The *Lancet Psychiatry* Commission on psychological treatments research in tomorrow's science

Emily A Holmes, Ata Ghaderi, Catherine J Harmer, Paul G Ramchandani, Pim Cuijpers, Anthony P Morrison, Jonathan P Roiser, Claudi L H Bockting, Rory C O'Connor, Roz Shafran, Michelle L Moulds, Michelle G Craske

Lancet Psychiatry 2018
5: 237–86

Division of Psychology, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden (Prof E A Holmes PhD, Prof A Ghaderi PhD); **Department of Psychiatry, University of Oxford, Oxford, UK** (Prof C J Harmer DPhil); **Oxford Health NHS Trust Foundation, Warneford Hospital, Oxford, UK** (Prof C J Harmer); **Centre for Mental Health, Imperial College, London, UK** (Prof P G Ramchandani DPhil); **Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health Research Institute, Vrije Universiteit Amsterdam, Amsterdam, Netherlands** (Prof P Cuijpers PhD); **Psychosis Research Unit, Greater Manchester Mental Heath Trust, Manchester, UK** (Prof A P Morrison ClinPsyD); **School of Psychological Sciences, University of Manchester, Manchester, UK** (Prof A P Morrison); **Institute of Cognitive Neuroscience, University College London, London, UK** (Prof J P Roiser PhD); **Academic Medical Center, Department of Psychiatry, University of Amsterdam, Amsterdam, Netherlands** (Prof C L H Bockting PhD); **Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK** (Prof R C O'Connor PhD); **University College London Great Ormond Street Institute of Child Health, London, UK** (Prof R Shafran PhD); **School of Psychology, The University of New South Wales, UNSW, Sydney, NSW, Australia** (Prof M L Moulds PhD); **and Department of Psychology and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA, USA** (Prof M G Craske PhD)

Executive summary

Background

Psychological treatments occupy an important place in evidence-based mental health treatments. Now is an exciting time to fuel treatment research: a pressing demand for improvements is poised alongside new opportunities from closer links with sister scientific and clinical disciplines. The need to improve mental health treatment is great; even the best treatments do not work for everyone, treatments have not been developed for many mental disorders, and the implementation of treatments needs to address worldwide scalability. Psychological treatments have yet to benefit from numerous innovations that have occurred in science, particularly those that have emerged in the past 20 years, and arguably vice versa. This Commission comprises ten parts that each outline an area in which we see substantial opportunity and scope for advancements that will move psychological treatments research forward.

Part 1: How do existing treatments work? Making the case for the mechanisms of psychological treatments

Beyond knowing that an intervention is efficacious, research initiatives are needed that clarify the key mechanisms through which interventions work. An experimental psychopathological approach enables the identification of mechanisms. Research on these mechanisms has considerable scope to facilitate treatment innovation.

Part 2: Where can psychological treatments be deployed? Research to improve mental health worldwide

We outline a number of factors to facilitate worldwide access to psychological treatments. Future research initiatives need to continue to develop and assess the efficacy of brief and flexible interventions that can be adapted to meet the needs of individuals across cultural contexts, and delivered and disseminated in a sustainable way.

Part 3: With what? The potential for synergistic treatment effects—using and developing cross-modal treatment approaches

The combination of psychological and pharmacological treatments needs to be better understood, both in terms of the clinical effect and the underlying shared and different mechanisms. Efforts to develop and investigate the efficacy of novel cross-modal treatments could contribute to treatment innovation.

Part 4: When in life? Psychological science, prevention, and early intervention—getting the approach right from the start

The social and economic tolls of mental health problems early in life make the development of effective prevention and early intervention approaches a priority. A preventive focus and a developmental approach are needed to identify risk factors for psychopathology, and identification of the optimal time at which to offer prevention approaches is needed to increase the likelihood of vulnerable young people growing up with positive mental health.

Part 5: Technology—can we transform the availability and efficacy of psychological treatment through new technologies?

New technologies provide exciting and timely means by which to disseminate and extend the efficacy and global reach of evidence-based interventions. eHealth and mHealth approaches that use information technology (eg, the internet, virtual reality, serious gaming) and mobile and wireless applications (eg, text messaging, apps) are examples of how technology has been harnessed to innovate psychological treatments and their availability and evaluation.

Part 6: Trials to assess psychological treatments

The findings of randomised controlled trials that assess psychological therapies inform policy and practice. Accordingly, the design and conduct of these trials warrants scrutiny and ongoing efforts for quality improvement (eg, reporting standards, specification of protocols, inclusion and exclusion criteria, choice of outcome measures, measurement of adverse effects, and prevention of bias in design and analysis). We outline several opportunities for further improvement that should enhance the credibility and quality of future trials.

