Innovations to improve outcomes and uptake of psychotherapies for mental disorders: a state-of-the-art review

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Psychotherapies have been found effective in the treatment of most mental disorders. However, substantial improvements are still much needed, and many innovations of therapies are currently being developed. We review the current status of promising innovations to improve the outcomes and uptake of psychotherapies for mental disorders, discussing the largest and most recent meta-analyses. Innovations are categorized into four domains: a) the digital field (including Internet-based interventions in general; mobile interventions; serious games; virtual and augmented reality; prescription digital therapeutics; blended therapy; avatar therapy; and chatbots/artificial intelligence-generated conversational agents); b) personalized treatments (research on predictors and moderators in large randomized controlled trials; use of individual patient data meta-analyses in personalization; machine learning approaches; personalized and modular therapies; and matching therapists to patients); c) new and improved therapies (cognitive bias modification; cognitive remediation; psychedelic-assisted psychotherapies; transdiagnostic therapies; research on effective components through factorial trials and component network meta-analyses; innovations in the understanding of the processes involved in psychotherapies, including research on common factors and the therapeutic alliance, and on the fidelity vs. flexibility question; research on prevention of adverse effects of therapies, the impact of increased session frequency or progress feedback on outcomes, and methodological innovations in trial designs); and d) dissemination and simplification of therapies (task sharing, digital interventions in low- and middle-income countries; and single-session interventions). These innovations vary in their maturity, from dozens of supporting trials to few or none. Methods to assess the strength of innovations suggest that no innovation will be a paradigm-shifting "silver bullet" that dramatically increases treatment outcomes, but that progress will only be possible through multiple, incremental improvements.

Key words: Psychotherapies, innovations, digital interventions, personalized treatments, cognitive bias modification, cognitive remediation, psychedelic-assisted psychotherapies, transdiagnostic therapies, factorial trials, therapeutic alliance, adverse effects, task sharing

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Almost one billion people suffer from a mental health condition worldwide[1]. Although evidence-based treatments are available for most disorders, the burden of disease, economic costs, and personal suffering caused by mental disorders are still enormous.

Psychotherapy is a first-line treatment for most mental disorders, and is one of the main instruments to treat these disorders. Hundreds of randomized trials and meta-analyses have shown that various psychotherapies are effective across a broad range of mental disorders, including major depressive disorder[2,3], anxiety disorders[4-8], post-traumatic stress disorder (PTSD)[9,10], obsessive-compulsive disorder (OCD)[11,12]; insomnia[13], borderline personality disorder[14,15], psychotic disorders[16], and bipolar disorder[17,18].

Effect sizes of treatments of mental disorders (including psychotherapies) have been found to be comparable to those found in general medical care[19]. Moreover, in the past few decades, evidence-based treatments (including psychotherapies) have become available for large populations, especially in high-income countries, and are often included in national health services at no or relatively low costs.

Yet, significant improvements are still needed. It has been estimated that current treatments can only reduce by 40% the disease burden of mental disorders in populations under optimal conditions in which all patients with a disorder receive an evidence-based treatment[20]. Furthermore, the actual number of patients who recover under treatment is modest. We found that the response rates (defined as 50% symptom reductions) for psychotherapies were 42% for major depressive disorder, 38% for PTSD and OCD, between 32% and 38% for anxiety disorders, and 24% for borderline personality disorder[21]. This means that a large group of patients – according to our estimates, even more than half – do not respond to psychotherapies. There are also indications that mental health care has not improved over the past decades[22]. We recently found, for example, that the outcomes of mental health care for depression have been stable since the 1990s, without any improvement despite the availability of more effective treatments[23].

Treatment uptake remains limited. Even in high-income countries, only a minority of patients receive adequate care[24]. Fewer than 40% of individuals with depression, anxiety, or substance use disorders receive any form of treatment[25], and, among those who do, less than half receive care that meets minimal quality standards[26]. Uptake is even lower in specific age and target groups in high-income countries, such as adolescents, young adults, older adults, minority groups, and groups with lower socioeconomic status[27-30].

It has also been estimated that more than 80% of the almost one billion people with mental health conditions live in low- and middle-income countries (LMICs), where evidence-based treatments are only sporadically available[1]. For example, only one in 27 people with depression receives adequate treatments in LMICs[26]. In many LMICs, there is less than one psychiatrist for every 100,000 individuals[31].

Thus, the need for more effective and widely accessible treatments is urgent. Fortunately, many innovative psychotherapies are currently being developed and tested. In this paper, we focus on these advancements, broadly defining innovations as "new ideas, methods or devices"[32,33]. Specifically, we examine innovations in psychotherapies that aim to enhance effectiveness, improve efficiency, or increase uptake. We do not address innovations in prevention, diagnostics, or the fundamental understanding of mental disorders.

Psychotherapy can be defined as "the informed and intentional application of clinical methods and interpersonal stances derived from established psychological principles for the purpose of assisting people to modify their behaviors, cognitions, emotions, and/or other personal characteristics in directions that the participants deem desirable"[34]. We do not use this definition in a very strict way and include also psychological treatments in general, for example unguided digital interventions.

This paper is divided in four sections, each of which describes a broad category of innovations: advances in the digital field, stratification and personalized psychotherapy, new and improved therapies, and dissemination and simplification of therapies. These four categories are not mutually exclusive, and some innovations could be positioned in more than one category.

For each of the innovations, we present an overview of what the innovation is, and a summary of what the evidence tells us about the effects (if possible, based on core meta-analyses).

INNOVATIONS IN THE DIGITAL FIELD

Internet-based interventions

One area in which many promising innovations of psychological treatments take place is the digital field. Research on Internet-based interventions for mental health problems started in the early 2000s[35-38], but most trials have been conducted in the last decade. These studies build on the earlier literature on (guided) self-help that already started several decades earlier[39], with clinical trials on anxiety beginning in the 1960s and 1970s[40,41], on problem drinking in the 1970s[42], and on depression in the 1980s[43,44].

A self-help intervention can be defined as a psychological treatment in which the patient works through a standardized protocol more or less independently[45]. The treatment protocol can be provided in a book, as an audio file, or in a digital format through the Internet. Self-help can be unguided, when the patient works through the protocol without any support, or guided, when a human supports the patient to work through the protocol. Internet-based interventions can be considered as (guided) self-help interventions which are administered through the Internet.

Most Internet-based interventions examined in randomized trials in the last twenty years draw on existing psychotherapies, usually cognitive behavioral therapy (CBT), which are then transformed into digital platforms. The platforms are not fundamentally different from books or other media, although they are usually complemented with automated tests, brief videos, or some other multimedia content.

There is considerable evidence that these Internet-based interventions are effective in the treatment of several mental disorders, although many of the trials and meta-analyses suffer from several types of bias[46]. In Table 1, we provide the effect sizes for Internet interventions compared to control conditions in major mental disorders, based on recent meta-analyses[12,47-53]. As can be seen from this table, most of the trials have been conducted in depression, but there are also many trials in anxiety disorders, PTSD, OCD, substance use disorders and suicidal ideation, and some trials in borderline personality disorder. There is also evidence that Internet-based interventions for depression and anxiety are acceptable and effective in routine care[54].

It is well established that there are no important differences between Internet-based and face-to-face treatments of mental disorders. Meta-analytic research has consistently shown that randomized trials across multiple mental health conditions directly comparing these two formats do not result in significant differences between them[55,56]. In addition, there are several network meta-analyses showing that there is no significant difference between individual therapy, group therapy and (digital) guided self-help. Such network meta-analyses have been conducted on CBT for depression[57], panic disorder[5], eating disorders[58], and OCD[59].

Table 1 Core meta-analyses of randomized trials examining the effects of Internet-based interventions compared to control conditions in adult mental disorders

	n	N	SMD	95% CI	I^2	95% CI
Depression[47]	125	32,733	0.43	NR	NR	NR
GAD[48]	9	1,203	0.62	0.31-0.93	81	61-88
Panic disorder with or without agoraphobia[48]	15	837	1.08	0.77-1.39	76	57-84
SAD[48]	20	1,960	0.76	0.62-0.91	53	11-71
PTSD[49]	27	5,421	0.36	0.19-53	82	NR
OCD[12]	12	769	0.42	0.14-0.69	59	23-78
Suicidal ideation[50]	8	NR	0.23	0.11-0.35	18	0-59
Substance use disorder[51]	18	NR	0.24	0.13-0.35	27	NR
Gambling disorder[52]	13	2,183	0.73	0.43-1.03	94	NR
Borderline personality disorder[53]	3	NR	0.17	-0.10 to 42	0	0-90

SMD – standardized mean difference, GAD – generalized anxiety disorder, SAD – social anxiety disorder, PTSD – post-traumatic stress disorder, OCD – obsessive-compulsive disorder, NR – not reported

Most research suggests that Internet interventions with human support are more effective than those without any support[5,57,59,60]. However, the superiority of guided over unguided interventions is likely more nuanced, due to several factors. First, comparisons between "guided" vs. "unguided" interventions could be confounded by other factors, if the former tend to spend more time on complex and possibly effective skills such as cognitive restructuring, while the latter tend to include simple but ineffective skills such as relaxation, or if the former tend to be compared more often to waitlist than the latter. Second, guidance comes in various levels. Some guidance may mean 15 min per week by telephone from clinical psychologists, while other may mean e-mails from trained but lay coaches. When additional support was decomposed into "automated encouragement", "human encouragement" and "therapeutic guidance", there was evidence that only the first two could contribute to effectiveness and adherence, while the last was not necessary[61].

A recent meta-analysis of 23 trials on depression in LMICs found comparable effect sizes (0.90 and 0.87) and no significant difference (p=0.88) between guided and unguided Internet interventions[62]. This suggests that the difference may not be true in all contexts or populations. Another recent meta-analysis of 154 controlled trials examining the long-term effects of Internet-delivered CBT in depression, anxiety, PTSD and OCD did not find a significant difference between guided and unguided interventions at 12-month follow-up[63]. In an individual patient data network meta-analysis of 39 trials comparing guided and unguided digital interventions for depression with control groups or with each other, it was found that both interventions were effective compared to controls[60]. Guided interventions were more effective than unguided ones, but not at follow-up. Baseline severity was the most important predictor of outcome: in mild depression, there was no difference between guided and unguided interventions; guided interventions were only more effective than unguided ones in more severe depression.

One important element of digital interventions is the level of support that needs to be provided[64]. It is clear that the support in guided self-help interventions can be provided by people who do not need to have an extensive clinical training. In the Improving Access to Psychological Therapies (IAPT) program in the UK[65], guided self-help (digital or otherwise) is part of a stepped care approach, and the first step (guided self-help) is provided by "psychological well-being practitioners", who received a relatively brief training and do not have extensive clinical experience or training. This relatively low level of training required is an important element that may help to disseminate evidence-based treatments of mental disorders across populations who currently have no or only limited access to such treatments.

Most Internet-based interventions are based on CBT or third-wave therapies, because it is relatively easy to transform these interventions into self-help materials, and there is a strong empirical basis of the effects of CBT across mental disorders. However, digital interventions based on other therapeutical approaches have also been found to be effective. For example, there are several randomized trials showing that psychodynamic interventions[66,67], and interventions based on interpersonal psychotherapy (IPT)[68-70] are also effective.

The mobile revolution

Internet-based interventions were originally designed for patients using a computer, completing weekly sessions and homework assignments. However, Internet usage has changed in recent years. Most people now rely on smartphones or, when necessary, tablets. Phones are not ideal for reading long texts or completing assignments. Instead of setting aside dedicated time, users check their phones briefly throughout the day[71]. As a result, conventional self-help materials, which require extensive reading and structured homework, are often unsuited for smartphones.

