

In regard to phenomenology, questions arose around the nature and structure of paranoia, particularly as it exists along the abovementioned continuum. For example, paranoia is typically considered detrimental, but an evolutionary perspective suggests that it may have adaptive aspects which help us navigate social life[4]. It is currently unclear at what point paranoia transitions from "normal" to pathological. Demarcations could be made based on severity and impact on functioning/behavior, but these are not yet clearly defined, and such delineations may not adequately consider the specific context of a person's previous experiences.

Another unanswered question is whether paranoia is a state, a trait, or possibly both. Fluctuations in paranoia over time are common, but why it fluctuates remains unclear. The Consortium members also questioned whether paranoia may be better conceptualized as an emotion, and noted the need to identify its physiological correlates, and how they differ from other constructs such as depression and anxiety. Consistent with the overarching goals of the Consortium, the need to better understand the experience and expression of paranoia in non-Western cultures was also highlighted.

Turning to measurement, paranoia has traditionally been assessed via self-report or clinician-rated interviews. While useful, these methods can be prone to bias, have limited reliability and, related to the point above, be unable to distinguish state from trait paranoia. The emergence of digital technologies, particularly ecological momentary assessment (EMA), offers the opportunity to assess paranoia *in vivo* with increased temporal resolution, allowing exploration of inter-individual variability and time-dependent changes[5].

However, EMA protocols differ widely across studies, using various rating scales and time frames that prevent pooling of data. Given this, the Consortium members noted the need for novel multidimensional assessments that do not rely solely on self-report, and for consensus-based protocols that facilitate international harmonization and pooling of data across sites. The need for robust and psychometrically sound tools that can be used cross-culturally was also highlighted, as well as the requirement for measures that can reliably differentiate valid safety concerns from paranoia.

Current mechanistic models of paranoia draw heavily on either psychological (e.g., negative emotions, reasoning biases, faulty/aberrant belief updating)[3] or neurobiological (e.g., hyperactivity of the amygdala, increased functional connectivity between limbic

and frontal systems)[6] factors, but an integrative theory is lacking. Further, existing models view paranoia solely as a quality that emanates unidirectionally from the individual, while it is beginning to be understood as a product of an individual's social interactions rather than just an intrinsic dysfunction[7].

The development and refinement of mechanistic models that can accommodate the continuum view and that incorporate social determinants of health (e.g., socioeconomic status, discrimination, neighborhood deprivation and crime), as well as cultural factors, are therefore needed[8]. In doing so, the Consortium members noted the need to conduct large scale investigations of variability in the prevalence of these potential mechanistic factors across the continuum, and to use experimental methods and/or interventions in attempts to alter these mechanisms and bolster causal inferences.

Finally, emphasis was also placed on the need to investigate whether the mechanisms for developing paranoia are the same as those for maintaining paranoia. Distinct mechanisms would require different intervention approaches that may further advance individualized medicine.

With respect to intervention, antipsychotic medications can alleviate paranoia in some individuals, but many people continue to have residual symptoms or experience no improvements at all[9]. Thus, the development of effective treatments is a priority for the Consortium, which recognizes the potential benefits of psychologically based interventions as well as novel pharmacological and neuromodulatory (e.g., transcranial magnetic stimulation) approaches.

In developing new interventions, the Consortium supports strategies that target identified mechanisms and that rigorously test treatments moving through proof-of-concept studies to large-scale randomized clinical trials. Open questions include how to personalize treatment for optimal outcome, how sustainable treatment gains are, and how treatment accessibility and adherence can be maximized. The need to think proactively and to explore avenues for fostering resilience against paranoia was also emphasized.

Finally, cultural impact should not be overlooked. Because paranoia has long been considered as an individual symptom of psychiatric illness, very little is known regarding how the broader culture may impact paranoia and vice versa. Research priorities in this area include examination of whether some cultures may propagate paranoia while others may weaken it, and how paranoia may relate to belief in, and proliferation of, conspiracy theories and growing distrust of authorities. Likewise, links between paranoia and increased feelings of social disconnection or fragmentation require investigation.

In addition to identifying these open questions, there was uniform enthusiasm for increasing collaborative efforts and developing research projects that leverage the international membership of the Consortium, which currently includes five member-generated working groups focusing on neural processes, attachment, social interaction, computational approaches, and phenomenology and psychometrics. A considerable subset of the Consortium investigators has also successfully launched a large-scale survey project designed to examine the psychosocial correlates of paranoia across cultures.

The Consortium currently brings together over 70 members spanning 22 countries, and is growing rapidly, with particular emphasis on including people from traditionally under-represented countries. Membership is open to all interested individuals, including researchers at all career stages, mental health professionals, and people with lived experience of paranoia and related symptoms. By fostering increased collaboration at local and international levels that addresses the open questions discussed above, it is hoped that research from the Consortium members will improve our understanding of paranoia and ultimately lead to better outcomes for all involved people.

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Views of international experts on challenges to early intervention for bipolar disorder

Bipolar disorder (BD) is a leading cause of disability worldwide, yet early intervention efforts lag decades behind early intervention for psychosis[1,2]. Lengthy delays between symptom onset and diagnosis are the norm[3]. During this period, individuals may receive inappropriate, ineffective and/or iatrogenic treatments[4], if they receive treatment at all.

The long-term burden of the disorder might be lessened if effective and less aggressive treatments are provided in the early stages [2,5,6]. It is unclear, however, how to implement early intervention and best support young people at risk for, or experiencing early stages of the disorder[1-3,5].

Through a partnership between Orygen (a world leader in early intervention) and the Daymark Foundation (a private family foundation in Canada), we aimed to address the following question: "How might we advance an early intervention approach for people at risk of, or at an early stage of BD?". Fifty-one international experts were invited to participate, with 28 consenting to partake in semi-structured interviews over Zoom. Participants included researchers, clinicians, peer support workers, philanthropic funders, and representatives from BD advocacy organizations. Some were also experts by experience (individuals with BD or carers). Through reflexive thematic analysis[7], nine challenges to advancing early intervention were identified, as detailed below.

- *Awareness*. There is limited recognition and understanding of BD (including early signs, at-risk states, and symptoms) across all stakeholders, including the community, mental health providers, clinicians and services. Limited awareness was viewed as a barrier to help-seeking, diagnosis, acceptance, and engagement in treatment and research. Widespread education was considered necessary for the community and across health care sectors to reduce stigma and to ensure earlier and timely diagnosis and treatment.
- *Definitions*. There is a lack of consensus on definitions and key constructs of early intervention in BD, including what constitutes an at-risk state, diagnostic delay, early stage, early intervention, and what age groups we should be focusing on. The diversity in how these constructs have been defined across settings and internationally was viewed as an obstacle to research.
- *Resourcing*. BD is under-prioritized and under-funded relative to other mental disorders, especially considering the personal and economic costs associated with the disorder. In clinical settings, there was the view of a lack of funding for BD-specific services, therapy and workforce training. In research settings, funding bodies were perceived as being uninterested in BD or having priorities that mismatched those of researchers. Early intervention funding was considered disproportionately directed to psychosis, despite the high potential of this intervention in BD. Philanthropic investment was considered essential for supporting early research, bringing people together, fostering collaborations, and providing the preliminary data to support further research funding applications.
- *Measurement and assessment*. There is a lack of objective measures, consistent approaches, and battery of tools validated for diagnosing, monitoring, and measuring outcome in at-risk and early-stage BD groups. Current tools were seen as burdensome, insensitive to nuances of BD, and lacking relevance for young people. Clinicians were viewed as lacking training and skills for assessing BD, particularly around assessment of bipolar and atypical depression, antidepressant non-response, hypomania, and family history. While some debate surrounded the clinical utility of biomarkers, digital technologies were thought to show promise for assessing symptom changes over time.
- *Data*. We need more meaningful data, harmonization of existing data, as well as development of bigger prospective datasets. Participants emphasized the need to look beyond symptoms, imaging and genetics, to data of greater relevance to young people (e.g., cognition and functioning). Longitudinal and real-time data (especially around sleep) were highlighted as important for understanding the natural history of at-risk states and the trajectory of BD, but collecting them is costly and can be hampered by attrition. Randomized controlled trials focused on early-stage BD were found to be rare. Across studies, a lack of harmonization of measures and inconsistent definitions were viewed as impeding our ability to pool and utilize existing data, as well as limiting future collaborative efforts to build large data sets. Learning health networks with integrated data systems were proposed by one participant as an important advance; however, none of them specifically focuses on early-stage BD as yet.
- *Treatments*. The evidence base for early intervention in BD is scarce, with uncertainty about which treatments to offer to which individuals, and when and how they should be delivered. Specific guidelines for at-risk and early-stage BD treatment have not been developed. There was consensus regarding over-reliance on medication. Antidepressant prescription was viewed as potentially harmful for young people at risk or in the early stages of BD. There was also concern that mood stabilizers, particularly lithium, are under-utilized. Limited access to psychological interventions, a dearth of developmentally appropriate therapies, and clinicians not having sufficient training, skills and confidence to deliver BD-specific therapies were highlighted as barriers to good treatment. Other therapies such as ketogenic diet, transcranial magnetic stimulation, bright light therapy, and melatonin were viewed as under-used. Integrated physical health monitoring and interventions were considered scant. The potential value of peer support interventions and digital technologies in BD treatment was recognized.
- *Service capacity and models*. There is a lack of capacity and expertise among clinicians across services to diagnose and treat early-stage BD effectively. It is unclear which service model is best equipped to support people in the early stages of BD. A range of care settings were considered. Although young people are first likely to present to primary care with symptoms, BD is often not recognized and treated. There was agreement that mental health services also overlook BD. Follow-up and continuity of care were reported as inadequate or absent, even after diagnosis or hospital discharge. Participants' views varied about the best service models for treating early-stage BD, ranging from specialized early intervention services for BD or services for youth with complex mood disorders, to transdiagnostic youth services, or integration of BD interventions within existing early intervention services for psychosis. Regardless of