Part 7: Training—can we cultivate a vision for interdisciplinary training across mental health sciences to improve psychological treatments?

Early examples of collaboration between basic scientists and clinicians translated into historical steps in the innovation of psychological treatment. Such synergy has become less apparent in the past few years. The improvement in links between clinical psychology, psychiatry, and basic research has the potential to deliver more advances in psychological treatments. We propose opportunities to improve training in interdisciplinary mental health sciences. This training approach would be the first step toward forging links between scientists and

Correspondence to:
Prof Emily A Holmes, Division of Psychology, Department of Clinical Neuroscience, Karolinska Institutet, SE-171 77 Stockholm, Sweden
emily.holmes@ki.se

clinicians in the next generation and bridging the gap between clinical practice and the basic research programmes that underpin psychological treatments.

Part 8: Whom should we treat, for what, and with what? Embracing the complexity of mental disorders from personalised models to universal approaches

Mental disorders are inherently complex (eg, heterogeneity in symptoms across disorders, high rates of comorbidity) and evidence-based treatments must address this complexity. Potential solutions include considering both highly individualised (ie, personalised) approaches and so-called universal or transdiagnostic approaches that target common mechanisms. A goal of future research will be to examine whether these approaches improve treatment effectiveness.

Part 9: Target: suicidal behaviour—protecting lives

Suicidal behaviour is one of many areas in which advances are needed. Despite developments in the understanding of risk factors that predict the likelihood of suicide attempts, and the treatment and prevention of suicidal behaviour, many questions remain. We specify areas for future research—eg, use of new technologies, the role of culture, input from individuals with lived experience of suicidal behaviour, and using a team-based approach in the development, assessment, and dissemination of prevention efforts.

Part 10: Active innovation and scrutiny of future psychological treatments research

The task of improving psychological treatments is an exciting prospect for scientists and clinicians with an interest in the so-called science of mental life. Clinicians, researchers, service users, carers, funders, commissioners, managers, policy planners, and change experts all have a part to play in improving psychological treatment. Some long-held ideas need examination, from the branding of psychological treatment types, to considering what people actually want treatment for. Scrutiny of new ideas should be rigorous and yet encourage innovation.

Introduction

Psychology and psychological treatments

Psychology from its inception was defined as "the science of mental life".[1] Psychological treatments have developed to occupy a key place in evidence-based treatments for mental health. Many pivotal techniques used in evidence-based psychological treatments arose from psychological research on processes in the 1950s and 1960s, with basic and clinical researchers often in the same department. During the past few decades, the psychological treatment field has drifted away from its scientific roots, while mechanistic studies have drifted away from treatment issues. Now is the time for greater synergy between basic and clinical researchers to invigorate psychological treatment research.[2] Psychological treatments offer great promise for continued innovation, not least because of the development of scientific methods and perspectives from many allied fields.

While researchers and industry struggle to produce new drugs for mental disorders, psychological treatments research might have the potential to deliver acceptable, effective, and safe treatment options more quickly.[3] Building bridges between psychological treatment and other modalities—eg, via combination approaches—could also benefit many service users, but will not be an easy task. New trials of psychological treatments are met with not only enthusiasm, but also controversy. Questions are constantly being asked about trial design, implementation, and interpretation. Do trial populations reflect real clinical populations? What is an appropriate control group? At what point should trial evidence be translated into day-to-day practice? How can an inter-vention be disseminated nationally and internationally? Existing assumptions are also being queried, for instance, is single-session therapy feasible? Is one consistent therapist an optimal or even necessary component of psychological treatment? How can new technologies best be harnessed?

We note that in the wider literature many terms are used, including mental health disorder, psychological disorder, psychiatric disorder, mental health problem, and other forms of terminology associated with psychological treatments, such as mental health difficulties and behavioural difficulties. In line with *Lancet Psychiatry* terminology and for consistency, the term mental disorder is used in this Commission.