It is not surprising that more and more research has shifted from "conventional" Internet interventions towards smartphone apps. A recent meta-analysis including 176 randomized trials examined the effects of smartphone interventions for depression and anxiety, of which more than two-thirds (67%) were conducted between 2020 and 2023[72]. The rapid increase in number of randomized trials may be further enhanced by the development of prescription digital therapeutics and investments from the industry[73]. Overall, the effects of smartphone apps are somewhat smaller than what is usually found for face-to-face treatments or conventional Internet interventions: the standardized mean difference (SMD) is 0.28 for depression and 0.26 for generalized anxiety[72]. While trials of smartphone apps are increasing, only a small fraction of the thousands of mental health apps available today has been tested in randomized trials.

Smartphones are different from conventional digital devices not only because they are used in a very different way, but also in that they make it possible to measure human behavior from sensors, keyboard interaction, and various features of voice and speech[74]. Sensors in smartphones that are often used for this purpose include GPS, bluetooth, accelerometer, microphone, illuminance, gyroscope, and Wi-Fi[75,76]. In addition to these passive measures, smartphones also allow the use of "ecological momentary assessment" (EMA), which is a self-report method that involves intensive longitudinal assessment of behavior and environmental conditions during everyday activities[77]. EMA has been used extensively in mental health research to investigate a variety of health behaviors, including substance use, eating, medication adherence, sleep, and physical activity.

What are the consequences of this different use of smartphones and of these additional possibilities of measuring behavior? The hope is that "digital phenotyping" will contribute to measurement-based care, allowing care managers to monitor remission and relapse[74], and to develop better precision treatments. However, this is not yet the reality, and research in these areas is still in its early stages.

More direct applications of the potential of smartphones and other mobile devices include "ecological momentary interventions" (EMIs) and "just-in-time adaptive interventions" (JITAIs). EMIs can be defined as treatments that are provided to people during their everyday lives and in natural settings, and are delivered using mobile technology[78,79]. They can be implemented as stand-alone interventions or as a supplement to existing treatments. These interventions have also been described as "therapist in your pocket" approaches, and have been claimed to have the potential to revolutionize clinical treatment[78,80].

Many EMIs are also JITAIs. These latter interventions are aimed at providing the right type and amount of support, at the right time, by adapting to an individual's changing internal and contextual state[81]. Because of the availability of increasingly powerful mobile and sensing technologies, the expectations for such interventions are high[81].

Although there is broad agreement on the potential of EMIs and JITAIs to improve treatments – including in the fields of suicide prevention[82-84], depression[85], and substance use problems[86] – there are not yet many randomized trials testing their effects on mental health problems. A recent systematic review of JITAIs identified only six randomized trials aimed at different mental health problems[87]. Because of the differences in target groups, methods and outcomes in these trials, it is not yet possible to estimate the actual clinical utility of these approaches. In contrast to many physical conditions (e.g., diabetes mellitus), most mental disorders are not associated with one clearly identifiable disease mechanism. In addition, the outcome in JITAIs needs to be obtainable in short intervals (e.g., steps taken within 2 hours) for the interventions to be properly adapted. By contrast, the outcomes of interest in mental disorders tend to be assessable on longer terms. Thus, the potential of JITAIs in mental health care could be inherently limited.

Serious games for the treatment of mental disorders

Another significant development is represented by serious games. These are games devised with a primary purpose other than just recreation, which are applied in health care, but also in education, engineering and defense[88-90]. An important point in this area is the potential to enhance people's motivation to engage in interventions[88]. Although there are worries that serious games may encourage excessive gaming and gaming disorder[91], it is important to examine whether these games may be beneficial in increasing uptake, improving outcomes and reducing dropout from mental health treatments.

A considerable number of randomized trials has focused on the effects of serious gaming on physical health and mental health promotion and prevention[92]. However, the number of randomized trials aimed at people with existing health problems is limited. In a recent meta-analysis of randomized and open trials of gamified interventions, only six of 42 studies were randomized trials in people with mental health problems[92]. In another meta-analytic review of randomized controlled trials (RCTs) of serious games with depression as an outcome, only four (out of 22) trials were explicitly aimed at people with depression at baseline[93]. In another meta-analysis examining the effects of serious games with anxiety as an outcome, only five trials (out of 22) were aimed at generalized anxiety, one at social phobia and two at specific phobias[94]. In a meta-analysis of the effects of serious games on depression in older adults, only one of the 17 included trials was actually aimed at older people with depression[95].

There are indications that serious games can have effects on depression and anxiety[93,94], when compared to inactive controls. However, there is too little research in clinical populations to state whether they are effective in these groups. It is also not yet clear whether these interventions really improve uptake and reduce dropout.

Virtual and augmented reality

Immersive virtual reality (VR) can be defined as a three-dimensional interactive computer-generated environment, which allows the user to experience real-time sensory and auditory perceptions and helps create the sensation of being present in that environment[96].

The first trials examining the effects of VR-based treatments were already conducted more than 25 years ago[97,98], and since then dozens of RCTs have shown that VR interventions are effective in the treatment of specific phobias, social anxiety disorder, and panic disorder with agoraphobia, when compared with passive control conditions such as waitlist, with effect sizes that are comparable to those of face-to-face treatments[99]. There is also some support for the effects of VR in the treatment of PTSD when compared to passive controls[100,101], and there are promising results in the treatment of eating disorders, substance use disorders, schizophrenia, and attention-deficit/hyperactivity disorder (ADHD)[99,102].

Most meta-analyses show that, when VR-based treatments of mental health conditions are compared with regular face-to-face interventions, there are no significant differences[102,103]. This means that the additional clinical benefit of VR-based treatments for mental health conditions is probably limited.

There are some promising new applications in the VR field that may have additional clinical value. One trial examined a self-guided intervention for acrophobia, enhanced with VR through the smartphone, and found considerable effects[104]. The self-guided nature of this approach may increase the uptake of evidence-based treatments for acrophobia and possibly other mental disorders.

Another interesting development is represented by multi-modal motion-assisted memory desensitization and reconsolidation (3MDR), a novel VR and motion-assisted exposure therapy which provides treatment in an immersive, personalized and activating context. This intervention has been tested in veterans with PTSD with a history of unsuccessful treatments[105], showing significant and large effects when compared to a non-trauma-focused treatment addressing daily stressors and symptoms. More research is needed to verify whether this treatment has additional benefits compared to a full conventional treatment of PTSD.

Another relatively new development is the use of "augmented reality" in intervention research. This is a technology that blends virtual and physical environments, enhancing one's perception of reality[106-108]. Most research has been done in anxiety and phobias, as well as in neurodevelopmental disorders. Although a few RCTs have been conducted[107], it is too early to say whether augmented reality can contribute to better treatments or an increased uptake of evidence-based treatments.

More emerging trends in digital interventions

There are several more important emerging trends in the field of digital interventions. One important emerging development with considerable potential are so-called "prescription digital therapeutics"[109-112]. These are digital interventions which are rigorously evaluated for safety and effectiveness and are authorized by national regulatory agencies, such as the US Food and Drug Administration (FDA). They can be prescribed by health professionals to people with mental disorders.

There are several prescription digital therapeutics that have been approved by the FDA, including apps for ADHD, PTSD and substance use disorders[109], but also for depression, anxiety and insomnia. It is possible that an extension of regulatory pathways for prescription digital therapeutics could lead to an increase in industry-sponsored trials and further speed up research in this area[113].

There is also more and more research on "blended therapy", which combines digital with face-to-face psychological interventions. The face-to-face component is delivered by a mental health professional, such as a psychologist, while the digital component is patient driven[114]. Although the effects of Internet interventions have been well established, the uptake and adherence are low, especially when they are delivered in routine care[115,116]. Furthermore, many patients prefer face-to-face therapies[114,117], and clinicians often raise concerns about the use of digital therapies alone, feeling that patients are not suitable due to symptom severity, lack of digital access and literacy, and perception of digital treatment as less engaging than face-to-face treatments[113]. From this perspective, blended therapy can be seen as a midpoint option between digital and face-to-face therapy[114,118].

A recent meta-analysis of 29 randomized trials showed that most trials of blended therapy were conducted in depression and anxiety, almost all were based on CBT, and blended treatments were more effective or non-inferior to treatment as usual[114]. Whether blended therapy indeed results in higher levels of uptake and/or higher efficiency is not yet well established.

Another interesting development is the Avatar therapy for reducing severity and frequency of auditory hallucinations in people with psychotic disorders[119]. In this therapy, patients create an avatar with the help of a therapist. The avatar is an audio-visual entity created with a computer program. Participants give a face to their auditory verbal hallucinations, and the therapist gradually gives control over the avatar to the patient. A growing number of RCTs shows that this is indeed an effective intervention for reducing the severity of persistent verbal auditory hallucinations[119-122].

With the recent rise of large language models (LLMs), such as ChatGPT or OpenLLaMA, many new studies have focused on chatbots and conversational agents, introducing LLM programs for people seeking mental health support. For example, platforms have been developed as personal digital companions, on-demand online counseling, and to provide emotional support[113,123]. Although the number of publications in this field has increased rapidly, recent systematic reviews have identified only few RCTs examining the effect of these interventions or comparing them to face-to-face therapies[123-126].

One meta-analysis of trials on artificial intelligence (AI)-based conversational agents for promoting mental health and well-being included 15 randomized trials[127], but most were aimed at non-clinical populations or groups with subclinical symptoms, and only one trial was aimed at adolescents with a diagnosis of depression or anxiety[128]. It can be expected, however, that this area will develop into a large new research field soon.

STRATIFICATION AND PERSONALIZED PSYCHOTHERAPY

Who benefits from which psychotherapy?

In the field of psychotherapy, it has been recognized for a long time that outcome research should not only focus on the effects of treatments, but also on "which treatment, by whom, is most effective for this individual with that specific problem, and under which set of circumstances"[129]. Most research on psychological treatments in the past five decades has focused on whether therapies are effective on average. RCTs comparing a psychological intervention to a control condition in a group of patients with a mental health condition can show if this intervention is effective in that population of patients. This approach has resulted in many hundreds of such trials, and we know quite a lot on the average effects of psychotherapies on most mental health problems.

Personalized medicine, including personalized psychotherapy, promises to move beyond data regarding the average effectiveness of treatments, to determine the best treatment for each individual[130-132]. This approach aims to identify subgroups of individuals within a heterogenous population, based upon unique characteristics such as underlying mechanisms, risk factors, course of disease, or treatment responses. There is not, however, one single research strategy that can directly lead to evidence on who benefits more from one treatment compared to another.

One approach to personalized psychotherapy is to identify and test potential predictors and moderators. Predictors, sometimes referred to as "prognostic factors", can be defined as characteristics that predict the overall course of a condition regardless of treatments. Moderators, also known as "effect modifiers" or "prescriptive factors", can be defined as characteristics that predict differential response to alternative treatments.

Early research to identify moderators of outcome

Much research in this area has focused on treatment of depression, probably because this is such a heterogeneous condition[133]. In an earlier systematic review, fifteen models for subtyping depression were identified[134]. These were divided into five categories: a) symptom-based subtypes, such as melancholia, psychotic depression, atypical depression, and anxious depression; b) etiology-based subtypes, exemplified by adjustment disorders, early trauma depression, perinatal depression, organic depression, and drug-induced depression; c) time of onset-based subtypes, as illustrated by early and late onset depression, as well as seasonal affective disorder; d) gender-based (e.g., female) depression; and e) treatment-resistant depression[134]. The authors concluded that none of these subtypes is absolutely distinct from the others, with substantial overlaps across symptoms, etiologies and time of onset, and that there is no strong evidence for treatments resulting in better outcomes in specific subtypes.