setting, reducing access barriers, improving workforce training, ongoing supervision and skill refinement, and better support for clinicians to diagnose and treat BD were considered essential for improving care.

- *Families*. Families have a key role in assessment and treatment, and should be better supported. They were viewed as an under-utilized resource to aid early detection and support treatment. They must advocate to be heard, in order to report family history, observations (e.g., possible BD symptoms), or their views about possible diagnosis and appropriate treatments. Suggestions regarding supports for families included groups for parents of young people at risk to aid early detection, family peer support, greater involvement with clinicians, especially during acute episodes, and traditional family therapies (including family-focused therapy).
- *Collaboration*. To advance early intervention in BD, we need to look at new opportunities for collaboration that involve all stakeholders, including those with a lived experience of BD. Lack of collaboration was reported to occur across all stakeholder groups, including the interface between researchers, clinicians, service providers, people with lived experience, families and other caregivers, advocacy organizations, and funding bodies.

These challenges identified by international experts lay the foundation for developing an agenda to advance the field. Further collaborative work, including those with a lived experience, may transform the global landscape of early intervention for BD and result in better outcomes for affected people, their carers, and society.

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Priorities and opportunities for lifestyle psychiatry: consensus from the LifePsych Society

"Lifestyle psychiatry" encompasses the role of modifiable behavioral health factors – such as physical activity, sleep, diet, and stress management – in preventing and treating mental health conditions[1]. Since lifestyle interventions are gaining recognition as fundamental components of psychology and psychiatry[1,2], the LifePsych Society has been established to advance research, education, and global integration of lifestyle medicine into mental health.

The inaugural LifePsych Society summit, held in June 2024, convened international experts working across various sectors, to discuss practical and sustainable integration of evidence-based lifestyle interventions into diverse mental health care contexts. Here we summarize the priorities and opportunities identified from the summit, focusing on: a) inclusive implementation strategies, b) emergent trends in lifestyle psychiatry, and c) future directions for lifestyle psychiatry and the LifePsych Society.

As to implementation strategies, there was broad consensus that, while published evidence has increased dramatically, more effort is needed to implement evidence-based interventions sustainably and effectively in diverse mental health care settings[3,4]. Various examples illustrated how principles of implementation science can be adopted to deploy lifestyle interventions flexibly across the continuum of care[4,5]. The importance of continuously evaluating locally implemented interventions was highlighted; this is essential in supporting adaptations based on feedback and changing circumstances, while providing a foundation for research to support their translation across different settings[3,5].

Advancing lifestyle psychiatry also requires developing and implementing culturally responsive and sustainable interventions in collaboration with colleagues from low- and middle-income countries. To meet the needs of target populations, interventions must be deeply rooted in the cultural fabric of the communities they aim to serve. Early engagement with local stakeholders was recognized as a key factor in ensuring that lifestyle interventions respect local traditions, beliefs, and capacities of the clinical and public health services involved[6].

Co-creating interventions with local experts as equal partners fosters a sense of ownership, helping to maintain momentum and continuous improvement as needs evolve[5,6]. Leveraging peer and community support networks can be particularly effective in resource-limited settings. Community-based lay health workers can be trained to deliver interventions, thereby expanding reach and reducing costs. This delivery model empowers individuals and strengthens community bonds, which facilitates sustainable behavior change.

Alongside individual-level interventions, it is vital that social determinants of mental health, such as food insecurity, are addressed to ensure the provision of comprehensive care[5]. Overall, the successful implementation of lifestyle psychiatry combines

implementation science, cultural sensitivity, and community engagement to meet the needs of diverse populations worldwide[6,7].

As to emergent trends, it was acknowledged that broadening the scope of lifestyle psychiatry by researching and evaluating innovative therapeutic modalities is essential for securing its role in the future of mental health care. Summit discussions highlighted the potential of mobile health applications and wearable devices to monitor real-time physiological and behavioral data – such as activity levels, sleep patterns, and heart rate variability. This supports the delivery of scalable, personalized lifestyle interventions with regular feedback and tailored adjustments.

The LifePsych summit highlighted the many opportunities that digital technologies offer for health promotion[8], especially for individuals with mental illness. However, it was emphasized that these technologies should complement, rather than replace, the traditional elements of health promotion, and that low-resource settings may face additional barriers towards technology adoption, which have yet to be overcome.

The discussion also addressed a paradox in using digital tools to improve lifestyle behaviors: the very technologies designed to promote health may lead to sedentary behavior and excessive social media use[1]. The importance of researching digital device usage as a "new lifestyle factor" was emphasized in this context. The focus is understanding how to utilize these technologies positively while mitigating their potential downsides[8].

Other innovative therapeutic modalities were also identified as promising areas for future research. Mindfulness, in particular, was highlighted as an increasingly evidence-based approach for improving mental health, especially in trauma recovery and stress reduction[9]. The broad applicability of mindfulness-based interventions was also recognized, as they are accessible, adaptable across cultures, and require minimal resources. Additionally, more nascent context-specific therapeutic approaches were discussed, including outdoor activities combining physical exercise, exposure to nature, nutritional interventions, psychoeducation, and community engagement to enhance mental health outcomes[7].

Concerning emerging research, recent mechanistic discoveries on how lifestyle behaviors may influence mental health – for example, by modulating inflammation, neurotrophic factors, and the microbiome-gut-brain axis – were identified as rapidly developing and promising sub-fields within lifestyle psychiatry[1,2].

These emerging innovations reflect a shift toward multidisciplinary and integrative approaches. To maximize impact, we must work with relevant bodies to develop and disseminate training in the evidence base and its application, and, in partnership with our colleagues in low- and middle-income countries, to ensure the development of culturally responsive, acceptable and engaging interventions. To facilitate this, sustained collaboration with stakeholders, from the inception of ideas right through to real-world implementation and scaling up, is crucial to achieving meaningful global mental health impact.

As to future directions, it was acknowledged that the future of lifestyle psychiatry holds significant promise, driven by a commitment to continuous research and refinement of evidence-based, culturally sensitive, and scalable approaches. The LifePsych Society aims to propel the field by fostering an international network that generates support, motivation, and exchange of resources and materials. Within this, a central priority is to make a tangible impact on global health care systems through accelerating the implementation of evidence-based interventions to improve mental health outcomes.

The collaborative environment of the LifePsych Society will facilitate ideas sharing and mentorship, and it has the geographical reach required to support multi-site studies and independent replications. The Society will also enable the co-creation of globally applicable resources that can be tailored to specific contexts to address diverse health care needs. A focus on inclusive development and implementation will remain paramount by incorporating voices from different backgrounds, disciplines and settings.

To operationalize its mission, the LifePsych Society will now move towards establishing a formal structure with clear goals, measurable objectives, and regular meetings. A declaration of intent will outline its vision, ethical guidelines, and strategic priorities, facilitating partnerships and attracting funding. Within this, the Society is exploring two initiatives aiming to encourage global uptake and promote interdisciplinary research: a) creating region-specific sub-networks to address local needs and increase the accessibility of in-person meetings, and b) developing a digital knowledge hub for disseminating research, case studies, and best practices.