A core role for psychological treatments in the future requires a research agenda

The burden of mental disorders is enormous, and yet pharmacological and psychological treatments scarcely reduce the disease burden. Since most patients prefer psychological treatments over pharmacological treatments,[4] increased research efforts are required to develop psychological treatments to a point at which they will have a substantial effect upon the mental disease burden worldwide. To realise the development of psychological treatments, a research agenda is needed that can guide the field for the coming years. For example, a 2014 commentary[2] on improving psychology treatments stated: "By the end of 2015, representatives of the leading clinical and neuroscience bodies should meet to hammer out the ten most pressing research questions for psychological treatments. This list should be disseminated to granting agencies, scientists, clinicians, and the public internationally. Mental-health charities can help by urging national funding bodies to reconsider the proportion of investments in mental health relative to other diseases."[2]

Mental disorders are widespread and costly

Every year almost one in five people worldwide develops a mental disorder,[5] and more than 750 000 people die by suicide.[6] In 2010, mental and substance-use disorders

accounted for 183·9 million disability-adjusted life-years,[7] with most of the disease burden caused by depressive disorders, anxiety disorders, and substance-use disorders. These numbers are likely to be an underestimation since these calculations assume that mental disorders are not associated with excess mortality, except suicide. However, people with mental disorders have a considerably higher risk of dying earlier than those without mental disorders.[8]

Apart from the personal suffering of affected patients and their families, mental disorders pose enormous economic challenges to communities and societies, in terms of production losses and health and social care expenditures.[9–11] The global cost of mental health conditions in 2010 has been estimated at US$2·5 trillion, and these costs are expected to grow to $6·0 trillion by 2030.[12] For this reason, conceptualisations of mental health need to expand beyond the notions of disease or infirmity to functionally related outcomes or, more broadly speaking, the ability to adapt and self-manage.[13]

Treatments make a small contribution to the reduction of the disease burden

Several evidence-based biological and psychological treatments are available for a range of mental disorders. However, these treatments are estimated to be able to reduce the disease burden by only about 40%, and only under optimal conditions and when all patients with a mental illness receive evidence-based treatment.[14] Globally, coverage (ie, the proportion of people who receive a consultation for a mental disorder) is typically much lower than 100%, with coverage well below 50% for some disorders (eg, eating disorders) in most regions,[15] and for some disorders (eg, alcohol-related disorders) coverage is below 10%.[16] The 2014 Adult Psychiatric Morbidity Survey,[17] noted a welcome increase in the number of people with common mental disorders who are receiving treatment. This increase has been largely attributed to the use of psychotropic medication.[17] Unfortunately, most patients who are treated for mental disorders do not receive evidence-based treatments, but instead receive a wide array of treatments including interventions that are not evidence based.[18]

Patient preference for psychological treatment options alongside restricted availability

In the USA, psychotherapy has assumed a less prominent role in mental health care than have treatments with medication.[19] For example, in the USA, antidepressant use almost doubled between 1996 and 2005, from 13 to 27 million individuals, whereas the percentage of people among antidepressant users who underwent psychotherapy declined from 31·50% to 19·87%.[20] In an office-based clinical practice, between 1999 and 2010, on average 8·6% of visits made by adults with depression included the prescription of a second-generation antipsychotic drug,[21] and the frequency of use doubled from 4·6% in 1999–2000 to 12·5% in 2009–10. By contrast, most patients seem to prefer psychotherapy over medication. A meta-analysis[4] of patients with a range of mental disorders (eg, depression, anxiety, insomnia, bipolar disorder, schizophrenia, substance-related disorders, eating disorders, and personality disorders) estimated that approximately 75% of patients prefer psychotherapy as their treatment as opposed to medication. However, some patients do prefer pharmacological treatment, whereas others might have no preference. In this Commission we do not seek to reinforce what we believe to be a misplaced dichotomy between biological and psychological approaches (see Part 3), instead we seek a research agenda that is open to multiple perspectives, does not neglect one perspective at the expense of another, considers links between both perspectives, is informed by patient preferences, and ultimately leads to the greatest clinical effect.

Although most patients prefer psychotherapy to medications,[4] the availability of such treatment is a major problem in many countries.[22] This paucity of availability is attributable to a range of factors, including financial constraints or the scarcity of trained psychotherapists who can deliver the evidence-based treatments. Therefore, psychotherapy is mostly delivered in high-income countries to those who can afford it and know how to find a therapist. In low-income and middle-income countries, psychological treatments are scarce—although notable exceptions exist (see Part 2).[23]

Several approaches are being developed to increase access to psychological services, such as the Increasing Access to Psychological Treatment (IAPT) programme in the UK, in which low-intensity psychotherapies are made available on a large scale and high-intensity therapies are available for those who do not respond to low-intensity therapies.[24] Internet-based interventions (see Part 5) can help in making psychotherapies available to those who need them since these interventions can be offered relatively inexpensively and with a low threshold for access. Another important development to make therapies more accessible is to use so-called lay health counsellors (see Part 2).