However, it is currently generally accepted that bipolar and psychotic depression are two subtypes that do need specific treatments. For seasonal depression, specific treatments have been developed[135]. It is also generally accepted that psychotherapy is the preferred treatment in mild depression, while severe depression may be treated with psychotherapy and/or pharmacotherapy.

A more recent and comprehensive review identified the key domains that should be considered when developing personalized treatments of depression[136]. These domains include clinical subtypes of depression, symptom profiles, severity, neurocognition, clinical staging, personality traits, comorbidities, family history, early childhood trauma, recent environmental exposures, resilience, and dysfunctional cognitive schemas. In this extensive review, only a few indications were found for specific effects of treatments in some of these domains. For instance, some preliminary evidence from an individual patient data meta-analysis was found that some specific symptoms of depression (i.e., depressed mood, feelings of guilt, suicidal thoughts, psychic anxiety, and general somatic symptoms) improve more with antidepressant medication compared to CBT[137].

An earlier suggestion that patients with melancholic depression respond less well to psychotherapy[138] was not confirmed in an individual patient data meta-analysis[139]. There is also not strong evidence that baseline severity moderates the effects of psychotherapies[140], or their effects compared to antidepressants[141]. It has been suggested that combined treatment is more effective than pharmacotherapy alone in people with depression and a comorbid personality disorder[142], but that is based on limited research. Furthermore, combined treatment is also superior to pharmacotherapy alone in the general group of people with depression.

A somewhat different and more pragmatic approach[143] was aimed at identifying moderators of differential treatment response in the literature. These moderators – i.e., symptoms and other easily assessed clinical features – could then be used to develop multivariate prediction equations of treatment outcomes. Again, very few significant moderators were found that could help to identify who would benefit more from one treatment compared to another. Three studies found that CBT is more effective than IPT in people with comorbid personality disorders[144-146]. One study reported that behavioral activation treatment is more effective than CBT when depression is more severe[147]. Another study found that CBT is more effective than IPT in the presence of a non-secure attachment style[148]. One more study reported that IPT is more effective than CBT in more severe depression[149], while another found the opposite[150]. Individual studies reported that CBT is more effective than pharmacotherapy in people who are not full-time employed, in married people, in the presence of high levels of stress[151], and in patients with a history of childhood trauma[152]. Further individual studies found that selective serotonin reuptake inhibitors (SSRIs) are more effective than CBT in depression with comorbid personality disorders[153], and when levels of negative affect and neuroticism are high[154]; that SSRIs are more effective than IPT when psychomotor symptoms are pronounced[155]; and that IPT is more effective than SSRIs in the presence of high somatic anxiety[155].

Based on the above three extensive reviews, we can conclude that until now there is very little knowledge on personalizing psychotherapies for depression. These therapies work on average, but knowledge on who benefits from which treatments is almost completely absent.

The major problem with earlier studies summarized in the above three reviews is that they did not have sufficient statistical power and focused on single variables. RCTs are typically designed to show that an intervention works, and that its average effect is significantly larger than the control or comparison condition. However, in order to establish a significant moderating variable, the number of included patients has to be increased considerably compared to establishing whether an intervention is effective[156]. According to a simulation study[157], the required sample size increases by four-fold to find an interaction of the same magnitude as the main effect, and exponentially to a factor of more than 100 for more subtle interactions of <20% of the overall effect. This means that a single trial should include hundreds of participants per arm to be able to identify a predictor or moderator. Such trials have hardly been carried out in the field of psychotherapy. For example, in a recent meta-analysis of randomized trials comparing psychotherapies for depression with control conditions, we included 669 comparisons, with an average of only 50 participants per condition[158].

Some larger trials with substantial numbers of participants have been conducted in the past decades, for example on CBT for depression in mothers in Pakistan (N=903)[159], and on collaborative care for depression and anxiety in India (N=2,796)[160]. However, these trials were not designed to identify predictors or moderators. In recent years, some large trials have been conducted that were aimed at developing personalized treatments, and others are planned.

For example, one trial examined the effects of guided and unguided Internet-based CBT for depression and anxiety in 1,319 university students in Colombia and Mexico[161,162], and included a substantial number of potential predictors and moderators of outcome. Overall, it was found that guided CBT was optimal in terms of remission from depression and anxiety for 81% of all participants, self-guided CBT for another 8%, and treatment as usual for the remaining 11%. The most important predictors of outcome were physical health, comorbid mental disorders, and exposure to recent and lifetime stressors. In another trial of unguided Internet-based CBT for subthreshold depression among Japanese university students (N=1,093), it was found that higher baseline severity was associated with better outcomes, and that several other predictors and moderators were potentially associated with the outcomes, including for example age[163].

New approaches: individual patient data (network) meta-analyses

One innovative approach to identify moderators and predictors is represented by individual patient data meta-analyses. In these meta-analyses, the primary data of multiple trials are collected, combined into a large, merged dataset, and subsequently analyzed jointly[156,164]. This integrated dataset can be used to examine whether baseline patient characteristics are associated with the outcomes of therapies. Because data from multiple trials are combined, the statistical power to examine predictors and moderators of outcome is substantially increased.

An overview of recently published individual patient data meta-analyses[141,165-180] is presented in Table 2. As can be seen, most meta-analyses of psychological treatments have been conducted in depression. Several studies found that higher baseline severity is associated with worse outcomes as prognostic factor and greater impact as effect modifier[165,167,169,170,172,174], but that was not confirmed in all studies, although they did have considerable statistical power to find such an association. Two studies found that older age was associated with greater effects[167,170]. Other meta-analyses identified some other predictors and moderators, but none was consistent across studies.

Most individual patient data meta-analyses on depression summarized in Table 2 included trials comparing psychological treatments with control conditions. These studies do not indicate whether one treatment is better than another in a specific group of patients. Only one meta-analysis compared two active treatments, CBT and pharmacotherapy for depression[141]. In this meta-analysis, no significant moderators were found indicating which patients benefit more from one of the two treatments, including baseline severity.

A different approach is represented by individual patient data network meta-analyses (not included in Table 2). In these studies, in contrast to "conventional" individual patient data meta-analyses, more than one active treatment is compared to control conditions. This makes it possible to identify characteristics of participants who benefit more from one treatment compared to one or more other treatments or control conditions.

In one individual patient data network meta-analysis of 39 RCTs (9,751 participants) on digital CBT for depression, several important variables were found to be associated with differential outcomes, including gender, relationship status, and employment status[60]. However, the most important moderator was baseline severity of depression. Both guided and unguided interventions had better outcomes than the control conditions, but no significant difference between these interventions was found among participants with mild depression, while guided CBT was superior to unguided CBT among participants with more severe depression. In another meta-analysis, data from three trials comparing cognitive-behavioral analysis system of psychotherapy (CBASP) with pharmacotherapy and combined treatment for depression were integrated (1,036 participants)[181]. It was found that baseline depression, anxiety, prior pharmacotherapy, age, and depression subtypes moderated the relative efficacy of the three treatments. Both the above meta-analyses generated web-based apps that allow to predict the outcome of each treatment for a specific individual with specific characteristics.

Although individual patient data meta-analyses are relatively new in the field of psychotherapies for mental health conditions, several have been conducted in recent years in areas other than depression. Some studies have focused on PTSD[175-177] (see Table 2), but only few significant and consistent predictors and moderators were identified. The same was true for meta-analyses on Internet interventions for alcohol problems[178] and for suicidal ideation[179], and on VR for anxiety[180].

When reviewing this area of research, it becomes clear that individual patient data meta-analyses have shown some evidence that treatment outcomes are linked to specific patient characteristics. Individual patient data network meta-analyses, in particular, show great promise in identifying which patients benefit from which treatments. However, despite the growing number of meta-analyses, little knowledge is yet available that can be directly applied in clinical practice. A general limitation is that only a small number of variables are typically available as potential predictors or moderators[156]. Included trials often assess different predictors and moderators, making it difficult to analyze a broad set of common variables. Paradoxically, the more trials are included, the fewer shared covariates can be examined. Establishing a consensus on core outcome sets[182], as well as standard predictors and moderators, for all new randomized trials would greatly enhance the value of these meta-analyses. Until then, their contribution will remain valuable but constrained.

Another important limitation of individual patient data (network) meta-analyses in the development of personalized treatments is that they can only generate correlational and not causal evidence, because patients are not randomized according to baseline characteristics. Whether the data come from large RCTs or from individual patient data meta-analyses, the constructed personalization algorithms are in essence prediction models. That means that, when a significant predictor or moderator is identified, a new randomized trial is needed to confirm that this predictor or moderator or their combinations can indeed improve outcomes for a specific group of patients. Such randomized trials should assign patients to an intervention according to the constructed model, which is then compared with a group of patients who are assigned to a certain intervention without using the model[156].

Machine learning approaches to personalized psychotherapies

One important innovative methodological approach is machine learning (ML). Broadly speaking, ML involves the use of

Table 2 Significant predictors and moderators of outcomes identified in individual patient data meta-analyses of randomized trials comparing psychotherapies for mental disorders with control conditions

	Comparison	n (N)	Predictors/moderators
Depression			
Bower et al[165]	Low intensity CBT vs. controls	16 (2,470)	Better outcomes associated with higher baseline severity
Weitz et al[141]	CBT vs. antidepressants	16 (1,700)	None
Furukawa et al[166]	CBT vs. pill placebo	5 (509)	None
Karyotaki et al[167]	Guided iCBT vs. controls	24 (4,889)	Better outcomes associated with older age, higher baseline severity, and being native-born
Karyotaki et al[168]	Unguided iCBT vs. controls	13 (3,876)	None
Kuyken et al[169]	Mindfulness-based CBT vs. controls	9 (1,258)	Better outcomes associated with higher baseline severity
Reins et al[170]	Digital interventions for subclinical depression vs. controls	7 (2,186)	Better outcomes associated with older age and higher baseline severity
Wienicke et al[171]	Psychodynamic therapy vs. controls	11 (771)	Larger effect associated with longer current episode duration and earlier onset
Driessen et al[172]	Combined psychodynamic therapy + antidepressants vs. antidepressants alone	7 (482)	Effects for combined therapy associated with higher baseline severity and longer episode duration
Karyotaki et al[173]	Task-sharing interventions for depression vs. controls	11 (4,145)	Better outcomes associated with presence of psychomotor symptoms
Buntrock et al[174]	Any intervention in subthreshold depression vs. controls	30 (7,201)	Better effects in people who never had treatment before; better outcomes associated with higher baseline severity
PTSD			
Wright et al[175]	EMDR vs. other therapies for PTSD	8 (346)	Worse outcomes for EMDR in unemployed people; males dropped out of EMDR more often
De Haan et al[176]	CBT with trauma focus in young people vs. controls	25 (1,686)	Larger effects associated with more severe symptoms at baseline
Hien et al[177]	Behavioral and pharmacological therapies for PTSD + substance use vs. controls	34 (3,938)	None
Other disorders			
Riper et al[178]	Internet interventions for alcohol problems vs. controls	19 (14,198)	Higher response in people >55 years of age
Sander et al[179]	Internet interventions for suicidal ideation vs. controls	8 (1,980)	None
Fernández-Alvarez et al[180]	VR for anxiety vs. controls	15 (810)	Married people had lower chance of deterioration

CBT – cognitive behavioral therapy, iCBT – Internet-based CBT, PTSD – post-traumatic stress disorder, EMDR – eye movement desensitization and reprocessing, VR – virtual reality

advanced statistical and probabilistic techniques to construct systems with an ability to automatically learn from data[183,184]. ML techniques include various non- and semi-parametric algorithms that can "learn" complex multivariate interactions from datasets, while conventional (parametric) models are more restricted in the number and complexity of patterns they can capture.