In conclusion, the future of lifestyle psychiatry depends on fostering inclusivity and innovation to produce impactful research and widescale implementation. As lifestyle psychiatry is poised to become an integral component of global mental health care[1,2], the LifePsych Society aims to facilitate global collaborations, establish shared priorities, and enhance the capacity for meaningful research across diverse settings.

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How can measurement-based care improve psychotherapy processes and mental health service delivery? A synthesis of expert perspectives

Measurement-based care (MBC) is an evidence-based multicomponent practice in which: a) patient-reported outcome measures are routinely collected; b) the feedback from these measures is shared with the patient; and c) the therapist and the patient use this feedback to make shared decisions regarding treatment[1-3].

Although MBC has been recognized as a key ingredient to improving mental health care[4], its effect size varies substantially among studies, from negligible to large[5]. MBC effectiveness seems to depend on type of feedback, treatment setting characteristics, implementation quality, and cultural differences[1]. To optimize MBC, we need a research and development agenda to understand the mechanisms involved for the various stakeholders in different treatment settings and cultures.

There are established ethical, clinical and institutional rationales for using MBC. Its tools can be used to model change, assess treatment response, personalize care, and prevent treatment failure. MBC can help patients feel more engaged, thereby improving their self-reflection and sense of ownership of the therapeutic process. By improving patient-therapist communication and collaboration, MBC can improve outcomes. Aggregated MBC data can support organizational goals such as quality monitoring and improvement efforts, and satisfy accreditation or other accountability standards. However, due to a variety of implementation barriers, the empirically based promise of MBC remains under-realized in real-world practice in health care systems around the globe.

The International Network for Psychotherapy Innovations and Research into Effectiveness (INSPIRE) is a group of leading researchers, developers and clinicians from Europe, Asia and the US who have been collaborating since 2017. The group focuses on developing scientific knowledge about improving mental health outcomes for patients by integrating MBC in clinical practice. The group is system-agnostic, has experience researching and developing many of the most widely used MBC systems used today, and prioritizes collaboration over competition in a shared aim for scientific knowledge integration.

The group recently synthesized collective insights to suggest a conceptual framework for how MBC works and how it needs to develop. There are three key themes in how MBC works to improve psychotherapy and mental health service delivery: adding perspectives; prompting action; and activating resources.

MBC provides information or perspectives not otherwise available to the therapist and the patient in the natural flow of the therapeutic interaction. For instance, it allows a comparison of various elements of the individual patient's clinical picture to relevant groups.

MBC provides prompts and support for therapists changing or adjusting their approach to an individual patient. A core example comes from MBC with clinical support tools[6,7], which offer feedback that one should address the therapeutic alliance or establish shared expectations. Direct alliance feedback prompts therapeutic focus on collaboration and the patient's needs in situations where an alliance rupture has occurred.

MBC activates resources within the patient, for example by providing insights and reflection, or supporting involvement in care. Responding to MBC measures may increase the experienced dose of treatment, in that it allows patients to reflect on their progress outside the sessions. Moreover, MBC supports collegial and professional discussion, interdisciplinary collaboration, and team competence. As such, this is both an individual stakeholder and a systems level process. In summary, activating resources works by empowering patients, therapists and systems in a program evaluation approach, aimed to improve treatment.

Five sub-themes were identified by INSPIRE collaborators as needed developments to enhance implementation and clinical use of MBC. First, *technological innovation* refers to the need for user-friendly, safe, equitable and available digital solutions to support MBC implementation. Too often, clinically and psychometrically sound MBC systems do not gain broad acceptance due to technological delivery barriers. Second, the MBC approach should be integrated into *training and practice improvement* efforts, such as graduate and professional training, coaching and supervision, to emphasize MBC as a dyadic process that demands clinical attention, skill and finesse. Third, *dissemination and implementation* refer to the need for translational practices. Advocacy is an important part of these efforts and may include communication and education directed toward patient end-users, to develop awareness and, ideally, a mandate for data-informed treatment. Fourth, *broadening scope* refers to the need for innovative research to explore applications beyond symptom measurement to inform MBC, to ensure the inclusion of other relevant patient experiences. Fifth, there is a need for evidence-based models of MBC as a vehicle to support *organizational learning and development*.

In this letter, we have synthesized the perspectives of an international group of experts to inform current MBC practice. We hope to contribute useful heuristics and language to structure trainings, communication and implementation processes for MBC. Better integration into clinical training programs, allowing for MBC to be part of basic clinical skills and identity, may be particularly benefi-

cial[8]. The idea that MBC can activate therapeutic resources within the patient seems especially important, considering current resource restraints of health care systems. Furthermore, clinical support tools, such as advice based on nearest neighbor and other machine learning approaches[9], are available in MBC research but not widely implemented in practice.

We suggest that research and development concerning MBC needs greater coordination across settings, cultures and systems, to balance the mutually dependent processes involved. Parallel investments in specific measure development, technological development, implementation science, clinical training and end-user dissemination can support greater forward movement, *if they are coordinated*. Measure-agnostic approaches, in which concepts co-develop rather than compete, and in which anonymous data on clinical use and implementation processes can be shared in the network, seem necessary for development of the field as a whole. MBC, as a shared technology that spans diagnoses and clinical orientations, supports the needed transition from a standard atomistic to a continuous clinical research model of care in learning organizations, in which all patients are invited to have their data part of ongoing clinical studies and innovations.

In conclusion, MBC has the potential to add perspectives, prompt action, and activate resources, all of which can lead to better patient outcomes. We suggest that the field of MBC needs to adopt a strategic approach to learning and knowledge transfer across many current boundaries.

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Shaping the future of autism care: the need for a precision medicine approach

The field of autism care is at a critical juncture. Despite significant efforts, there has been little to no improvement in the efficacy of interventions in recent decades[1]. The most widely implemented interventions are based on a categorical framework, assuming that broadly applied strategies can meet the needs of the majority of individuals with autism. They incorporate behavioral techniques targeting domains believed to be foundational to autism (e.g., motivation, joint attention, self-initiation), with the assumption that improving these skills will bring positive effects across a broad range of outcomes.

Systematic reviews show that, at the group level, these interventions demonstrate some efficacy, particularly in enhancing IQ and certain aspects of language[1]. However, outcomes are inconsistent, and many individuals experience limited gains. This variability likely reflects the limitations of current diagnostic criteria, as individuals with autism often present with diverse and divergent profiles, which are rooted in distinct neurobiological underpinnings and frequently accompanied by other co-occurring diagnoses.

The autism field has increasingly recognized these challenges, emphasizing the need for personalized interventions, and exploring biomarkers that may help predict intervention outcomes. Furthermore, the neurodiversity movement has highlighted the importance of stakeholder input in defining intervention targets and techniques. However, innovation at the level of intervention design and implementation has been limited, resulting in slow progress.

We argue that the principles that have guided the development and evaluation of the most widely used autism interventions represent a barrier to advancing precision medicine, and that, without a fundamental redesign (moving beyond overly broad approaches to those grounded in precision medicine principles and current evidence-based taxonomies), efforts to tailor interventions to individual needs are unlikely to yield meaningful success. Interventions should be developed based on both theoretical frameworks and clinical evidence to address distinct aspects of the clinical phenotype, and applied according to each individual's profile. Importantly, they should be designed in collaboration with stakeholders

to ensure scientific rigor, social validity, and acceptability.

The evolving understanding of clinical phenomena has highlighted that categorical approaches exemplified by the DSM and the ICD cannot fully capture clinical complexity and heterogeneity, spurring re-evaluation of their validity and utility[2]. Consequently, there has been an increased embrace of dimensional alternatives[3], such as the Research Domain Criteria (RDoC) and the Hierarchical Taxonomy of Psychopathology (HiTOP), which provide a testable framework for exploring the relationships between narrowly defined, biologically meaningful processes and granular, data-driven clinical phenotypes.

While RDoC seeks to ground psychiatric classification in a scientifically supported model of biobehavioral dimensions that transcend current disorder boundaries, HiTOP aims to establish an empirically-based classification system rooted in the natural covariance structure of symptoms and traits, organizing them into a hierarchical structure, ranging from narrow clusters of features to more general spectra. By organizing symptoms into a hierarchical structure and highlighting the interplay of risk and resilience processes at both individual and environmental levels[4], RDoC and HiTOP allow for intervention at multiple levels – whether targeting specific symptoms or broader spectra. This approach holds the potential for more effective and personalized interventions, addressing both the specific needs and the broader dimensions of the phenotype.