Psychological treatment research in tomorrow's science

Improved psychological treatments are needed to help reduce the burden of mental disease worldwide. The landscape of psychological treatment research is ready for innovation, offering exciting and auspicious opportunities for research in the mental health sciences. Insights from different fields of science might allow us to "stand on the shoulders"[25] of existing evidence-based psychological treatments and see further to improve psychological interventions. Greater collaborative endeavours between clinical and basic researchers of many disciplines will help in this regard.[2]

In this Commission, we discuss opportunities to focus future research efforts to improve worldwide mental health. Suitable areas of inquiry for future research

include: understanding the mechanisms that underlie psychological treatments, increasing worldwide access to treatments, developing cross-modal treatment approaches, and enhancing preventive and developmental approaches. To address each of these themes, new tools will be needed, which will be provided by new technologies, improved trial methodologies, and improved training in interdisciplinary mental health sciences, to name but a few sources. In this Commission, we discuss how the goals of people developing and delivering psychological treatments should be to embrace challenging areas, such as the inherent complexities of mental disorders and issues such as suicide prevention. The array of challenges ahead to which a psychological perspective can contribute will require fresh innovation.

Research into these areas will require ideas to be tested, and rejected or developed in line with scientific methods and challenges of mental health of the time (as opposed to therapeutic habit and allegiance to a specific manner of clinical training, or science focused inwardly on itself rather than on genuine application); therefore, attitudes within mental health science will need to change. To illustrate, we make an analogy with a British contemporary art initiative that is engaged with Trafalgar Square's empty plinth in London, UK. Statues are on three of the four plinths in the corners of Trafalgar Square and the fourth plinth stood empty for over a century (figure 1). Now, the so-called Fourth Plinth Programme[26] invites world-class artists to make "astonishing" new artworks for the centre of the capital city. Commissions create a rolling programme of temporary artworks rather than settling permanently on one figure or idea. The resultant sculptures tend to be shown for a year, although sometimes only for a few months, and sometimes the plinth is empty for a period of time; however, the momentum of the programme and scrutiny over the choice of statues continues. Some artworks stand the test of time, whereas some might not. Associated initiatives encourage projects and creative thinking around past and present artworks displayed on the fourth plinth. However, the best use of the fourth plinth remains a subject of debate and discussion in the public, media, and art world.

Figure 1: **The fourth plinth in Trafalgar Square, London, UK**

Like the Fourth Plinth Programme, psychological treatments research needs innovation, rotation of ideas, and robust critical debate as a clear part of advancing research. Although the objects of inquiry might change, the principles of seeking to improve research efforts towards improved mental health will persist. Instead of being prescriptive regarding the future of psychological treatments research, this Commission sets out various suggestions and principles to guide research that should apply across different mental disorders and transdiagnostic processes, approaches, countries, and, indeed, to the new and future generations of mental health researchers. These principles might change over time and how best to strengthen psychological treatments should be a subject of research, debate, and discussion, involving the fields of both psychological treatments and mental health science, and many fields beyond these.

When considering the traditional delivery method of psychological treatments, the changes that can come about from two people talking with each other for a matter of hours during therapy sessions are fascinating, sometimes remediating years of mental distress. Although clearly the presence of another person can be helpful, evidence-based psychological treatments involve far more than just skills that boost therapeutic alliances. Therapeutic effects are now known to be achievable without a therapist being physically present (eg, via internet therapy, see Part 5) and some psychological techniques can be effective when delivered by lay workers with modest training (see Part 2). Moreover, neuroscience continues to reveal how efficiently the mind can work under various parameters (eg, in modulating memory) by a range of techniques that may or may not require another person to be present. The emotional, behavioural, and social changes rendered through therapy pose mechanistic questions for mental health science—eg, how do effective psychological treatments work? The identification of specific targets for mechanistic questions might be facilitated not only by quantitative methods but also by qualitative methods—eg, detailed narratives of individuals' experiences as they undergo psychological treatments. Once potential targets have been identified in this way, they could be subjected to experimental investigation to establish causality for therapeutic change.

We now focus and elaborate on the ten key themes that we see as instrumental to consider in the development of an agenda to progress mental health treatment research. These themes, which were decided as part of a consultation meeting in December, 2015 (panel 1), are not exhaustive and many more are to be welcomed for future scrutiny.

Part 1: How do existing treatments work? Making the case for mechanisms of psychological treatments

Introduction

Although some psychological treatments are effective, little is known about the processes through which therapeutic change occurs. As Alan Kazdin stated in his 2007 review,[27] many evidence-based therapies are available but little understanding exists of the mechansims of change or precisely how they work. Understanding mechanisms of action is essential to derive and hone treatment strategies to directly target the mechanisms, remove irrelevant strategies, and develop novel approaches that are more expeditious and effective than current treatments. Knowledge of mechanisms also allows improved precision in matching psychological treatments to the needs of individuals to improve outcomes compared with current methods.