Although there are many potential pitfalls when applying these techniques, they do afford many opportunities for psychiatric research when applied correctly[185,186]. The use of ML techniques is increasing rapidly in mental health research, not only in predicting and improving treatment outcomes, but also for example in detection and diagnosis[183,187], and clinical administration[183].

Several of the studies previously discussed in this paper used ML techniques. For example, EMIs and JITAIs often use ML, as do prediction models built from large trials[161,162], and individual patient data (network) meta-analyses[60,188]. However, there is also a growing body of research specifically aimed at the development of algorithms to predict who benefits from treatments in RCTs. Although most of this research has been conducted in pharmacotherapy and neurobiological treatments[185], there are also several studies in psychotherapy.

One influential method, called the "personalized advantage index" (PAI), has been used extensively in psychotherapy research[189-191]. The first demonstration study on PAI used data from an RCT comparing psychotherapy with pharmacotherapy for depression[191]. Five baseline characteristics of patients were found to predict differential response (marital status, employment status, life events, comorbid personality disorder, prior medication). These characteristics were used to calculate the PAI for each patient. For 60% of the participants, a clinically meaningful advantage was predicted for one of the treatments relative to the other. When these patients were divided into those randomly assigned to their optimal treatment and those receiving the other treatment, outcomes in the former group were superior, with a moderate effect size (SMD=0.58). A recent systematic review identified 19 comparative outcome trials in which the PAI was examined[192]. The results suggested that the PAI has the potential to improve outcomes with an SMD of 0.32, although this may be an overestimation due to the considerable methodological problems with the studies, such as overfitting/model optimism.

It has also been argued that, in addition to large RCTs and individual patient data meta-analyses, large observational treatment samples – such as electronic health record databases – can be used to develop precision treatment rules[193,194]. For example, a proof-of-concept study, using electronic health records to develop an individualized treatment rule for veterans with major depressive disorder, found a considerable improvement in outcomes with minimal additional costs[195].

There are also several other types of studies using ML techniques to improve outcomes of psychotherapies. For example, some studies predict whether patients need high- or low-intensity therapies[196-198]. Others have developed personalized modular treatment plans on a person-by-person basis[199], or have developed a system for optimal treatment strategy selection and personalized adaptive recommendations during treatment[200], or have used natural language processing techniques to discover patterns of therapist-patient interactions that predict treatment response[201,202]. However, despite the quickly growing number of studies in the field, most ML approaches to predict responses to psychotherapies are still in the early stages of development and are not yet ready for implementation in routine care[185,203].

It is increasingly recognized that, regarding the prediction of therapy outcomes, ML techniques have limitations. Over the past decade, the development of ML-driven prediction models has surged across all fields of medicine, with statistical experts warning that most models are too unreliable, impractical, or both, to inform practice[204-206]. All prediction models face the so-called bias-variance trade-off[185], where a model's data adaptivity must be balanced against the risk of overfitting. ML techniques offer great flexibility in detecting complex interactions, but also increase the risk of identifying spurious associations – particularly in psychological treatment research, where even large trials (>1,000 patients) can be considered "small data".

A related issue is that training data are often restricted and noisy, resulting in an unfavorable signal-to-noise ratio[207]. Consistent with this, even in very large samples, simple regression models have not been outperformed by more complex ML approaches[208], including in the prediction of psychotherapy outcomes[209]. Psychological interventions also depend heavily on contextual and setting-specific factors, which further limits the generalizability of ML-based prediction models[210].

To demonstrate that ML-driven treatment recommendations are effective in routine care, new randomized trials are needed, in which patients are assigned either to treatment based on the prediction model or to "ordinary" treatment (as we already noted for predictors and moderators found in individual patient data meta-analyses). Only if such trials show better outcomes for patients receiving model-based treatment, we can assume that these models truly improve patient care.

Matching therapists to patients

Up to now, we have discussed research using ML techniques to determine patient characteristics that could predict outcome. A different approach is to develop methods to match patients better with therapists. It is well established that the outcomes of treatments vary considerably across therapists[198,211]. It has been estimated that about 5 to 8% of outcome variance is attributable to systematic differences between therapists[212]. There are also several studies showing that some therapists are more effective in some problem domains than others, while almost all therapists are at least effective in one specific domain[213].

In a recent study with a large sample of patients, ML techniques were used to identify subgroups of therapists that were differentially effective for highly specific subgroups of patients[198]. This resulted in 17 classes of patient-to-therapist matches with varying outcomes per class, but the predicted outcome in patients was 60% higher if they had been matched with the therapist using this method.

This matching of patients to therapists is also supported by results from an RCT of 218 patients treated by 48 therapists[214]. Before the trial, therapists were classified as effective, neutral or ineffective across 12 problem domains, based on their historical cases. In the trial, patients were either randomized to a therapist who was effective in their problem domain (matched care), or pragmatically to any therapist (care as usual). The matched care was significantly more effective than care as usual in terms of symptom reduction and functional impairment (SMD=0.75), and global distress (SMD=0.50), with no adverse events. To the best of our knowledge, this is the only trial which examined matching of therapists to patients, but the approach is certainly promising and may improve outcomes of therapies substantially[215].

Randomized controlled trials of personalized and modular psychotherapies

There is a growing number of RCTs examining the effects of personalized psychotherapies. These studies go beyond predicting the outcomes of therapy. They have already developed a personalized treatment, and compare it to ordinary therapy. The personalized therapies are tailored to specific characteristics of patients.

Some personalized treatments are developed using ML techniques. For example, in one of these studies, patients received either ordinary stepped care, or stratified care in which they were assigned to low- or high-intensity CBT according to a ML algorithm[216]. It was found that stratified care was more effective than ordinary stepped care, although the costs were also somewhat higher.

Other personalized treatments tested in RCTs are based on clinical factors that are assumed to be associated with differential outcomes. For example, the Trier Treatment Navigator is a system that combines prediction and outcome tracking tools, providing feedback to clinicians and supporting them to apply targeted clinical problem-solving strategies when poor treatment response is likely[217]. A randomized trial comparing this system with ordinary therapy found significant effects of the former (SMD=0.30)[217].

One recent meta-analysis included nine RCTs comparing personalized psychotherapies with standard therapies[218]. This meta-analysis did find a small but significant effect of the personalized psychotherapies (SMD=0.22), although only one of the studies had a low risk of bias. Furthermore, few of the included personalized psychotherapies were based on empirically derived recommendations models, being instead only expert-opinion based. This meta-analysis cannot, therefore, be considered as strong evidence that personalized psychotherapies are indeed more effective than standard therapies.

A specific type of personalized therapy is represented by "modular psychotherapies". In these therapies, the clinicians are provided with an evidence-based toolbox, which includes treatment modules that can be used depending on the clinical problems of the patient at baseline, and decision tools that guide the selection of the different modules[219-221]. Probably the best-known modular therapy is MATCH (Modular Approach to Therapy for Children with Anxiety, Depression, or Conduct Problems)[221]. This contains treatment modules aimed at the treatment of depression, anxiety and conduct problems in youth, which form a menu for clinicians from which they can select modules for the treatment of an individual patient. MATCH is tailored to fit each youth's specific needs at intake. Decision flow charts guide the selection and sequencing of modules, with a default module sequence suggested, but changes in the sequence specified to address treatment difficulties[221].

There are several RCTs that have compared the effects of MATCH to standard care. Some of these trials have found that MATCH had superior results when compared to standard treatment of depression, anxiety and conduct problems in youth[221-223], but that was not confirmed in other trials[224-226]. Meta-analytic evidence integrating these results is not yet available.

Apart from MATCH, there are several other modular therapies that have been tested in RCTs. For example, in one study, it was found that modular CBT for children with autism-related symptoms was significantly more effective than standard treatment in reducing these symptoms[227]. Two other trials examined the effects of modular therapy in children with anxiety disorders, and found significant effects when compared with usual care[228] and waitlist[229].

Not all trials have found superior effects of modular psychotherapies. In one trial in adults with alcohol use disorders, patients were randomized to either usual care or a targeted modular treatment[230]. Patients in this latter arm were allocated to one of three treatment modules focusing on craving, positive expectancy, or impulsivity, based on an assessment at baseline. No significant difference was found between modular psychotherapy and usual care. Another study compared a standard CBT self-help program with a tailored program in which the content of the sessions differed depending on the anxiety symptoms at baseline[231]. Again, no significant difference at post-test or follow-up was found. An earlier trial on modular psychotherapy for anxiety in older primary care patients also did not find a significant benefit when compared with routine care[232].

In a recent proof-of-concept trial[220], patients with depression and psychiatric comorbidity were either randomized to standard CBT or to CBT plus transdiagnostic modules, depending on early trauma-related mechanisms. There was a non-significant superiority of the modular therapy over standard CBT, but patients randomized to the former were nearly three times as likely to experience remission at the end of therapy.

These results are conflicting and do not allow to state whether modular psychotherapies are more effective than standardized ordinary treatments. A meta-analysis or systematic review could shed some more light on this issue, but to the best of our knowledge no such review has yet integrated the results of trials in this specific field.

NEW AND IMPROVED PSYCHOTHERAPIES

The development of new psychotherapies

In the past decades, several hundreds of psychotherapies for mental health problems have been developed. The Wikipedia list of psychotherapies currently includes 218 separate therapies[233]. Although it is not clear how this list was composed, it is probably only a selection of all therapies that have been developed over the years. The development of new therapies is a continuing process[e.g., 234-238].

Many new therapies claim to have better outcomes than "conventional" psychotherapies or to be based on better theoretical or clinical frameworks. However, most research does not support these claims. Network meta-analyses are well-suited to examine the comparative effects of psychotherapies for specific mental disorders, because they include not only RCTs directly comparing different therapies, but also indirect comparisons. For example, when two therapies are not compared directly in RCTs, their effects can still be estimated when both therapies have been compared with a waitlist control group or a third therapy.

Most network meta-analyses do not indicate superior effects of one therapy over another. For example, a large network meta-analysis of 331 RCTs with more than 34,000 patients on eight types of psychotherapy for depression found no significant differences between the effects of these therapies[2]. Only non-directive supportive counseling was found to be less effective than other psychotherapies, but that was probably an artefact, because this therapy is also often used as control condition[239]. Other network meta-analyses for other disorders have also not found significant differences between the effects of psychotherapies. One network meta-analysis on generalized anxiety disorder found no significant difference between eight major types of psychotherapy[240], and another on seven types of therapy for PTSD also found no significant differences[241].

However, not all research supports the notion that all psychotherapies have comparable effects. A network meta-analysis examining the relative efficacy of therapies for social anxiety[242] found that most therapies had comparable effects, but also that individual CBT was more effective than psychodynamic therapy, while there was no significant difference between individual CBT, group CBT, and exposure and social skills. Another network meta-analysis examining eight psychotherapies for panic disorder found comparable effects for most therapies, but did find that behavioral therapy and CBT were more effective than third-wave CBT[4].

Conventional meta-analyses are also not consistent. In a review of 15 meta-analyses of RCTs directly comparing 23 psychotherapies for different disorders with other psychotherapies, only five found significant differences[243], and all significant differential effect sizes were small.

Thus, most evidence suggests that psychotherapies for mental disorders either have comparable effects, or in some cases can have small differential effects. This implies that many new psychotherapies are not so innovative, and may not contribute much to improving relevant outcomes. Therefore, it goes beyond the current overview to discuss all new psychotherapies that have been developed.