Indeed, interventions that draw on the above described approaches have shown significant promise. For instance, the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP)[5] – designed to target negative affect, cognitive processing biases, and behavioral avoidance vulnerability processes – has demonstrated significant effects across diagnostic categories[5]. Further, recently emerging approaches provide discrete evidence-based modules tailored to address specific symptom presentations. For instance, when compared to standard treatments and usual care, the Modular Approach to Therapy for Children with Anxiety, Depression, Trauma, or Conduct Problems (MATCH)[6] was significantly more effective for addressing symptoms related to anxiety, depression, and disruptive behavior in youth[7]. Crucially, transdiagnostic and modular approaches are aligned with clinical realities, as previous studies have demonstrated that clinicians prioritize addressing specific presenting symptoms rather than relying on traditional diagnostic categories[8].

There have been few efforts to integrate these approaches into the design and implementation of autism interventions. Instead, most intervention studies take an "all comers" approach, using a standardized session content sequence rather than tailoring specific manual elements. While treatment targets may be individualized (e.g., per needs assessment), the therapeutic strategies are not; they tend to be applied consistently across different targets and child factors. Moreover, the therapeutic mechanism is often assumed rather than systematically tested. This is because the efficacy of components and techniques for addressing specific symptoms or skills has not been individually tested, and the intended outcomes are often far removed from the proposed therapeutic mechanisms.

The design and application of current intervention packages also pose challenges in identifying predictors of treatment response. It remains unclear whether predictors are specific to particular techniques or aspects of the intervention, or they pertain to the entire sequence of sessions used in a given trial.

Given the current state of the autism intervention field, there is a lack of clear guidelines for identifying which approaches are best suited to specific individuals. In contrast to the structured design and empirical evaluation of interventions, clinical practice often involves clinicians selecting techniques from comprehensive intervention manuals based on each child's unique needs. This disconnect between how interventions are developed and trialed in research and their application in real-world settings calls into question the external clinical validity of the accumulated evidence base.

We propose that researchers, guided by theory and evidence, carefully select specific components (akin to developing modules) from existing comprehensive interventions to target well-defined, empirically-validated symptom domains or aspects of functioning. These components should be tested through adaptive trial designs while identifying profiles of individuals most likely to benefit. Furthermore, we emphasize the importance of leveraging transdiagnostic research to understand risk and resilience processes across neurodevelopmental and neuropsychiatric conditions, including autism. For example, self-regulation difficulties and anxiety contribute to various symptoms, including insistence on sameness, compulsions, and challenging behaviors[9]. Evaluating interventions such as MATCH and UP, which target self-regulation and anxiety, in children exhibiting these clinical challenges – particularly those with autism – represents a crucial next step, especially given the lack of effective treatments addressing insistence on sameness in autism.

We advocate for a cautious and evidence-based transition to transdiagnostic and modular interventions, as opposed to their uncritical adoption, in the autism field. It is crucial to conduct thorough evaluations in consultation with individuals with autism, caregivers and clinicians to identify modifications that align with community priorities and preferences. This approach not only promises better outcomes but also acceptance among affected individuals, families and clinicians, reducing training redundancies and associated costs.

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Leveraging brief video interventions to increase treatment-seeking among depressed youth: a randomized controlled trial

Youth with depressive symptoms often do not seek professional help, hindered in part by stigma and limited access to mental health care. Recent digital approaches have shown promise in reducing stigma and encouraging mental health treatment-seeking intentions[1]. Brief, social contact-based videos have a particular potential to strongly influence youth, especially when delivered through the social media platforms that this population already broadly uses.

Social contact involves sharing personal stories of individuals who have experienced mental health challenges, which can help reduce stigma and encourage positive attitudes toward treatment[2]. Leveraging the accessibility and engagement potential of social media provides a meaningful advantage in reaching young adults who might otherwise avoid or delay seeking help. Although such interventions have been shown to raise treatment-seeking intentions, few studies have examined whether they produce actual behavior change, especially among youth most in need of support[3].

We conducted a randomized controlled trial aimed to address this research gap by examining the impact of three brief 2.5-3 min video interventions on treatment-seeking intentions and behavior among young adults with depressive symptoms. The videos featured young women of different racial/ethnic backgrounds (Black, Latina and White), portrayed by professional actors, who shared a scripted personal story about their struggles with depression and recovery. These scripts were informed by interviews conducted with individuals with lived experience of depression, ensuring authenticity and cultural relevance. The video interventions were compared with a written vignette conveying identical content. The study tested whether the videos' emotional and visual appeal could foster not only intentions to seek help, but also formal steps toward mental health treatment.

We recruited young adults (ages 18-25) with self-reported depressive symptoms through Prolific, an online research platform. Participants qualified on the basis of a minimum score of 5 on the Patient Health Questionnaire-9 (PHQ-9). Of the 2,624 screened individuals, 1,559 met the inclusion criterion. After excluding 14 youth who failed attention or validity tests, 1,545 participants (63% female; mean age: 22.7±1.9 years) were randomly assigned to either one of the three video intervention groups (combined N=1,159) or the written vignette group (N=386). Demographic characteristics did not differ between the study groups.

Treatment-seeking intentions were measured at baseline, immediately post-intervention, and at 30-day follow-up using the Attitudes Toward Seeking Professional Psychological Help Scale - Short Form[4]. Emotional engagement with the videos was assessed using the Emotional Engagement Scale[5]. At 30-day follow-up, treatment-seeking behavior was evaluated by asking participants if they had contacted the provided referrals or sought treatment elsewhere. The post-intervention assessment was completed by 1,533 participants (99.2%); the 30-day follow-up assessment by 1,264 participants (81.8%). Demographic characteristics did not differ between completers and non-completers.

We found an effect of the video interventions on both treatment-seeking intentions and actual behavior. For treatment-seeking intentions, a 2 x 3 ANOVA revealed a significant group-by-time interaction ($F_{1,2}$=4.0, p=0.018). A significant change was observed between baseline and 30-day follow-up ($F_{1,1}$=8.0, p=0.005). Among the 1,098 participants not in therapy at baseline (71.1%; N=834 video, N=264 vignette), a significant association was found between study group and seeking treatment post-intervention (χ^2=5.8, p=0.016). Participants who sought help showed greater increases in intentions (baseline to post-intervention: 0.71±1.4; baseline to 30-day follow-up: 0.96±1.7) compared to non-help seekers (0.34±1.2 and 0.21±1.5, respectively) (t=2.4, p=0.016; t=3.8, p<0.001).

Emotional engagement emerged as a critical factor in driving these outcomes, with higher reported engagement correlating with greater increases in intentions (r=0.145, p<0.001) and a higher likelihood of seeking help (r=0.1, p<0.001). Notably, 84% of help seekers reported high emotional engagement with the video, compared to 61% of non-help seekers (χ^2=13.8, p<0.001).

These results align with Mayer's cognitive theory of multimedia learning, which posits that dual engagement of visual and auditory channels enhances cognitive processing and retention over time[6]. Video content thus appears to foster deeper cognitive and emotional processing than static text, contributing to sustained impact. Given the widespread adoption of social media among young adults, brief video interventions may provide a scalable, practical approach for disseminating mental health messages. Culturally resonant videos – featuring relatable characters from diverse backgrounds – may further enhance engagement, broadening the intervention's relevance and efficacy across diverse youth populations[7].

The study focus on young adults with depressive symptoms, rather than the general population, highlights the value of targeting interventions for those in greatest need. Many public mental health campaigns aim to shift general attitudes but often fall short in prompting behavioral change among those who would benefit

most[8]. By specifically addressing individuals already experiencing symptoms, our intervention successfully translated intentions into greater real-world help-seeking behavior. This targeted approach could be vital in closing the gap between mental health awareness and treatment uptake.

This pathway – from emotional engagement to intentions and ultimately to actual help-seeking behavior – is a rare finding in stigma research. Few interventions have demonstrated a shift from intentions to real-world behavior, as most research has focused solely on treatment-seeking intentions[9]. The pathway underscores the critical role that emotional investment plays not just in shifting perceptions but also in overcoming barriers to action. The association between emotional engagement and increased treatment-seeking intentions suggests that emotionally resonant videos effectively drive intentions, a crucial first step toward encouraging behavioral change. That participants moved beyond intentions to real-world treatment-seeking marks a significant contribution to the field, showcasing the potential of emotionally engaging interventions to transform mental health awareness into actionable outcomes for vulnerable populations.