Research into the mechanisms of treatments offers an exciting opportunity for psychological treatment research. However, most studies in psychopathology have simply described differences between groups of individuals with and without a diagnosis and identified a mechanism of action by use of these differences—an approach that cannot identify causal mechanisms. To move the field toward understanding causality, research on mechanisms should be optimised by framing research within the context of clinical treatment to understand how existing treatments work, and derive new and improved treatments.

What is a mechanism of psychological treatment?

Mechanisms of psychological treatment are defined as "the steps or processes through which therapy (or some independent variable) actually unfolds and produces the change. Mechanisms explain how the intervention translates into events that lead to the outcome."[27] A mechanism is an explanatory construct and not simply an intervening variable that explains the statistical association between an intervention and an outcome. For example, the finding that changes in a patient's perceived self-efficacy and outcome expectancy statistically mediates the subsequent changes in anxiety and functioning[28] does not explain how the changes in self-efficacy and outcome expectancy lead to those outcomes. The underlying changes responsible for symptom improvement could involve multiple processes, including, but not limited to, neural systems, other physiological systems, cognitions, emotions, and behaviours.

The processes through which psychological treatments produce change often overlap with or complement mechanisms that are responsible for the onset or, in particular, the maintenance of psychopathology (hereafter referred to as mechanisms of psychopathology). The US National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative is directing the search for mechanisms of psychopathology away from the constraints of categorical diagnostic criteria and towards dimensions of observable behaviour and neurobiological measures.[29] The RDoC initiative aims to "elaborate a set of psychological constructs linked to behavioral dimensions for which strong evidence exists for circuits to implement these functions, and relate the extremes of functioning along these dimensions to specified symptoms (i.e., impairment)."[30] Essentially, the RDoC framework aims to identify biopsychological explanations or so-called process constructs for clinical events; these same process constructs could explain change in clinical events throughout treatment. The provisional list of RDoC explanatory constructs includes negative valence systems, positive valence systems, cognitive systems, systems for social processes, and arousal or modulatory systems, with each construct comprising more specific subconstructs.[30] The constructs are assessed with measures that represent at least seven levels called units of analysis: genes, molecules, cells, neural circuits, physiology, behaviour, and self-report. Identifying a mechanism using one unit of analysis does not exclude mechanisms identified using other units of analysis.

Mechanisms of psychopathology vary from being predominantly distal (eg, effects of early life adversity upon inflammatory markers for depression that might not become apparent until many years later[31]) to predominantly proximal (eg, ongoing biases in autobiographical memory for depression;[32] see Roiser's 2015 article[33] for a discussion of these ideas). Mechanisms of psychopathology also vary from being predominantly fixed (eg, within genes, albeit with variations in expression) to predominantly malleable (eg, negative interpretation bias for ambiguous stimuli). Psychological treatments generally target the predominantly proximal and malleable mechanisms of psychopathology—eg, attention bias

Panel 1: **Methodology and approach used in preparing this Commission**

- This Commission arose from an initial consultation meeting in December, 2015, in which researchers from a variety of backgrounds with interests or expertise in psychological treatments research met to discuss challenges in the field, and to lay out possibilities for a future research agenda for advancing the science of psychological treatments
- The group's common interest was captured by Kazdin's call to arms to "reboot psychotherapy research and practice to reduce the burden of mental illness"[22]
- Attendees' backgrounds in terms of subject disciplines included clinical psychology, psychiatry, neuroscience, experimental psychology, and pharmacology
- The language of the meeting was English, and attendees were from the UK, Europe, and the USA; in this Commission we have only cited papers that have been published in English
- The Commission expresses the authors' collective views about some of the key areas in which we see scope for improvements in the field; our goal was not to provide an exhaustive literature review, or a systematic review of specific topics; rather, we have cited sources that are relevant to the issues that we have discussed in the context of each of the ten themes
- We note that many important topic areas and perspectives continue to develop, and that this Commission is a start for necessary and continued discussion

modification training for anxious individuals who have selective attention bias towards threat-relevant stimuli.[34] Alternatively, psychological treatments can target factors that differ from mechanisms of psychopathology but compensate for them—eg, compensatory cognitive training for psychosis.[35] Although less commonly targeted, distal mechanisms can be particularly good targets for prevention efforts. Notably, not all treatment mechanisms are directly tied to mechanisms that are responsible for the onset or maintenance of psychopathology; some treatments work through independent processes—eg, applied behavioural analysis techniques for individuals with autism.[36]

What is the state of the field?