An important category of psychological interventions that is new is represented by the so-called "bottom-up" therapies[244]. Traditionally, almost all psychological interventions have been developed top-down, with clinicians designing treatments based on their experience and knowledge of the literature. Although the rationale of these therapies typically sounds intuitive and credible to patients, the methods to develop them are not systematic or reproducible, and the processes to select, combine and weigh the evidence are entirely subjective. These methods are also heavily influenced by the founder's unique sociocultural background, values and perspectives, and the manuals are developed by the founder, based on subjective principles. As we saw earlier, many of these top-down therapies have been found to be effective in the treatment of mental disorders, but the exact mechanisms through which they work remain unclear and are based on clinical experience and selective reading of the literature.

Bottom-up interventions start with psychological theories of factors that cause or maintain symptoms of mental health problems[244]. Based on these theories, targets for experimental manipulation are selected, and interventions focusing on these targets are developed. Probably the best-known example of a bottom-up intervention is exposure, that goes back to the theoretical work on systematic desensitization in the 1950s[245]. Most therapies developed since then were top-down[244]. In the past years, however, several new bottom-up interventions have been developed and tested in RCTs.

We will discuss here the two most important categories of bottom-up therapies: cognitive bias modification (CBM) and cognitive remediation (CR). There are several other bottom-up interventions, such as consolidation/reconsolidation therapies[246], and memory specificity training[247,248], but these have been examined in only a few trials.

In this section, we will subsequently consider some other recent developments concerning new psychotherapies or new approaches aimed to improve the outcomes of psychotherapies.

Cognitive bias modification

CBM is based on a large body of research showing that biases in attention, interpretation and memory are associated with mental health problems and may contribute to them. This has been confirmed for depression[249-251], anxiety[251,252], eating disorders[253,254], substance use disorders[255,256], and psychotic experiences[257]. CBM is a psychological intervention aimed at correcting such biases. Participants engage in structured, computer-based repetitive tasks that train them to modify their automatic responses. These tasks can be gamified to maintain engagement, and immediate feedback is usually provided to reinforce the desired cognitive patterns[258].

CBM and related interventions – such as attention bias modification (ABM), interpretation bias modification, and "approach and avoidance" training – have been examined in dozens of RCTs and a considerable number of meta-analyses. Overall, these interventions seem to have a moderate and significant effect on the biases they are aimed at[259]. The effects on symptoms of mental health problems are less clear.

A large network meta-analysis of 75 trials on CBM for anxiety and depressive disorders[260] differentiated between four types of CBM: ABM; CBM aimed at interpretation bias (CBM-I); the combination of ABM and CBM-I; and approach and avoidance training. For anxiety, only CBM-I had a significant effect when compared with waitlist (SMD=–0.55) and sham training (SMD=–0.30). In depression, CBM-I also had a significant effect when compared with waitlist (SMD=–0.63).

A meta-analysis of 14 trials on CBM for alcohol and smoking addiction did not find a significant effect on substance use, but did find a significant effect on relapse[261]. A meta-analysis of 23 trials in children and adolescents with or without mental health problems found small and non-significant effects on mental health[262]. A meta-analysis of 29 RCTs in anger and aggression found small but significant effects on both variables[263].

Overall, the evidence suggests that CBM and related interventions can have an effect on cognitive biases, and some types may also have small effects on mental health problems. It is not clear, however, if such interventions can improve clinical practice. A meta-analysis of trials comparing the combination of CBM and CBT with CBT alone in people with anxiety disorders did not find that CBM significantly improved the outcome of CBT[264]. More research is therefore needed to examine if and how CBM can be used in routine care, and if it actually improves outcomes in real life settings.

Cognitive remediation

CR targets cognitive deficits (of attention, memory, executive function, social cognition, or metacognition) using scientific principles of learning, with the ultimate goal of improving functional outcomes[265]. Cognitive impairments have been well established in several mental disorders, including schizophrenia, bipolar disorder, depression, ADHD, PTSD and OCD[265,266]. CR can include many different techniques to improve these impairments, but should contain at least four core elements: facilitation by a therapist, cognitive exercises, procedures to develop problem-solving strategies, and procedures to facilitate transfer to real-world functioning[267].

The ideas underlying CR go back several decades[268,269]. However, in the last years the number of trials examining CR has increased exponentially, including a growing number of computerized CR interventions[270,271]. For example, in a recent meta-analysis of 67 randomized trials of CR in schizophrenia, it was found that more than 80% were conducted after 2010[272]. This increase in research on CR is undoubtedly also related to its growing use through digital technologies[273,274].

A recent meta-analysis of 67 trials on CR in schizophrenia found small but significant and durable effects on cognition (SMD=0.23) and global functioning (SMD=0.26)[272]. Another meta-analysis of 73 trials investigating more detailed outcomes[275] also found small-to-moderate size improvements in all domains of cognition studied (SMD range: 0.19 to 0.33), as well as a small significant effect on negative symptoms (SMD=0.16), but not positive symptoms or overall levels of symptomatology. A meta-analysis of 21 trials on CR in depression resulted in a small significant effect on depression (SMD=0.28) and daily functioning (SMD=0.22), and a moderate effect on cognitive functioning (SMD=0.60)[276]. This is comparable to the results of other meta-analyses of trials on CR in depression[277,278].

The outcomes of CR in other mental disorders are not consistent. A meta-analysis of seven trials in bipolar disorder resulted in small significant effects on working memory, planning and verbal learning, but not on functional outcomes[279]. Another meta-analysis of 11 trials on CR for adolescents with mixed mental disorders also showed small but significant effects on cognition, but not on clinical symptoms or social functioning[280]. In a small meta-analysis of eight trials on CR in anorexia nervosa, no significant effects were found on cognitive functioning or symptomatology[281]. These meta-analyses on CR in disorders other than schizophrenia or depression should be considered with caution, because the number of included trials was small, and results may not be significant because of low statistical power.

Overall, CR seems to have small but significant effects on negative symptoms in schizophrenia, and on symptoms of depression. Considering these outcomes, more research could be focused on how these interventions can be implemented in routine care, and if the effects are retained in real-life settings.

Psychedelic-assisted psychotherapies

An increasing number of studies is focusing on the effects of psychedelic-assisted psychotherapies in mental disorders[282,283]. Psychedelics are powerful psychoactive substances that alter perception and mood, and affect numerous cognitive processes[284]. Combining them with psychotherapies has the potential to enhance the effects of the latter.

Most research in this area has focused on the use of psychedelics – psilocybin, lysergic acid diethylamide (LSD) or ayahuasca – for depression[282], and to a lesser extent of methylene-dioxy-methamphetamine (MDMA) for PTSD[285,286]. There are also trials exploring the use of psychedelics in other disorders[282], including borderline personality disorder[287], body dysmorphic disorder[288], OCD[289], and alcohol use disorder[290].

Although the effects of psychedelic-assisted psychotherapies have been examined most extensively in depression, the number of trials is still small (the largest meta-analysis, focusing on psilocybin-assisted psychotherapy, includes nine RCTs[291]). It is also remarkable that the number of meta-analyses in this small area of research is almost as large as the number of primary trials. The above-mentioned meta-analysis[291] indicated a large effect size of psilocybin-assisted psychotherapy (SMD=0.78; N=596) when compared to placebo or waitlist control conditions.

MDMA-assisted psychotherapy for PTSD has also been examined in several trials and meta-analyses. The largest meta-analysis[285], including nine RCTs (N=297), found a large effect of MDMA-assisted therapy on symptoms of PTSD (SMD=-1.10), when compared with placebo or low-dose MDMA.

Although these effects seem rather positive, and these treatments have been claimed to represent a new paradigm for mental health care[292], the number of studies and of participants in these studies is too small to draw strong conclusions. The potential impact of conflicts of interests of researchers, and the potential selection bias in the trials[293] are further problems. Moreover, participants in the trials can be expected to be positive about the effects of psychedelic-assisted therapies. Many of them hope to be assigned to the treatment condition and will be disappointed when they end up in the control group[292,294]. Since it is not possible to mask participants, they are typically aware if they are in the treatment or control group, which may have an impact on the outcomes. Furthermore, psychedelics can be expected to have short-term effects, while from a clinical perspective it is much more important to achieve long-term effects, when the direct impact of psychedelics has passed. Unfortunately, hardly any research on the long-term effects of these therapies has been conducted.

Another important problem is that the psychotherapies that are actually implemented are not described clearly in the reports of the trials[295]. This means that psychedelic-assisted therapies consist of two components of which the effects are not clear: the psychedelic and the psychotherapy. It is unclear to what extent each of these components is responsible for the assumed effects of the therapies[293,296]. The conclusion is that psychedelic-assisted psychotherapies may have the potential to increase the effects of treatments of mental disorders, but this is still uncertain. The current evidence is insufficient to reach a final conclusion about their potential.

Transdiagnostic psychotherapies

Most psychotherapies focus on specific disorders, and RCTs examining the effects of these treatments usually focus on one specific disorder[21,297,298]. However, comorbidity between mental disorders is very high. For example, comorbidity between depression and anxiety has been estimated to be as high as 60% for case-level disorders[299], and is probably even higher when subthreshold cases are considered[300]. It has also been argued that depression and anxiety in fact constitute one cluster of internalizing disorders and share similar psychological and biological mechanisms[301]. Analogously, it has been suggested that the same underlying processes are involved in different eating disorders[302]. Psychological treatments of different mental disorders also often share the same core elements. For example, cognitive restructuring has been found to be effective in most major mental disorders[297].

Transdiagnostic psychotherapies are treatments that apply the same underlying principles across different mental disorders, without tailoring the protocol to specific diagnoses[303,304]. These approaches focus on identifying common and core maladaptive temperamental, psychological, cognitive, emotional, interpersonal and behavioral processes that can be targeted in treatment. People with different disorders can be treated with the same protocol, which makes it easier for them to access care without needing multiple, disorder-specific therapies, and has the potential to spare time and resources, without reducing the effects of therapies.

Transdiagnostic approaches have been claimed to offer more flexible, inclusive and effective treatment options[305]. Most of them have been developed for depression and anxiety disorders (sometimes also including PTSD, OCD and somatoform disorders), and are based on CBT principles[300,306-310]. However, transdiagnostic treatments have also been developed in the field of eating disorders. Enhanced CBT was specifically designed to target the underlying processes that are assumed to maintain different types of eating disorders[302].

Several dozens of RCTs have examined the effects of transdiagnostic psychotherapies, most of which were conducted after 2010. A handful of trials have examined enhanced CBT for eating disorders[311], but most research has focused on transdiagnostic treatments of various anxiety disorders or depression and anxiety. One large, recent meta-analysis of transdiagnostic treatments in emotional disorders included 53 trials and found that the treatments had considerable effects on depression (SMD=0.74) and anxiety (SMD=0.77)[309]. However, the nine comparisons between transdiagnostic and disease-specific treatments resulted in a small, non-significant difference (SMD=0.09).

The best example of a transdiagnostic psychotherapy is the unified protocol (UP) for emotional disorders[312], which was the first and is the most examined transdiagnostic treatment of depression and anxiety. One recent meta-analysis examining the effects of the UP included 19 randomized trials[313]. This study found moderate effects for depression and anxiety when compared to waitlist control conditions (SMD=0.59), but also small significant effects when compared to other active treatments (SMD=0.38).

Many transdiagnostic psychotherapies that are examined in RCTs are conducted through the Internet, and include guided and unguided versions. One recent meta-analysis included 57 trials and found moderate effects for depression (SMD=0.52) and anxiety (SMD=0.45) when compared to passive controls[307]. Only three trials compared transdiagnostic interventions with other treatments, so that a comparison of the relative effects is not yet possible.

Overall, this body of research shows that transdiagnostic psychotherapies are effective in the treatment of depression and anxiety, but it is unclear if they have better effects than disease-specific treatments. One could argue, however, that transdiagnostic treatments have several advantages when compared to disease-specific treatments, which makes them more useful even when the effects are comparable.