Some limitations of this study need acknowledgement. Our online recruitment strategy may limit generalizability, and social desirability bias might affect self-reported help-seeking behavior. Additionally, the 30-day follow-up period, while informative, is relatively short. Extended follow-up could better assess the long-term sustainability of behavior changes and verify their effect. Future studies might also explore social media engagement metrics, such as "likes" and "shares", as measures of intervention reach and impact.

In conclusion, our findings demonstrate the effectiveness of emotionally resonant, interpersonal video content in driving behavior change among young adults with depressive symptoms. Brief social contact-based videos provide a practical and scalable approach to reducing mental health stigma and improving access to care. As youth increasingly rely on digital platforms, these results highlight the need for targeted, accessible interventions to bridge the gap between mental health awareness and action. Future research should focus on refining these digital strategies by exploring social media engagement metrics and conducting extended follow-ups to maximize their long-term impact and reach among vulnerable youth populations.

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The videos used in this study are available at https://vimeo.com/855523889/b2404ed527, https://vimeo.com/855524132/d80c1eca26, and https://vimeo.com/855530021/21534c2245.

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Incorporating suicide prevention in the WPA Action Plan 2023-2026

The WPA Action Plan 2023-2026 has structured its commitments around two main components: advancing good clinical practices and enhancing preventive public mental health initiatives[1-4]. The Plan is aligned with the United Nations 2030 Agenda for 17 Sustainable Development Goals (SDGs), emphasizing the critical intersection of SDG 3.4 on mental health and well-being with the remaining SDGs[5]. Reducing suicide rates is one of the indicators for the progressive fulfilment of SDG 3.4, highlighting the urgent need for effective public mental health strategies and clinical interventions.

A total of 970 million people live with a mental disorder worldwide, accounting for 13% of the global population. Of these, females make up 52.4%[6]. Approximately 418 million disability-adjusted life years (DALYs) are attributable to mental disorders (16% of global DALYs)[7]. The economic value associated with this burden is estimated at about USD 5 trillion[7]. Nevertheless, on average, countries allocate just 2% of their health budget to the treatment and prevention of mental health conditions[6], a level of investment that is largely inadequate to tackle the unmet mental health needs.

Despite a 36% decrease in rates over the last 20 years, suicide still claims over 700,000 lives annually and remains one of the leading causes of death worldwide among young people[8]. The decline in rates is not uniformly distributed across countries and regions. For instance, in the World Health Organization (WHO) Region of the Americas, suicide rates have increased by 17% during the same period[6].

The risk factors for suicide are complex, requiring multifaceted prevention strategies that include treatment of underlying psychiatric disorders, restrictions on access to means of suicide, and comprehensive public and clinical health interventions[9]. The strongest risk factor for suicide is a previous suicide attempt[8]. Globally, for every suicide death, there may be up to 20 suicide attempts[6].

Timely treatments and ongoing follow-up care for individuals with a history of suicide attempt are among the best practices. One such intervention is the WHO Brief Intervention and Contact (BIC) Program, which is at a crossroad of health care-directed psychiatric treatment strategies and public mental health approaches, utilizing community resources and volunteers[10]. The program is an essential post-suicide attempt strategy within a comprehensive chain-of-care model, underscoring the importance of ongoing structured follow-up in reducing suicide risk[9]. It also emphasizes that public mental health and clinical components must work together, mutually strengthening each other to achieve the best possible outcomes on a broad scale.

The objective of the WHO BIC Program is to reduce a person's risk for suicide post-discharge by enhancing engagement in treatment, building self-efficacy, and increasing social support and connectedness[11-13]. The program consists of two major elements: a brief motivational session prior to discharge from a hospital after a suicide attempt, and a structured support for 18 months after discharge, with more intensive follow-up at the beginning and gradual attenuation after three months, according to a set schedule.

The program was evaluated in a multicentre randomized controlled trial (RCT) conducted in five countries (Brazil, India, Iran, Sri Lanka and China)[10] within the WHO SUPRE-MISS initiative[14]. The RCT assessed the effectiveness of the program for individuals who presented at an emergency department following a suicide attempt. There was a statistically significant reduction of suicide rate in those who received the program in comparison with a control group that only received treatment as usual[10].

The WPA Action Plan 2023-2026 aims to promote the integration of the BIC model and its evaluation methods into WPA Member Societies' clinical practice, to reduce mortality due to suicide. The description of the BIC Program and the evaluation methods are available on the WPA website, along with supporting video materials on how to perform BIC training and follow-up contacts. Both a pre-post design and a more rigorous RCT protocol are presented on the website for those who want to implement and evaluate their local BIC intervention.

The aim of the straightforward and easy-to-implement pre-post design is to ensure that each local hospital, clinic or ward can readily integrate evaluation activities into ordinary clinical practice, and estimate results in local suicide preventive work. This approach can help uncover the local potential and any hindrances that may be faced in conducting suicide preventive initiatives, offering critical insights into local structures and resources.

Incorporating the BIC model and evaluation in clinical practice not only targets immediate suicide prevention, but also strengthens capacity building of young clinicians in research methodology in different continents. This, in turn, can foster trans-cultural collaboration among mental health professionals by promoting a comprehensive and culturally sensitive approach to care, as the WPA includes 147 psychiatric associations from around the globe.

In line with SDG 17, which emphasizes the importance of partnerships for sustainable development, collaboration among governments, professional bodies (such as WPA Member Societies), private entities, patients and clients, and civil society is vital for advancing mental health worldwide. This BIC Program, as a collaborative effort, is crucial for addressing the pervasive and escalating challenges of mental health and suicide globally.

By promoting evidence-based interventions such as the BIC Program, the WPA Action Plan 2023-2026 underscores the WPA's leadership role in providing strategic guidance, fostering innovation, and creating opportunities for knowledge exchange and capacity building across diverse cultural and health care settings. This comprehensive approach ensures that mental health care is not only evidence-based, but also adaptable and sustainable across different regions and communities.

The WPA also promotes the EDIT principle[15], which stands for Equality across genders, ages and ethnicities, Developmental life course perspective, Inclusion of under-represented groups, and Transcultural awareness. By embedding these values into its initiatives, such as the BIC Program, the WPA ensures that public mental health and psychiatric clinical activities, research, education and

meeting organization are inclusive and responsive to the diverse cultural and developmental needs of global populations.

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Patterns and innovations in the unfolding of Latin American psychiatry and mental health

The 24th World Congress of Psychiatry, held in Mexico City in November 2024, hosted a Presidential Symposium entitled "Past, present and future of Latin American psychiatry", dealing with patterns and innovations in Latin American models and programs for diagnosis and care in clinical psychiatry and public health, within a broad international framework. Here we summarize some highlights of that Symposium, focusing on the areas of conceptualization of health, diagnosis and health care.

Concerning conceptualization of health, the World Health Organization (WHO), in its 1948 inaugural constitution, proclaimed that health is a state of complete physical, emotional and social well-being, and not merely the absence of illness or infirmity. Quite notably, the Andean cosmovision held that health is a state of harmonious equilibrium among the person's interior, social and natural worlds[1], a definition of stunning post-pandemic value.

Concerning diagnosis, the WHO assumed responsibility for decennial revisions of the International Classification of Diseases (ICD) in 1946. However, the complexity and particular vicissitudes of disease classifications in the field of psychiatry and mental health have stimulated the design of more detailed and comprehensive diagnostic models. In these efforts, some Latin American colleagues have been pioneers, such as the Venezuelan D. Curiel, developer of the first national collaboration center for the ICD; the Peruvian H. Delgado, as systematizer of psychopathology and clinical psychiatry; the Chileans J. Horwitz and J. Marconi[2], who published in 1966 the world's first structural and operational definitions of mental disorders; and the Brazilian J. Leme Lopes, who put forward a multiaxial conception of psychiatric diagnosis as early as in 1954. Another breakthrough has been the Third Cuban Glossary of Psychiatry, which represents both a systematically constructed adaptation of ICD to national reality and needs and an application of the multiaxial approach[3].

The WPA International Guidelines for Diagnostic Assessment (IGDA), based on an international survey of all WPA Member Societies and published in 2003, also exemplify this comprehensive approach. In 2010, the WPA Classification Section and the International College of Person-Centered Medicine published a theoretical model for Person-Centered Integrative Diagnosis (PID), providing an integrated assessment of the totality of health, including ill and positive health, risk and protective factors, and experience and values at stake when seeking clinical care. The PID model, along with ICD terms and codes for identifying mental disorders, were applied as a Latin American practical guide for psychiatric diagnosis (GLADP-VR)[4]. It has been found through surveys[5] that Latin American psychiatrists who used this guide preferred this option to the original ICD-10 as well as to the DSM-IV and DSM-5.