Pivotal evidence-based psychological treatments have evolved by specifically targeting identified mechanisms of psychopathology, one example of which is the treatment of panic disorder. Through a series of experimental investigations and animal modelling, interoceptive conditioning (ie, acquired fear of visceral or other internally generated stimuli due to pairing with an aversive outcome, such as pairing an elevated heart rate with the possibility of a heart attack) and catastrophic misappraisal (ie, misinterpretations of interoceptive stimuli as harmful or threatening) were recognised as mechanisms underlying the fear of bodily sensations that characterises panic disorder.[37–39] Psychological treatments for panic disorder were developed to target specific mechanisms in the form of interoceptive exposure[40] (ie, repeated exposure to interoceptive stimuli in the absence of aversive outcomes) and cognitive restructuring[41] (ie, reasoning skills to replace catastrophic interpretations with evidence-based interpretations). This type of treatment has been shown to be particularly effective for panic disorder, and more effective than non-targeted supportive psychotherapy (Hedges' g 0·35, 95% CI 0·04–0·65).[42] Similarly, the conceptualisation of instrumental reinforcement of compulsions led to a treatment for obsessive compulsive disorder known as exposure and response prevention.[43] In this conceptualisation, the distress-reducing effects of compulsive washing in response to obsessive thoughts of being contaminated act to reinforce and therefore increase compulsive washing with each subsequent obsessive thought. The treatment combines exposure of the individual to reminders of the obsessive thoughts (eg, a dirty piece of clothing) or the thought itself (eg, the thought of being covered in germs) with the prevention of washing. This approach is very effective for patients with obsessive compulsive disorder, and more so than non-targeted psychological control conditions, such as relaxation training (1·29, 0·76–1·81).[44] Another example is behavioural activation therapy, which targets deficits in positive reinforcement as a contributing factor for depression.[45] This approach aims to increase access to positively rewarding stimuli and achieve actions that are value driven and overcome task-related avoidance.[46] In a meta-analysis of behavioural activation treatments for depression,[47] this form of treatment was found to be highly effective compared with comparison-control interventions, which included wait-list and non-targeted psychological control conditions (0·87, 0·60–1·15 when collapsed across control conditions).

Overall, the development of psychological treatments via a mechanistic approach has resulted in more precise, efficient, and effective treatments than those that do not target specific mechanisms. However, the largest effect sizes come from comparisons with non-treatment or wait-list control conditions, with the wait-list control conditions potentially inflating the effect sizes;[48] some of the findings of meta-analyses mentioned earlier included wait-list control conditions.[47] The observation that comparisons of mechanistic treatment approaches with usual care typically yield lower effect sizes than comparisons with non-treatment or wait-list controls[49] could be an indication of the importance of common factors that are relevant to all psychotherapies—eg, goal consensus, therapeutic alliance, empathy, expectations, and therapist effects.[50] Notably, common factors do not obviate the importance of mechanistic research but rather imply the value of taking common factors into account when assessing the mechanisms of specifically targeted therapeutic approaches.

However, despite purported treatment mechanisms, little evidence exists on the precise mechanisms through which psychological treatments actually work. Although mechanistic developments in neuroscience have sparked interest in the psychopathology community, most studies to date have not investigated mechanisms of treatment. Even the study of mediation is often hindered by insufficiently rigorous methodology.[27] For example, although good evidence supports the efficacy of interoceptive exposure and cognitive restructuring for panic disorder, and that the extinction of the fear of interoceptive cues and reduction in catastrophic appraisals occur as a result of treatment, little direct evidence exists that the treatments work through the extinction of the conditional fear of interoceptive cues or reduction of catastrophic appraisals—a claim that requires that the changes in the purported mechanisms explain the subsequent changes in the symptoms. Similarly, although behavioural activation for depression might lead to changes in reward processing, no evidence is apparent that the treatment works through changing neural and behavioural sensitivity to reward.

To make matters worse, the focus of psychological research has slowly shifted away from mechanistically informed approaches toward modifying or adapting existing manualised psychological treatments, sometimes superficially, for different populations and settings. This approach of modification most commonly applies to cognitive and behavioural therapies. Although this shift in focus has been valuable for the advancement of treatment implementation in different settings, it has resulted in a

regrettable divorce from the foundations of mechanistically informed psychological treatments that in turn has impeded the investigation of their mechanisms of action.