A new generation of dismantling studies

A considerable body of research within the psychotherapy field has focused on identifying the core elements or components of these treatments. This research can clarify how therapies work, remove inactive or irrelevant components, and potentially make therapies more effective and cost-effective[314,315]. Understanding how therapies work may also make it easier to train therapists and disseminate therapies more widely[314].

Traditionally, components of therapies are examined in RCTs in which a full therapy is compared with the same therapy with or without a specific component. Although many of such dismantling trials have been conducted, they rarely have enough statistical power to examine if adding or removing a component is related to larger or smaller effects of the intervention. The dismantling trials covered in systematic reviews and meta-analyses rarely included more than 100 participants, while much larger trials are needed to find differential effects[316-318]. For example, based on the assumption that a minimally clinically important difference for depression is SMD=0.24, a dismantling trial would need 274 participants in each condition[316].

There are two important new developments in this area of research that could generate more knowledge on effective components of psychotherapies. The first is the introduction of the so-called "factorial design"[314,315]. This design allows to examine multiple components in one study and to explore the main effects of these components as well as the interactions among them. The basic idea is that participants are randomized to any combination of components in the intervention. Because the number of potential experimental conditions increases exponentially as the number of components of the intervention increases, some studies make use of the so-called "fractional factorial design"[314]. This is a variation on the factorial design in which only a pre-specified selection of the possible conditions is examined to make the study more manageable.

Although (fractional) factorial designs have been used in other areas of the biomedical field[319-321], their use in psychotherapy research has started only recently[322]. Table 3 presents an overview of recent factorial trials on psychotherapies and the most important outcomes[71,322-327]. As can be seen, the results have been somewhat disappointing, but future research may help to shed more light on effective components for specific disorders.

The other recent important development that can help with the finding of effective components of psychotherapies is represented by component network meta-analyses. This is an extension of standard network meta-analyses that can be used to disentangle the associations with outcomes of different components of an intervention[328,329]. Several such meta-analyses have been carried out in recent years, including one conducted with the individual participant data of the included trials[61].

Table 4 gives an overview of the most important component network meta-analyses and a summary of their outcomes[13,17,61,330-332]. One interesting finding is that relaxation, often included in packages of CBT because it is considered to be easy to practice, has been found to be possibly harmful across several disorders, including panic disorder[331], depression[61] and insomnia[13]. Although the results of these studies certainly provide some directions for potentially effective and non-effective components, further research is needed to detect more clear outcomes.

Innovations in understanding processes involved in psychotherapies

Apart from dismantling studies, there are large research areas focusing on the processes involved in psychotherapies that can explain how they work. The hope is that this research will increase our understanding of psychotherapies and will make it possible to strengthen their effects or make them more efficient. Here we describe where this field currently is. We first explain why it is difficult to examine the change processes in psychotherapies. Then we focus on the current state of knowledge on three core topics: specific versus common factors in therapy, the therapeutic alliance, and fidelity versus flexibility.

Although RCTs provide an excellent design for examining *if* a

Table 3 Selected factorial trials aimed at examining components of psychotherapies for mental health problems

	Disorder	N	Intervention	Components	Main findings
Andersson et al[323]	Depression	197	Internet-based CBT	Self-tailored vs. clinician-tailored treatment; scheduled therapist support vs. support on demand; clients in supervision vs. not in supervision	Only self-tailored treatment was a little more effective than clinician-tailored treatment.
Bur et al[324]	Depression	316	Problem-solving therapy with CBT	Human support vs. not; diagnostic interview vs. not; motivational interviewing vs. not; automated e-mails vs. not	Human support resulted in better outcomes at post-test, but not at follow-up. The other three factors were not associated with better or worse outcomes.
Furukawa et al[71]	Depression	3,936	Unguided smartphone CBT	Behavioral activation; cognitive restructuring; problem solving; assertion training; behavior therapy for insomnia	All included skills and their combinations were superior to all control conditions.
Kelders et al[325]	Depression	239	Acceptance and commitment therapy	Human vs. automated feedback; text message coaching (present or absent); interaction (high or low); tailoring of success stories (high or low); personalization (high or low)	Human support was associated with better outcomes; no significant differences for any of the other components was found.
Sakata et al[322]	Depression	1,093	Unguided smartphone CBT	Self-monitoring; behavioral activation; cognitive restructuring; assertiveness training; problem solving	Depression reduction was not significantly associated with any component.
Sipka et al[326]	Social anxiety	464	Internet-based CBT	Psychoeducation; cognitive restructuring; attention training; exposure	All components were associated with improvement when compared to waitlist, but psychoeducation and exposure brought more improvement than the other two components.
Watkins et al[327]	Depression	767	Internet-based CBT	Activity scheduling; functional analysis; thought challenging; relaxation; concreteness training; absorption training; self-compassion training	None of the components was associated with better outcomes at post-test or 6-month follow-up, except for absorption training that had better outcomes at 6-month follow-up.

CBT – cognitive behavioral therapy

Table 4 Selected component network meta-analyses of psychotherapies for mental disorders

	Disorder	n	N	Intervention	Components	Main findings
Coventry et al[330]	PTSD	18	933	Psychological treatments	14 combinations of the following 11 components: active control; cognitive restructuring; imaginal exposure; in vivo exposure; mindfulness; multidimensional; psychoeducation; relaxation; support; virtual reality exposure; waitlist	Interventions that took a multicomponent approach were more effective than those that did not. None of the other individual components or examined combinations differed significantly from waitlist.
Furukawa et al[61]	Depression	48	11,704	Guided and unguided digital CBT	Waiting; conventional drug treatment; non-specific treatment effect; psychoeducation; cognitive restructuring; behavioral activation; interpersonal skills training; problem solving; relaxation; third-wave components; behavior therapy for insomnia; relapse prevention; homework required; initial face-to-face contact; automated encouragement; human encouragement; therapeutic guidance	There was suggestive evidence that behavioral activation might be beneficial and that relaxation might be harmful.
Furukawa et al[13]	Insomnia	241	31,452	CBT	Educational (sleep hygiene, sleep diary); cognitive (cognitive restructuring; third-wave components; constructive worry); behavioral (sleep restriction; stimulus control; relaxation; paradoxical intention; other (nonspecific treatment effect; waiting; conventional drug treatment); delivery (individual, group, in-person; online guidance; human encouragement; automated encouragement)	Cognitive restructuring, third-wave components, sleep restriction and stimulus control are critical components of CBT; sleep hygiene education was not essential and relaxation is potentially harmful; in-person therapist-led programs were most beneficial.
Miklowitz et al[17]	Bipolar disorder	39	3,863	Psychological treatments	Psychoeducation; psychoeducation including skills training; self-monitoring; self-management; cognitive restructuring; maintaining daily rhythms; behavioral activation; interpersonal problem solving; communication training; group format; family format; individual format	Cognitive restructuring and regulating daily rhythms were the most potent components for reducing severity of depression and manic symptoms; the least potent component was behavioral activation (and for depression also the individual therapy format).
Pompoli et al[331]	Panic disorder	72	4,064	CBT	Waiting; placebo effect; support; psychoeducation; breathing retraining; relaxation; cognitive restructuring; interoceptive exposure; in vivo exposure; virtual reality exposure, third-wave components; face-to-face setting	Interoceptive exposure and face-to-face setting were associated with better treatment outcomes. Muscle relaxation and virtual-reality exposure were associated with significantly lower efficacy.
Williams et al[332]	Early psychosis	37	4,599	Various early interventions	Pharmacotherapy; case management; psychological treatment; family intervention; social intervention	The addition of psychological interventions reduced negative psychotic symptoms at 3-month follow-up. No other significant finding at 3-month follow-up was found.

PTSD – post-traumatic stress disorder, CBT – cognitive behavioral therapy

treatment works and how large the effects are, they do not directly provide information on *how* treatments work. Much research has been done on mediators, but, when these are examined in trials, the findings are always correlational rather than causal[243,333]. This means that, when a mediator is significantly associated with the outcome of therapy in a trial, this can be explained in three different ways: a) the change in the mediator causes the outcome; b) the improvement in the outcome causes the improvement in the mediator; or c) a third variable causes the improvement in both the outcome and the mediator.

This issue of causality cannot be settled completely. But there are several factors that can help to make the causal relationship between a mediator and an outcome more plausible: a temporal relationship between mediator and outcome (change in the mediator comes before change in the outcome); a dose-response association; evidence that no third variable causes changes in the mediator and the outcome (usually by including many potential third variables in the study); supportive experimental research;

and a strong theoretical framework that can explain why the mediator is probably indeed a causal factor. There are also improvements in the methodology, such as the so-called "causal inference framework" that provide logical foundations for research in this area[334-336]. Working mechanisms, however, remain extremely difficult to examine.

This complexity of examining mechanisms of change in psychotherapies has resulted in many discussions about how they actually work. One important discussion is about common versus specific factors as key mechanisms of change[243]. The common factors model assumes that all therapies work through factors such as the alliance between therapist and patient, a rationale for causes of the problems and how to solve them, modeling, and catharsis, which are present in all therapies[211,337]. The specific factors model assumes that therapies work through specific mechanisms, such as changing maladaptive thoughts, changing actual behavior, or learning how to stop avoiding fearful situations.

Proponents of the common factors model often point to meta-analyses of outcome studies, which show that all therapies have comparable effects[243]. However, this does not necessarily prove that they work through common mechanisms. Component network meta-analyses can provide some insight on whether specific components have independent effects, which would support the specific factor model. Table 4 provides an overview of these meta-analyses, and several of them do suggest that some components contribute independently to the effects of therapies.

The most important common factor is undoubtedly the therapeutic alliance, i.e. the relationship between therapist and patient. This alliance has three components: the bond between the therapist and the patient, the agreement about the goals of therapy, and the agreement about the tasks of therapy[337]. The largest meta-analysis examining the association between the therapeutic alliance and outcome at one time point included almost 300 studies in adults[338]. There was a strong and significant association between the outcome and the alliance (correlation r=0.28, which corresponds to an SMD of 0.58), and this was true for face-to-face as well as for Internet-based therapies. A meta-analysis of studies in children and adolescents found a somewhat smaller, but still significant and substantial effect size (r=0.18, which corresponds to SMD=0.37).

As stated previously, an association between alliance and outcome cannot be considered as causal evidence showing that the alliance causes change. However, the above-mentioned meta-analysis in adults[338] also included a number of studies that examined the temporal association (change in the alliance precedes change in outcome), as well as an adjustment for baseline characteristics of patients that could explain the association. This supports the hypothesis that the alliance is a causal factor in generating change in patients, although the empirical evidence in this respect cannot be considered very strong[243].

Two different components of the alliance have been recently differentiated[339]. The "trait-like" component refers to the general ability of patients to form satisfying relationships with others, which also affects their capacity to form a satisfactory relationship with the therapist and to benefit from treatment. This trait-like component does not make alliance sufficient to generate change by itself, but can enable the use of other aspects of treatment that may induce change, such as effective techniques. The "state-like" component refers to changes in alliance that occur during treatment, which can be assumed to be the result of in-session work between patient and therapist. This component may contribute to trait-like changes in patients, which in turn enables the use of other aspects of treatment. This distinction between "trait-like" and "state-like" components of the alliance should be examined in more depth, but it does provide a new perspective, and may generate new knowledge on the mechanisms of change in therapy.