Concerning health care, the Andean cultures have promoted – since early times – accompaniment, social commitment and solidarity in the care for health issues and general well-being. This has been expressed in Quechua and Aymara terms meaning "let's go all together, nobody is to be left behind" and the continued validity of ancestral medicine as shown by the Andean Health Organization[6]. Such cultural tenets are, however, seriously threatened and undermined by the prevalent dehumanization and commercialization of modern societies.

Current health care throughout Latin America, including both mental and physical health, is plagued by the fragmentation of health services, their severe underfunding (in reference to the standards of the Organization for Economic Cooperation and Development), and the grossly unequitative distribution of health services and health professionals across socio-economic and ethnic groups and rural vs. urban areas. This ongoing challenge is consistent with the recognition by the United Nations of Latin America as "the most unequitative region of the world"[7].

Psychiatric care in Latin America, as in many areas around the world, was asylum-based until the middle of the 20th century. Since then, quite slowly and irregularly, the settings and purpose of mental health care have been evolving towards community-based care and the clinical and social recovery of psychiatric patients. The fragmentation, underfunding and unequitative distribution of

health services, however, remain active and strongly limit progress.

At the same time, intriguing conceptual and strategic health developments have been emerging in Latin America, perhaps more intensively than in other world regions. The major WHO Conference on Primary Care in Alma Ata (1978) has had its key message powerfully reformulated by one of its architects and WHO Deputy Director General, the Peruvian D. Tejada de Rivero, as "integral care of all by all". Recent conferences of the Latin American Network of Person Centered Medicine have enriched and further developed this health strategy by centering it on people and adding inter-care or mutual care to it[8].

In terms of horizons envisioned for the future emerging from the Mexico City Symposium, one may list the following: a) strengthening the diagnostic value of identified disorders through person-centered, contextualized and development-related information; b) broadening the scope of diagnostic models through the diagnosis of whole health status (both ill and positive health) and the elucidation of risk and protective factors as well as experience and values pertinent to seeking care; c) potentiating care activities by adding to the pointed treatment and alleviation of disorders the stimulation of internal resources, the engagement of contextual supports, and the promotion of longitudinal personal development (from personal history to personal life project); and d) consideration of the heuristic value of the person-centered approach to enhance the understanding of and actions in health, education and other social activities, and of the emerging concepts of whole person, whole health and whole care.

Some of these horizons have been recently outlined by the Pan American Health Organization[9]. They are quite consistent with the 2015 United Nations Sustainable Development Goals, anchored on five Ps (Person, Planet, Peace, Prosperity and Partnership).

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Reflections on the current status of psychiatric epidemiology and public mental health

In October 2024, our WPA Epidemiology and Public Health Section organized a meeting in Bangkok, Thailand. This was the 20th meeting of our Section, founded in 1967, which for decades has convened psychiatric epidemiologists together to share research and develop collaborations. In this meeting, we engaged scientists from 33 countries across six continents. The theme was "Changing environments, well-being and population mental health", reflecting the speed and scale of change across the world which is affecting population mental health.

Since its origins, psychiatric epidemiology has grappled with measurement of mental health conditions and methods to assess their population distribution, causes, correlates and outcomes. Debates still unfurl over what constitutes mental health, and the reliability, validity and utility of our diagnostic systems[1]. These discussions are especially useful when involving colleagues from countries and cultures with different norms, health systems, and ways of thinking and being.

Within these long-standing debates, interest in mental health and its determinants has been galvanized in recent years, due to a confluence of factors, including the COVID-19 pandemic[2], the rise of social media, the visible impacts of climate change[3], and increases in global conflicts, displacement and forced migration. Indeed, increases in mental health and distress in recent years have been documented in many countries. The role of psychiatric epidemiology has thus never been more important, in that designing rigorous studies aimed at accurate, comprehensive and population-based assessments of disorder and distress is critical to documenting the scope and magnitude of these problems and the potential interventions to address them.

Collecting data on these phenomena has never been more possible, and yet never been more challenging. More possible, because across the world there are now many new streams of data. We have greater access to electronic health records, linked population registries, and digital devices that track our steps, sleep and heart rate, and provide accessible modalities for querying populations about their mood and stressors. Moreover, major efforts are ongoing to collect large databases for genetic sequencing. More challenging, because fundamental issues of selection bias, undefined target populations, and incomplete phenotyping threaten the validity and utility of the science that we produce using these exceptional-

ly large resources. Further, we are called to improve the ethical conduct of our research in people most vulnerable to exploitation and harm[4].

All this leads to a fundamental question: what is psychiatric epidemiology today, and what do we want to be as a field? In part, we are the field of counting – counting the ill, counting lives lost. We are also the field tasked with identifying the causes of these counts within and across populations. In that sense, we are also tasked with solidifying the frame of what we will theorize, measure and analyze as potential causes. New tools for identifying the biological underpinnings of brain and behavior are exciting developments for psychiatric epidemiology. Yet, among the many themes of our meeting in Bangkok, a renewed challenge to seriously consider social determinants of health emerged as paramount.

In many countries there are legacies of conflicts, war and oppression, and political regimes that have expanded or contracted their people's ability to make meaningful connections and develop resources for families and communities. Indeed, it is evident that the social determinants of mental health are quite similar across countries and cultures[5]. Those exposed to trauma, to poverty, to instability at home and in their communities have increased risks of a wide range of psychiatric disorders, from depression and anxiety to post-traumatic stress disorder and psychosis. The differences within and across countries are often in the prevalence of these experiences, based on the political regime, on response to poverty through national policy, and on public and medical health systems that provide service resources for those affected. Global conflicts remain in the forefront not only of our scientific discussions, but also of our scientific community. The effects of recent political violence on the incidence of trauma and psychiatric disorders in many regions across the world contribute in fundamental ways to current population mental health.

The legacies of global conflict on our scientific understanding of social determinants of mental health is just one part of the story, however. As scientists, we are charged with providing rigorous methods by which humanity's experiences of these events can be documented, but often we are experiencing the events ourselves in our communities. Conducting research in these circumstances is often both vital and dangerous for researchers themselves. Data collection efforts across the world were disrupted due to the COVID-19 pandemic, and members from currently conflict-affected regions cannot participate in our meetings for safety reasons. This instability limits our ability to bear witness to suffering, in both the scientific literature and in exchanging scientific ideas with our peers.

A letter to the editor published in the *British Journal of Psychiatry*[6], that was quoted at our meeting in Bangkok, criticized a study of psychiatric patients' symptoms after nights of rioting in Belfast in 1969[7]. These riots occurred amid The Troubles, a 30-year period of political violence in Northern Ireland that had profound psychological consequences, elevating levels of mental disorders across multiple generations. The author of the letter criticized the study based on the lack of a systematic random sample, and the potential for selection bias therein. The author of the study responded with a stunning turn of phrase: "If one were to attempt a random sample in these circumstances, one might well encounter a random bullet".

Like in Belfast during The Troubles, psychiatric epidemiological research has to be conducted while navigating complex political landscapes, avoiding sometimes metaphorical and sometimes literal bullets[8]. In conflict-affected regions, understanding complex historical and social contexts is essential for both the safety of researchers and the validity of findings. Yet, there is tremendous promise for the future of psychiatric epidemiology across the world. Innovations in digital technology for collecting data and delivering interventions across the world, even in the most marginalized places, hold promise for our abilities to make a difference. In our meeting we learned about innovative new technologies[9], with high-caliber science applying a critical eye towards assessment and validity.

We are in a different world as we emerge out of the global pandemic, and psychiatric epidemiology must continue to shift alongside the needs of the populations that it serves. Within these changing environments, however, central truths remain that those with less power, resources and opportunities are those most affected by mental health problems, and that these imbalances often persist across generations and can be enhanced in periods of conflict. Our ability to conduct rigorous research has to adapt to these realities, while maintaining ethical standards and scientific integrity. It requires innovative methodologies that balance scientific rigor with sensitivity to vulnerable communities, and must be coupled with a commitment to translating findings into actionable policies that promote mental health equity.

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Report of the WPA Scientific Section on Quality Assurance in Psychiatry

The WPA Section on Quality Assurance in Psychiatry focuses on quality improvement initiatives in the mental health field internationally. Recognizing that there are significant gaps between what is known to be effective (best practices) and what is actually delivered, the Section attempts to define barriers and explore solutions to improve the quality of care rendered in different settings. Defining the optimal characteristics of practice guidelines and indicators, reviewing established guidelines, and contrasting guidelines for the same disorder among different countries have been among the main activities of the Section[1]. Other efforts have explored quality assurance initiatives of systems of care and the impact that these projects have had on clinical outcomes.