Why is it important to understand the mechanisms of psychological treatments?

Without an understanding of the mechanisms of psychological treatments, pathways to intervention development and refinement remain restricted. With a knowledge of how change occurs as a result of treatment, therapeutic strategies can be developed that are more direct, precise, and effective.[51] Also, those therapeutic strategies that do not affect the crucial processes can be removed, making treatments more efficient and effective.[51] Moreover, by refuting a claimed mechanism, research attention can be redirected toward investigating alternative mechanisms and the development of novel treatments that are effective and efficient (panel 2).

Understanding the mechanisms of psychological treatment might uncover moderators of treatment outcome, and thereby lead to improvements in the precision of matching treatments to the needs of individuals.[51] For example, initial interest in training for attention bias modification for anxious individuals waned as a result of mixed findings and small effect sizes.[52] Subsequent research has provided some indication that the effects of training attention bias are larger for individuals with a greater attention bias at baseline,[34] and for those with low-expressing forms of the serotonin-transporter-linked polymorphic region (5-HTTLPR) of the serotonin-transporter gene (*SLC6A4*),[53] than for those with high-expressing forms of 5-HTTLPR. As another example, extinction-based exposure therapy to trauma cues for individuals with post-traumatic stress disorder (PTSD) have been suggested to function in part by enhancing prefrontal cortex inhibitory regulation over the responses of the amygdala.[54] Neuroscientists have identified that some individuals with PTSD fit into subtypes, with the majority showing hyperactivation of the amygdala and hypoactivation of the prefrontal cortex when exposed to trauma reminders, and about 30% showing the reverse pattern of hypoactivation of the amygdala and hyperactivation of the prefrontal cortex.[55] If exposure therapy can be established to work at least partially through enhancing the prefrontal cortex regulation of the amygdala, then exposure therapy might be more effective for the former set of individuals with PTSD than the latter. These examples show ways in which the field of psychological treatment could progress. Conclusive findings will depend upon replication of these results within substantially larger samples.

Not only is the identification of such mechanistic moderators valuable for precision in matching treatment to individuals, but it also improves the elucidation of psychological treatment mechanisms.[51] To follow the previous example of individuals with PTSD, by studying the entire sample (ie, those showing amygdala hyperactivation and those showing amygdala hypoactivation) the extent to which change in amygdala activation serves as a treatment mechanism is likely to be nullified. By recognising baseline differences between individuals, differential mediational pathways could be uncovered—eg, the possibility of amygdala deactivation for those who initially present with hyperactivation, and activation for those who initially present with amygdala hypoactivation. These are illustrative examples, but a mechanistic approach to moderation avoids the default approach of trial and error that assumes that a given psychological intervention strategy works through the same mechanisms for everyone. Another example of a speculative mechanistic hypothesis is the theory that behavioural activation for depression,[46] which involves scheduling activities that are rewarding, leads to symptom improvement for some individuals through enhancing approach motivation or initial responsiveness to reward within positive-valence systems, whereas for other individuals the treatment might reduce threat or potential threat within negative-valence systems or even modulate arousal systems through regulating sleep–wake cycles.

Additionally, psychological treatments with a mechanistic focus can be turned into training in everyday habits that pertain to prevention of and recovery from mental ill health—eg, training in mindfulness techniques to reduce affective memory bias and development of, or relapse into, depressive ruminative states.[56] Another example is the delivery of cognitive behavioural therapy (CBT) as an adjunct to usual primary care for individuals who are depressed and have not responded well to medication alone. In one study,[57] short-term focused CBT was associated with significantly reduced depression 3–5 years after treatment compared with usual care alone. Similarly, another study[58] found that cognitive therapy decreased the recurrence of depression over a 10-year interval in patients with remitted depression who had a history of recurrent depression compared with usual treatment. Together, these data suggest that CBT and cognitive therapy provided patients with skills that were embedded into their daily lives and led to sustained long-term improvements.