Another important issue in the process of therapy is the so-called "fidelity versus flexibility" question. This refers to whether a therapist should adhere strictly to the manual of a therapy, or can be more flexible in its application depending on the needs of the patient[340-342]. In RCTs, fidelity is an important element to strengthen the internal and external validity of the trial, and protocols with strong adherence of therapists are also those that are typically considered for implementation in routine care[341]. Fidelity also helps in limiting the number of sessions and facilitates training of therapists. In the IAPT program in the UK, aimed at increasing uptake of psychological treatments, fidelity to the protocols has been suggested to enhance efficacy considerably[65]. However, there are also several criticisms of treatment protocols. They have been called "cookbooks", they have been claimed to detract from the therapeutic alliance, and to be narrow and not broadly applicable[341]. It has been suggested that broader therapies, such as transdiagnostic approaches, offer more flexibility while retaining fidelity[340].

It remains unclear if more fidelity is associated with better outcomes. One earlier meta-analysis of 32 studies did not find that fidelity was significantly associated with outcome[343]. However, a more recent and extensive meta-analysis of 62 studies differentiated between adherence (prescribed methods are actually implemented in therapy), competence (knowledge, skills and appropriateness with which the methods are delivered), and integrity (that should include adherence, competence and treatment differentiation)[342]. This meta-analysis did find a significant association between integrity and outcome in two different groups of studies (r=0.15 and r=0.23).

It should be kept in mind that all this research is correlational, and cannot provide a definite answer to the "fidelity versus flexibility" question. To answer this question, new trials are needed in which patients are randomized to a fidelity or a flexibility condition, and to the best of our knowledge such trials have not been conducted. At this moment, it is not clear whether increasing or reducing fidelity can strengthen the outcomes of therapies.

Other innovations aimed to improve outcomes

One further innovation with the potential to improve outcomes of psychotherapies is the frequency of sessions. Meta-analytic research on psychotherapies for depression has suggested that, in individual therapy, the effects are not associated with the number of sessions, the contact time between patient and therapist, and the length of treatment[344,345]. However, meta-regression analyses did indicate that the frequency of sessions is significantly associated with the outcomes. Sessions twice per week are more efficacious than sessions once per week (SMD=0.60)[345].

Because meta-regression analyses do not provide causal, but only correlational evidence, more direct evidence is needed to confirm this finding. One RCT was conducted in which 200 outpatients with depression were randomized to once or twice weekly sessions of CBT or IPT[346]. It was found that those having sessions twice a week had better outcomes than those receiving sessions once a week (SMD at month 6: 0.55). Although these are preliminary findings that need to be confirmed in further research, this may be a promising innovation to improve the effects of psychotherapies.

Another innovation with the potential to improve outcomes is progress feedback. Outcome instruments are administered regularly throughout therapy[347] and monitored by the therapist. This allows the clinician to adjust treatment when there is too little progress, so that poor outcomes might be prevented[348-350]. The results of meta-analyses of RCTs that compare treatments with or without progress feedback have been mixed, with most of them finding small significant effects[351-353], but others finding no significant effects[354,355]. These meta-analyses, however, included subsets of studies aimed at specific target groups or using a specific feedback instrument, and all covered less than 20 trials. The largest meta-analysis in all target groups and any instrument included 58 trials[349], and found a small but significant overall effect of progress feedback (SMD=0.15). More research is needed to verify the effects of progress feedback, but this seems to be a promising method to improve outcomes.

Preventing and reducing adverse effects of psychotherapies

One important way to improve the outcomes of psychotherapies is to prevent or reduce their adverse effects. This is now widely recognized as a major priority for research and practice of psychotherapy[356-358].

For a long time, it has been assumed that adverse effects are not relevant in psychological interventions. The belief that psychotherapy, being "just talking", could not cause harm has led to patients rarely reporting these effects. Adverse effects are also not well reported in RCTs. For example, a meta-analysis of deterioration rates in psychotherapies for depression[359] found that only 6% of trials reported these rates.

One major problem in this area is the lack of consensus on what constitutes an adverse effect in psychotherapy. Clinically significant deterioration and suicide attempts are clearly important adverse effects. However, there is less clarity on what other events should be considered adverse effects. For instance, non-response and dropout could also be viewed as adverse outcomes, as they might prevent patients from receiving adequate care or experiencing spontaneous remission[360]. Other adverse effects that are often mentioned include treatment dissatisfaction, lack of therapeutic alliance, anxiety or rumination about therapy, emergence of new symptoms, stigmatization, and perceived negative effects of treatment on family/friends[356,357,361,362]. A systematic review of tools used to assess negative effects of psychotherapy included nine instruments[362]. They covered 17 domains of negative effects, but none of them covered all these domains.

One cluster of negative outcomes that has been examined extensively is represented by deterioration rates. Table 5 gives an overview of the results of meta-analyses providing data on deterioration rates in psychotherapies compared to control conditions[180,349,359,363-369]. Most research has been done in depression, but there are also some studies in anxiety disorders and PTSD. The deterioration rate in psychotherapies varied between 1 and 6%, while in the control conditions was between 5 and 17%. In almost all meta-analyses, the deterioration rate was significantly lower in psychotherapy compared to the control group.

Although there is now more attention to adverse effects of psychotherapies, and deterioration has been examined extensively in recent years, there is still a long way to go before methods to reduce adverse effects can improve clinical practice. More consensus on what adverse effects are is very much needed, and then more research should make clear how prevalent the different adverse effects are, and what methods can be used to prevent or reduce them.

Other methodological innovations in research on psychotherapies

In the past years, several new methodologies (in addition to those already described) have been developed that can help to speed up innovations in research on psychotherapies.

One important new design is the so-called "stepped wedge design", which is especially useful in research on the implementation of interventions in clinical practice[370]. This is a cluster-randomized trial in which all clusters (such as clinics or communities) start in the control condition. At regular intervals (the "steps"), a randomly selected subset of clusters moves from the control to the intervention condition. This continues until all clusters have received the intervention. This design makes it possible to examine the impact of the implementation of the intervention in routine care, and is increasingly used in mental health research[371-375].

Another important methodological innovation is represented by "platform trials"[376], which have transformed other areas of medicine, including oncology and infectivology, but are only now beginning to be used in mental health research[376,377]. In platform trials, an infrastructure with a master protocol is developed, allowing to compare multiple interventions against a single control group [378], to add new treatments as they become available, or to drop some when they turn out to be not useful.

Several platform trials on pharmacological interventions have been developed recently for PTSD, depression and psychosis[376]. In the field of psychological treatments, a recent study[71] tested the differential efficacy of five CBT skills (behavioral activation, cognitive restructuring, problem solving, assertion training, and behavior therapy for insomnia) on a smartphone app among people with

Table 5 Core meta-analyses examining reliable deterioration rates in psychotherapies versus control conditions

	Type of meta-analysis	Disorder	Type of psychotherapy	Control	n	N	Deterioration rate Psychotherapy	Deterioration rate Control	Relative outcome (95% CI)
Cuijpers et al[359]	Conventional MA	Depression in adults	Any therapy	Any	18	1,665	4%	11%	RR=0.39 (0.27-0.57)
Cuijpers et al[363]	MA imputed	Depression in adults	Any therapy	WL	101	NA	5%	13%	RR=0.27 (0.22-0.33)
Cuijpers et al[364]	MA imputed	Depression in youth	Any therapy	Any	38	NA	6%	13%	RR=0.40 (0.28-0.57)
De Jong et al[349]	Conventional MA	Any	Therapy with progress feedback	CAU	26	NA	5%	5%	OR=1.16 (0.99-1.35)
Fernández-Alvarez et al[180]	IPDMA	Anxiety disorders	VR interventions	WL	15	810	4%	15%	OR=4.87 (0.05-0.67)
Hoppen et al[365]	Conventional MA	PTSD	Any therapy	Passive	8	NA	1%	11%	RR=0.21 (0.15-0.28)
Karyotaki et al[366]	IPDMA	Depression	Self-guided digital interventions	Any	13	3,805	6%	9%	OR=0.62 (0.46-0.83)
Lofthouse et al[367]	MA imputed	PTSD in youth	Any therapy	Any	60	5,113	1%	13%	NA
Mather et al[368]	IPDMA	Depression in people with diabetes mellitus	Any therapy	Any	12	2,070	3%	7%	RD=-0.03 (-0.05 to -0.01)
Rozental et al[369]	IPDMA	Multiple disorders	Internet interventions	Any	29	2,866	6%	17%	OR=3.10 (2.21-4.34)

Some RRs and ORs are above 1 and others below, but they all indicate lower deterioration rates for psychotherapies compared to control condition (except for De Jong et al[349]). MA – meta-analysis, IPDMA – individual patient data meta-analysis, PTSD – post-traumatic stress disorder, VR – virtual reality, WL – waitlist, CAU – care as usual, NA – not available, RR – relative risk, OR – odds ratio, RD – risk difference.

subthreshold depression. The CBT skills were examined in four 2x2 factorial trials embedded in a large master protocol. This design, together with the digital infrastructure, enabled recruitment of 5,361 participants with or without subthreshold depression. The five skills were found to be differentially superior to three control conditions (delayed treatment, health information, and self-checks), not only on depression but also on anxiety, insomnia and well-being.

New methodologies are also being developed in the field of meta-analyses, such as the meta-analytic research domains (MARDs)[379]. These are living systematic reviews that cover a whole research domain, regardless of age, target group, or comparator, providing an overview of everything that can be known about the field from RCTs. MARDs have been developed for psychological treatments of depression[380], mental health problems in children and adolescents[381], suicidal behavior[382], and anxiety disorders[4]. They can be expected to bring meta-analytic research to a new level.

DISSEMINATION AND SIMPLIFICATION OF PSYCHOTHERAPIES

Conventional psychotherapies are in fact beneficial only to a tiny minority of those who could benefit from them[348,383-385], since more than 80% of the almost one billion people with mental disorders live in LMICs, with little access to them, and only a small proportion of patients in high-income countries receive these therapies. Here we focus on innovations in psychological interventions which can make them more scalable and easier to implement in large populations.

Task sharing

One major problem in the implementation of psychological treatments in LMICs is that the task force to deliver them does not or hardly exist. One solution to this problem is the so-called "task sharing", the delegation of tasks to community or primary care-based non-specialist workers with no formal degree or training in implementing mental health care[173,386]. Task sharing is indeed considered to be one of the main innovations to improve access to evidence-based psychological therapies in low-resource settings[383-386].

Task-sharing interventions have involved a wide variety of non-specialist health workers, such as community health workers, midwives, nurses, primary care providers, village health workers, complementary alternative health providers, teachers, religious and traditional healers, and community members[386]. Task sharing is firmly established in the delivery of care for maternal-child health and for human immunodeficiency virus (HIV) infection in low-income settings, but is also growing in global mental health care[383-386]. Although task-sharing interventions are especially important in low-resourced settings, they are also increasingly considered in higher-income contexts[387-389].

A considerable number of trials examining the effects of task-sharing interventions has been conducted. The largest meta-analysis was aimed at perinatal mental health[387]. It included 44 RCTs (18,101 participants), and found small but significant effects on depression (SMD=0.24) and anxiety (SMD=0.30). Some smaller meta-analyses estimated the effects of task sharing in LMICs compared to control groups, focusing on transdiagnostic behavioral activation interventions for common mental disorders (20 trials; SMD =0.59 for depression; SMD=0.61 for anxiety; SMD=0.38 for PTSD/trauma)[390], and for depression (11 trials, SMD=0.32)[173].

A systematic review of 19 trials on task-sharing interventions for substance use and substance use disorder in LMICs suggested positive effects, but, because no meta-analysis was conducted, this finding should be considered with caution[391].

Digital interventions in LMICs

Guided Internet-based interventions can be delivered by trained lay counsellors without extensive training. Self-guided interventions do not require any human contact with patients. These interventions have, therefore, much potential from the perspective of global mental health, especially since the majority of the world population now owns a smartphone and has access to the Internet[392].