The Section was founded in 1995. During the past three decades, it has organized symposia at every World Congress of Psychiatry and at numerous WPA meetings. It has explored the development, dissemination, implementation and revision of guidelines mainly for schizophrenia (e.g., the English version of the S3 Guideline for Schizophrenia by the German Association for Psychiatry, Psychotherapy and Psychosomatics, DGPPN[2]), comparing their quality across countries by means of the AGREE instrument[3-5]. Members of the Section have published numerous articles and book chapters on psychiatric treatment guidelines.

The related issue of quality indicators of mental health care systems[6,7] has also been a focus of the Section, in collaboration with the European Psychiatric Association and the World Health Organization (WHO) Collaborating Centre DEU-131, partly supported by the German Federal Ministry of Education and Research. The resulting work has been published, presented and discussed at various international meetings.

"Quality" is important for mental health systems from several perspectives (i.e., the person, family, service providers, policy makers), and improving quality contributes to destigmatization. Quality of care can be promoted by means of the PDCA (Plan, Do, Check, Act) cycle, which includes establishing quality policy, planning and standards; assessment (tools) for measurable quality indicators; quality control, monitoring and improvement[8]. All quality-related activities should be managed following the principles defined by ISO 9001: customer focus, leadership, people engagement, process approach, improvement, evidence-based decision-making and relationship management.

Significant gaps have been reported in the awareness, planning and delivery of quality care, but also in terms of training for psychiatrists and other mental health professionals at every level of the clinical education system. To address these topics, our Section has developed an educational online self-learning course on quality management in mental health care. The course consists of six thematic modules providing knowledge and skills for mental health care providers and other stakeholders from around the world, aiming to guide the development, implementation, improvement and promotion of quality management. It has been developed with the WHO Collaborating Centre DEU-131 and the University of Rochester, and has been promoted and presented at various international conferences, including recently the World Congresses of Psychiatry 2023 in Vienna and 2024 in Mexico City. It is freely accessible through the WPA website (wpa.learnbook.com.au/course).

According to the WHO[9], universal health coverage is achieved when "all people and communities can use the promotive, preventive, curative, rehabilitative and palliative health services they need, of sufficient quality to be effective". This is an emerging priority of health systems worldwide, and central to the United Nations' Sustainable Development Goal 3 (Good Health), Target 3.8. There is growing evidence on the relationship between quality of care and universal health coverage, especially related to the governance and efficiency of health care services and systems. Several knowledge gaps remain, particularly related to monitoring and evaluation, including equity. Further research, evaluation and monitoring frameworks are required to strengthen the existing evidence base to improve universal health coverage.

In addition to the areas of practice guidelines, quality indicators, and quality management education and training, our Section has also focused on issues related to the use of restraints (members of the Section participated in a major study on deaths related to restraints), funding of mental health services, pharmacologic treatment of alcohol use disorder, suicide prevention programs, forensic psychiatry assessment and reporting, ethical issues in psychiatry, treatment of older adults, home health care initiatives, and integration of physical and mental health programs.

Our Section plans to continue and expand its work. Accordingly, it is embarking on a project to revitalize its membership by recruiting new young members, especially from Asia and Africa. The Section also plans to intensify intra- and inter-sectional collaboration by making its website more informative. One further important step will be to rethink the concept and rename the Section (e.g., with a stronger focus on quality management and universal health coverage), to make its purpose and work more clear and attractive for potential new members.

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The role of psychiatry in primary care: WPA Section contributions

The WPA Section on Psychiatry, Medicine and Primary Care was established to foster collaboration between psychiatry and primary care, focusing on pertinent topics in health care. Here we summarize and highlight the strides made in this crucial collaboration. In addition, we present recent activities of the Section.

In the past decades, there has been significant progress in integrating psychiatry and behavioral health care into primary care settings. Given the growing recognition of the pivotal role of mental health in physical health, quality of life, and overall well-being, as well as the global shortage of psychiatrists and trained mental health professionals, particularly in low- and middle-income countries (LMICs) and rural areas, this integration has become a global public health and policy priority. Some key developments in this area include the following.

Collaborative care models involve a team-based approach, in which primary care providers work closely with psychiatric/behavioral health consultants to deliver coordinated and comprehensive community-based care for patients with mental health conditions. This approach has been found to be effective in improving patient outcomes and satisfaction, while enhancing the health care workforce's capacity to identify mental health conditions and provide support to those in need of mental health services[1].

Primary care providers are increasingly using *validated screening tools* to identify patients at risk of mental disorders, and user-friendly screenings for mental health challenges are becoming an integral part of primary care delivery[2]. This facilitates early detection and timely intervention, leading to better outcomes for patients. The cost-effectiveness of identifying at-risk and early-onset individuals is well established, as is the case with cancer, cardiac and diabetic screening programs worldwide.

Efforts have been made toward enhancing primary care providers' psychiatric knowledge and skills through *training programs and continuing education activities*. This enables primary care providers to better recognize, diagnose and manage mental health conditions in their patients. This training can also address mental health promotion and maintenance of optimal mental and physical health through lifestyle psychiatry interventions in primary care settings.

With advances in technology, *digital services* are becoming more widely available and used in primary care settings. This allows patients to receive mental health care support remotely, improving access for those in underserved areas, such as LMICs and rural areas, and patients with limited mobility. These developments also help better connect primary care providers with mental health specialists, ensuring continuity of care[3].

The relationship of *lifestyle interventions* with prevention and treatment for mental health is well researched[4]. In line with the WPA Action Plan 2023-2026[5-9], the focus on these interventions is now gaining traction. Primary health care practitioners are often the first contact point for the population and are already experts in lifestyle interventions. That should now include lifestyle interventions for mental health.

Overall, the integration of psychiatry into primary care is crucial in addressing the mental health needs of the global population and improving health outcomes. By working together, primary care providers and psychiatrists can provide more holistic and patient-centered care for individuals with symptomatic and syndromal mental health conditions, as well as collaborate in preventive and mental health promotion efforts.

As the Section on Psychiatry, Medicine and Primary Care has grown over the past few years, the number of its ongoing scholarly projects has expanded. Members of the Section collaborated in the development of a US National Institute of Mental Health (NIMH) grant addressing a novel approach to community-based mental health care in rural Malaysia. This grant focuses on a collaborative model of care, screening and assessment, and training and education of local community providers, including schools and community leaders outside the medical profession. In addition, the project utilizes cell phone-based applications developed in the region by the local University.

Section members and leadership have delivered numerous contributions at recent WPA meetings, including the World Congress of Psychiatry in Vienna in 2023, and the WPA Thematic Conference held in Malta in 2022. Topics have included the role of lifestyle psychiatry in primary care; mental health care of refugees and victims of trauma and abuse; depression, anxiety and substance abuse in primary care; and digital psychiatry. During the abovementioned World Congress, the Section leadership met with the President of the World Organization of Family Doctors (WONCA) to discuss future collaborations and the role of telemental health in primary care.

A major focus of the Section has been on training the next generation of psychiatrists in the importance of inter-professional collaboration, and engaging and empowering them during their training. Educational activities run by the Section started with the support and collaboration of the Association for Community Mental Health Promotion (ACMHP). Out of this collaboration, the SEED (Students' Education, Empowerment and Development in Mental Health) group was established. This group, headed by the Section officers, holds a monthly YouTube session for medical students and early career psychiatrists from around the world. To date, 30 videos have been produced with contributions from experts and global leaders within WPA, and a manuscript is currently in press.

Given the expanding number of projects, the Section has created workgroups in various areas of interest to its members. It is also working in collaboration with other WPA Sections on topics of common interest, such as the role of exercise in mental health with the Section on Exercise and Sports Psychiatry.

The current Section officers are committed to continuing to contribute to the growth and development of the field. As a first step, and in order to ensure that this process continues to build on previous achievements, the Section has formed a consulting group

composed of previous Section chairs and highly experienced WPA leaders, and has developed the Section's action plan 2023-2026. We would like to take this opportunity to invite WPA members to join and contribute to our Section.

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Urbanization and emerging mental health problems: the role of the WPA Section on Urban Mental Health

During the past century, there has been a constant tendency worldwide for people to move into urban areas and megacities, aiming to better living, working and health conditions, including easier access to social and health services. Out of a total world population of 8.1 billion, the urban population will rise to more than 5.5 billion by 2050[1].