The largest meta-analysis of digital interventions for depression and anxiety in LMICs included 80 randomized trials (12,070 participants), most of which were conducted in 2020 or later[393]. This meta-analysis was very liberal in its inclusion criteria (physical exercise interventions were also included, as well as studies in high-risk groups without depression or anxiety at baseline), but it did find substantial and significant effects for depression (SMD=0.61) and anxiety (SMD=0.73).

Another meta-analysis of RCTs in LMICs focused exclusively on digital psychological interventions for people with depression and/or anxiety, and included 21 trials (5,296 participants)[62]. The interventions resulted in substantial effects on depression (SMD=0.77) and anxiety (SMD=1.02), and small but significant effects on quality of life (SMD=0.32), when compared with control conditions. Over the longer term, the effects were smaller, but remained significant for all examined outcomes.

An important finding of this meta-analysis was that no significant difference (p=0.93) was found between interventions with human support (SMD=0.90 against controls; 15 studies) and unguided interventions (SMD=0.87 against controls; 8 studies). Most previous research suggested that interventions without human support have significantly smaller effects than those with support[57]. This may not be true, however, in LMICs, for example because usual care differs considerably from high-income countries. This is a highly important finding from a dissemination point of view, because delivery of unguided interventions is much cheaper than that of guided interventions.

Single-session interventions

Another method to make treatments more scalable and easier to implement is to make them shorter. Meta-analytic research on

Table 6 Summary of innovations in psychotherapies for mental disorders and their main supporting evidence

	Description of innovation	Core studies on outcomes
Innovations in the digital field		
Internet-based therapies	Guided and unguided self-help interventions applied digitally	>250 RCTs in multiple disorders and several meta-analyses have shown effects (see Table 1)
Smartphone apps	Apps on mobile phones	A meta-analysis of 176 RCTs[72] showed small significant effects for common mental disorders
Ecological momentary interventions	"Therapist in your pocket" approaches; use of sensors from smartphones/devices to intervene during everyday life	Potential to improve treatment for a broad range of problems, but too few RCTs available to make a final judgment; no meta-analysis yet available
Just-in-time adaptive interventions	Interventions providing the right type and amount of support, at the right time, by adapting to an individual's internal and contextual state	Potential to improve treatment for a broad range of problems, but too few RCTs available to make a final judgment; no meta-analysis yet available
Serious games	Games that are not devised just for recreation, but also to address mental health problems	Few RCTs in people with mental disorders; some potential effects on depression/anxiety[93,94]
Virtual reality	Three-dimensional interactive computer-generated environments creating the sensation of being present in the environment	>50 RCTs in multiple disorders; overall positive effects, but not more effective than ordinary treatments[102]
Augmented reality	Technology that blends virtual and physical environments, enhancing one's perception of reality	Too few RCTs available to assess if it has additional value over ordinary treatments[107,108]
Prescription digital therapeutics	Digital treatments rigorously evaluated for safety and effectiveness, and authorized by national regulatory agencies	Several treatments approved by FDA in ADHD, PTSD, depression, substance use[109]
Blended therapy	Combined face-to-face and digital treatments	Nine RCTs showed positive effects, but not yet clear if it results in better effects and/or uptake
Avatar therapy	Patients with psychosis create an avatar aimed at reducing auditory hallucinations	A growing number of RCTs shows effectiveness in reducing severity of persistent verbal auditory hallucinations[119,120]
Chatbots/conversational agents	Chatbots that operate through artificial intelligence	Only few RCTs; not yet possible to examine effects or compare with ordinary therapies[126,127]
Personalized treatments		
Predictors/moderators in large RCTs	Research on characteristics of people who respond better to specific treatments	Very large RCTs are needed to examine predictors/moderators; a few have been done, but no clear outcomes yet
Individual patient data (network) meta-analyses	Meta-analyses in which the primary data of RCTs are combined into one dataset	Growing number of published meta-analyses, especially in depression, but until now only limited evidence for significant predictors/moderators (see Table 2)
Machine learning approaches	Techniques allowing researchers to evaluate many predictors/moderators at the same time, in large datasets	Growing number of studies, but until now only limited evidence for significant predictors/moderators
Matching therapists to patients	Patients are assigned to therapists that have been shown to be effective for their problem area	This may increase outcomes, which is confirmed by a well-designed RCT[214]
Personalized/modular therapies	Personalized therapies are tailored to specific characteristics of patients; modular therapies are toolboxes from which the clinician selects modules that are relevant for a patient	Growing number of studies; no consensus yet on what relevant characteristics are; some studies are positive, other negative; MATCH is the best examined modular therapy for youth, but its outcomes are mixed
New and improved therapies		
Cognitive bias modification	Therapy aimed at changing cognitive biases through structured, computer-based training to modify automatic responses	Some types have small but significant effects on depression and anxiety; effects on alcohol problems are unclear[260,261]
Cognitive remediation	Therapy targeting cognitive deficits (attention, memory, executive function, social cognition, metacognition)	Effects on some cognitive deficits in schizophrenia[271]; small significant effects on negative symptoms in schizophrenia[275] and on symptoms of depression[276]
Psychedelic-assisted psychotherapy	Therapies in which psychedelics are used to augment psychotherapy effects	Small number of trials; effects are positive and strong[282], but there are many methodological problems
Transdiagnostic therapies	Treatments that apply the same underlying principles across disorders, without tailoring the protocol to specific diagnoses	A meta-analysis of 53 RCTs in emotional disorders found large effects on depression and anxiety[310]; unclear if they are more effective than disorder-specific therapies

Table 6 Summary of innovations in psychotherapies for mental disorders and their main supporting evidence *(continued)*

	Description of innovation	Core studies on outcomes
Factorial trials	Trials can examine the effects of multiple components of an intervention	Growing number of trials, but too little research yet to draw definite conclusions (see Table 3)
Component network meta-analyses	These can disentangle associations of components of interventions with outcomes	Growing number of meta-analyses, but too little research yet to draw definite conclusions (see Table 4)
Focus on common factors and therapeutic alliance	Unclear whether effects of therapy are mostly caused by common or specific factors; alliance is the most important common factor	A meta-analysis of 295 studies found a strong correlation between alliance and outcome[338]
Focus on adverse effects	It is not clear what adverse effects of psychotherapy exactly are, but deterioration rates are relatively well examined	Multiple meta-analyses show that clinical deterioration rates vary between 1 and 6% in therapy and between 5 and 17% in control conditions (see Table 5)
Increased session frequency	Higher frequency of sessions may be associated with better outcomes	Indirect evidence from meta-analyses[346]; more RCTs needed to confirm the findings
Progress feedback	Outcome instruments are administered regularly throughout therapy and monitored by the therapist	Meta-analyses show small, but significant effects[349]
Dissemination and simplification of therapies		
Task sharing	Tasks are delegated to non-specialist workers with no formal degree or training in mental health	Meta-analyses find positive effects in depression and anxiety[388,390]
Digital interventions in LMICs	Guided and unguided self-help interventions applied digitally, developed mostly for depression and anxiety	Meta-analyses show positive results in depression and anxiety[393]; no significant difference between guided and unguided interventions[62]
Single-session interventions	Structured programs that intentionally involve only one visit or encounter with a clinic, provider or program	Review of 16 meta-analyses found overall positive effects on anxiety and depression[394]

RCT – randomized controlled trial, FDA – US Food and Drug Administration, ADHD – attention-deficit/hyperactivity disorder, PTSD – post-traumatic stress disorder, MATCH – Modular Approach to Therapy for Children with Anxiety, Depression, or Conduct Problems, LMICs – low- and middle-income countries

psychological treatments for depression has shown that the number of sessions in individual therapy are not associated with the outcome[344,345]. This suggests that it may be possible to reduce the number of sessions without reducing the effectiveness of therapies. It has also been found that dropout rates are very high in psychotherapies, and that many patients who start therapy often do not receive more than one session[394-396]. This is in stark contrast with the design of most therapies, which typically include 6 to 60 sessions[344,345].

Single-session interventions can be defined as "structured programs that intentionally involve only one visit or encounter with a clinic, provider, or program"[394,397]. Other names that have been used include "one-session treatment"[398], "ultra brief intervention"[399], and "one-at-a-time therapy"[400]. Research on these interventions is not new, going back to the 1980s[398,401]. However, since the need for scaling up interventions has been emphasized in recent years[383,384], research on single-session interventions has increased considerably.

A recent umbrella review covered 24 systematic reviews of single-session interventions[394], including 16 meta-analyses encompassing 322 RCTs (40,629 participants). Most included meta-analyses reported positive outcomes for anxiety (significant effects in 8 of 9 meta-analyses), depression (5 of 6), substance use (8 of 10) and externalizing problems in children (2 of 2). Outcomes were less certain in eating problems (one meta-analysis with positive effects and one without) and suicidal behavior (one meta-analysis with positive outcomes in adults, but not in youth). Four meta-analyses included trials directly comparing single-session with multi-session interventions, with two indicating no significant differences[402,403], one better outcomes for single-session interventions[404], and one better outcomes for multi-session interventions[405]. A second-order meta-analysis of the trials from 12 meta-analyses resulted in a pooled effect of SMD=0.25 in favor of single-session interventions[394].

Overall, it seems that single-session interventions can have positive effects on mental health problems. Because they are much more scalable than longer interventions, their potential is considerable. However, not all research on these interventions is positive. An earlier meta-analysis of single-session debriefing after psychological traumas (not included in the above-mentioned umbrella review) did not find that these interventions were effective in this population[406]. This suggests that single-session interventions have the potential to be effective, but research on the type of interventions, the population and the setting is needed, before dissemination can be considered.

CONCLUSIONS

We reviewed the current state of innovations that may improve outcomes and uptake of psychotherapies for mental disorders (see Table 6 for a summary). We categorized the innovations into the domains of the digital field, stratification and personalization, new and improved therapies, and the dissemination and simplification of treatments. We also touched upon methodological innovations, such as new methods to personalize therapies, and new trial designs that can improve or speed up clinically relevant outcome research.

We recently developed a simple method to assess the strength of innovations in the treatment of depressive disorders, based on the total number of treatments needed to achieve a response in 100% of patients[407]. This method indicates that none of the current innovations is likely to serve as a "silver bullet" that will dramatically improve outcomes. Although obtained for depression, similar results can be expected for other mental disorders. Rather than expecting a paradigm-shifting breakthrough, we should therefore focus on innovating the practice of psychotherapies incrementally, through various small-scale improvements. This path is more laborious, and it may often yield solutions that remain imperfect, context-dependent, or elusive. Yet, this approach aligns with modern theories of how science progresses in medicine and beyond [408-411], and it has the potential to meaningfully enhance outcomes in the future.

In this paper, we have specifically focused on innovations that have the potential to improve outcomes and uptake of psychotherapies for mental disorders. There are many other innovations in relevant areas that we did not focus on, such as for example the rapidly developing field of digital phenotyping[412], and alternative systems for diagnosing mental disorders[413].

We did not conduct pre-planned, systematic searches for each of the innovations, because that was not feasible, considering the number of innovations and the width of such searches. This means that we may have missed relevant studies that support some innovations. We also had no way of systematically identifying the innovations, so we relied on our knowledge and reading of the literature. Because of the large number of studies that we included in this paper, it was also not possible to assess the quality and risk of bias in the included trials and meta-analyses.

We can conclude that there are currently many innovations in the field of psychotherapies in different stages of development and with varying levels of empirical support. None of these innovations will be a silver bullet that dramatically improves the outcomes and uptake of treatments, and only the joint implementation of several of them may produce tangible improvements.

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