Urbanization brings with it a unique set of advantages and disadvantages. While new values and novel lifestyles are more easily spread in urban society, urbanization has also initiated a dissolution of social relations and a decrease of social control, with traditional family dynamics, human bonds and schooling/working styles being disrupted. Overcrowding forces urban residents into excessive competition and continually causes tremendous stress.

These factors contribute to the development of mental health problems. The majority of novel-emerging mental disorders first appeared in urban areas. Historically, eating disorders are a clear example. A survey revealed that the incidence of bulimia nervosa shows a dose-response relation with degree of urbanization, being five times higher in cities than in rural areas[2].

Both man-made and natural disasters – such as terrorism, wars, pandemics and climate change – can bring catastrophic damage to urban dwellers. Megacities are now frequent targets of terrorism. After disasters, weak social control in cities increases criminality. Isolation, financial difficulties and loss of dignity of elderly are commonplace in megacities, leading to an increased incidence of physical as well as mental diseases. In this context, novel mental health problems that transcend existing concepts are emerging in urban areas. We psychiatrists should be more sensitive to the risks of urbanization, and should discuss how to respond to them to as great an extent as possible.

The WPA Section on Urban Mental Health was established in the year 2000 to provide a global platform to discuss urban mental health problems and their solutions among psychiatrists, epidemiologists and other experts. In 2015, the Section set up four subsections: a) global impact of demographic changes due to urbanization on mental health; b) mental health of slum dwellers (conduct problems, early pregnancies, drug abuse and traffic, comorbidity of mental and physical disorders); c) urban lifestyle and stress-related mental health; d) impact of terrorism and disasters on mental health in urban areas.

Since 2021, the renovated Section has shared the aim to establish a global platform on emerging mental health problems in urban areas, by collaborating with other WPA Sections, scientific societies, and organizations such as the World Health Organization (WHO) and the Asian Federation of Psychiatric Associations. Based on the values of collegiality, diversity, inclusion and transparency, we are planning to propose innovative guidelines to deal with such unfamiliar problems, intended for clinicians and practitioners in real-world clinical settings globally.

To fulfill our aims and tasks, we organize regular online meetings every four months, webinars (e.g., covering social isolation, aging society, youth mental health, digital mental health), and Section Symposia during all World Congresses of Psychiatry. We also aim to produce expert consensus surveys to better define priorities for action within urban mental health care domains. Since the insights of young generations are important in urban life, we are actively welcoming young members to our Section.

Social isolation is one of the crucial mental health problems of the 21st century. Since the late 1990s, in Japan – especially in urban areas – pathological social withdrawal in youth, called hikikomori, has been emerging, and now it is spreading globally[3]. Our Section has contributed to enhance the awareness of this condition internationally[3-5]. We are currently promoting a novel method of hikikomori diagnostic evaluation (HiDE), through webinars and symposia, so that it can be utilized around the world[5]. In July 2024, the WHO Regional Office for the Western Pacific (WPRO) organized the Technical Consultation on Loneliness in Cities, where our Section members had a leading role[6].

Urbanization is a crucial risk factor for social isolation and loneliness[7], and digital technology has been regarded as a possible solution, but also a possible risk factor to induce novel psychopathologies[8]. The government of Japan has used the expression "digital garden city" for a metaverse-based platform which combines the urban and rural, and is promoting its utility[9]. Such digital inno-

vations are expected to be applied as therapeutic tools to achieve early intervention for patients who have traditionally been difficult to reach with mental health care.

The digital world enables every human being to meet anyone in a virtual space, transcending the limitations of physical space and time. On the other hand, these new virtual worlds may promote a dissociation of body and mind, and give rise to novel psychopathologies that have never been imagined[10]. In addition, maladaptive usages of digital tools for self-care behaviors may induce mental health problems such as Internet/smartphone addiction and gaming disorder. Thus, our Section has started to collaborate with the WPA Working Group on Digitalization[10] to monitor and respond to mental health problems due to the novel digital city.

As urban mental health will stay at the forefront of psychiatry for the foreseeable future, the WPA Section on Urban Mental Health will continue to address the mental health problems that arise as a result of urbanization, in collaboration with other WPA Sections and other relevant international organizations, aiming to better define the many factors that contribute to urban mental health, and to formulate specific solutions and intervention programs.

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Breaking the glass ceiling: women's scientific participation in the 24th World Congress of Psychiatry

Diversity in academic and professional meetings is essential for fostering innovation, inclusive dialogue, and equitable representation of voices from varied backgrounds. Scientific meetings serve as critical platforms for knowledge exchange, cross-cultural collaboration, and professional networking[1,2]. They also enhance the visibility of clinicians and academics, facilitating recognition and professional growth[3]. However, ensuring diverse participation across dimensions such as gender, ethnicity, geographic regions, and professional standing remains challenging.

The increasing number of women working in medicine and academia reflects societal changes and the efforts of individuals and organizations over the years[4]. Previous research has explored women's participation in medical congresses, showing a strong positive correlation between the proportion of women on planning committees and the representation of women as speakers[5]. This highlights the importance of involving women in decision-making roles to improve gender equity.

The WPA Action Plan 2023-2026 emphasizes the goal of achieving equality across genders, developmental stages, inclusivity, and transcultural facets (EDIT) in clinical and public mental health practices, as well as in research[6]. Systematically collecting and reporting data on the diversity of participants and speakers at WPA meetings can inform targeted initiatives and allow to measure progress over time.

This piece represents a step in this direction, by analyzing women's representation among the scientific speakers at the 24th World Congress of Psychiatry, held in Mexico City from 14 to 17 November 2024. The Congress attracted 1,730 abstract submissions, of which 1,685 were accepted. The contributions included in the final program were 1,383. Women submitted 51% of the total abstracts, had a slightly higher (52%) acceptance rate, but accounted for 49% of the final program contributions. This slight discrepancy between acceptance rate and actual contribution may raise questions about the potential barriers preventing women from attending meetings, even when their work is accepted.

The representation of women was balanced in the presidential symposia (50%) and accepted symposia (50%). However, men remained predominant in courses (70%), Spanish language sessions (69%), meet-the-experts sessions (67%), state-of-the-art symposia (65%), distinguished lectures (63%), and panel discussions (56%). In contrast, women were more represented in the short oral poster presentations (53%) and e-poster viewings (51%). This distribution may, in part, reflect long-standing structural inequities that have historically limited opportunities for women to reach senior positions, while keeping them concentrated in junior roles, a concept that has been described as "sticky floor".

Interestingly, gender trends were apparent in the thematic content of presentations. For example, in the short oral poster presentations, some topics such as those concerning mental health users and caregivers were almost exclusively represented in contributions by women, whereas topics such as mental health economics, evolutionary psychiatry, and dissociative disorders appeared exclusively in contributions by men.

Structural barriers contributing to gender disparities in meeting attendance have been identified in previous studies. Family obligations were reported as barriers by 55% of female and 37% of male

parents/guardians; limited funding also hindered participation, with 38% of junior faculty reporting financial constraints[8]. Women are more likely to hold part-time or adjunct positions that do not provide funding for travel, further exacerbating these barriers[8]. Additional challenges include travel costs and difficulties in obtaining visas. Efforts to address these challenges could include securing travel grants for early career professionals, providing childcare support options at home or at the meeting, and enabling online meeting participation.

Barriers to participation can also manifest during the events themselves. For example, studies have shown that men ask more and longer questions than women during meetings[9]. Women may not speak up in discussions or have shorter speaking times in presentations, further reducing their visibility[10]. Women psychiatrists have reported negative attitudes about their abilities in self-promotion and networking[11]. As meeting speakers serve as important role models, promoting women in prominent sessions is essential to fostering the professional aspirations of younger women [2,12].

The 24th World Congress of Psychiatry has shown progress in promoting women among speakers. Ensuring gender diversity at meetings generates a ripple effect, inspiring institutions to adopt similar practices and fostering an inclusive professional ecosystem. Nevertheless, challenges remain. More work is necessary to achieve equitable representation across all demographic groups, from all continents and professional levels, to secure inclusion and promote meaningful participation and engagement of underrepresented groups.

Collecting and analyzing data on the broader diversity of participants in meetings is important to visualize the nuances of underrepresentation. Women are often treated as a single, uniform group, neglecting the distinct experiences shaped by factors such as ethnicity, age, motherhood, or sexual orientation. Future research could integrate meeting program data with survey responses from attendees, capturing individual-level details, to better understand participation dynamics. Building on the achievements of this Congress, future events can move closer to the goal of the EDIT principles[6].

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