***Panel 2:* Reasons for understanding the mechanisms of psychological treatments**

- To hone treatments to target the processes that are responsible for change more directly and efficiently
- To uncover essential moderators of treatment outcomes and improve precision in treatment matching
- To develop training programmes for the prevention of and recovery from psychopathology
- To eliminate wasteful and inefficient treatments
- To provide evidence for specificity in treatment beyond non-specific factors that are responsible for the so-called dodo-bird effect

Not understanding the mechanisms of psychological treatments could be detrimental—eg, the development of novel and effective treatments could be hindered by the continued modification of the procedural elements of existing treatments without fully understanding the processes that lead to change. We encourage the development of a larger evidence base of critical processes for therapeutic change and, specifically, of which psychological treatments—existing and newly developed—affect which processes. This evidence base should include common and specific factors of psychotherapies.[30] Additionally, knowing the psycho-logical treatments that exert their effects primarily through common non-specific factors rather than through more targeted specific factors, would be informative, as well as whether the common and specific factors are of greater relevance to one mental disorder or individual than another. Such an evidence base would offer the potential to move the field beyond the long-standing debate of whether all psychological treatments are equally effective (ie, the dodo-bird hypothesis[59]) and whether differential treatment effects exist.[60] We have the opportunity to assess whether matching treatments that are mechanistically focused to individual patients with underlying dysregulation leads to superior outcomes when compared with targeting non-specific factors that are common across psychological treatments. Of course, applying personalised treatments that are mechanistically focused and understanding the role of common factors are not the only ways in which psychotherapy can improve outcomes; other factors that warrant consideration include the personal resources and social context of those in need, and the service delivery systems by which treatments are delivered.

Experimental psychopathology

Understanding mechanisms of psychopathology involves substantial explanatory specificity, and hence is driven by theory.[27] The mechanisms are elaborated through plausible and coherent reasoning on the basis of integration with broader scientific knowledge, and at the same time the explanation provided must be specific in how change in the mechanism accounts for change in the outcome.[27] Once theoretical mechanisms have been elaborated, investigators in the field of experimental psychopathology then assess the validity of the mechanism's causal influences upon selected outcomes (panel 3).

Showing that experimental manipulation of a proposed mechanism leads to symptom change is a powerful method for validation. Experimental studies of this kind in human participants can identify key processes that maintain or change aspects of psychopathology. These studies can also elucidate which of the processes' underlying psychopathology can (or cannot) be modified, and can therefore identify appropriate treatment targets. Burgeoning interest in the mechanisms that underlie psychopathology has been fuelled by advances in cognitive science and neuroscience.[51] For example, an increased activation in affective brain networks and a decreased activation in cognitive control and social cognitive networks has been seen in the brains of young people when they listen to criticism from their mothers, and this activation has been identified as a potentially key mechanism in emotional development.[61] These findings could inform strategies aimed at increasing effective parenting to reduce the risk of mental health problems in offspring.

The direct application of identified mechanisms of psychopathology to mechanisms of psychological treatment is well represented in fear learning and exposure therapies for anxiety disorders—eg, pharmacological drugs that facilitate the consolidation of fear-extinction learning (eg, d-cycloserine) have been shown to have beneficial effects in the context of exposure therapy;[62] although some mixed effects have been reported, possibly due to mechanistic moderators.[63] Another study[64] has shown that retrieving memories that are already stored induces a process of reconsolidation. Once retrieved, the memory has to be rewritten into a long-term memory, which requires neurochemical processes (de novo protein synthesis) in the brain. These processes give rise to the fascinating possibility of changing memories post factum during the period of reconsolidation on retrieval. One study[65] found that engaging an individual with a highly visually absorbing computer game after a memory-reminder cue interrupted the reconsolidation of intrusive visual memories induced by experimental trauma. Pharmacological drugs (eg, propranolol) and behavioural techniques (eg, extinction) have been shown to interrupt the reconsolidation process in human beings, albeit with mixed results,[66] restricting boundary conditions and conceptual challenges.[67]

Evidence that disturbances in autobiographical memory can be potential mechanisms of depression has led to novel therapeutic strategies for depression, including memory specificity training and positive memory elaboration.[32] Additional mechanistic research is needed, and particularly in young people for whom innovative psychological treatments are needed that can precisely target narrowly specified mechanisms that

***Panel 3*: Recommendations for identifying potential mechanisms of psychological treatments**

- Develop a model of explanatory specificity
- Experimental investigation of an explanatory construct to establish causal validity
- Human studies to show that manipulation of a proposed construct leads to symptom change (experimental psychopathology)
- Animal studies to allow more precision and elucidation of targets that cannot be studied in human beings
- Reverse-translation models by use of clinical research to inform models that will be tested in animals
- The flow of iterative and reciprocal information between experimental psychopathology studies in human beings and animals

are consistent with developmental models of causality (see Part 4).

Purported mechanisms can be tested in animals with much more precision with regards to measurement and causality than is possible in human beings. Animal studies are invaluable for identifying basic processes and mechanisms that are not possible to address in human beings because of practical or ethical constraints. Indeed, the first clinical applications of d-cycloserine for exposure therapy and disruption of reconsolidation for fear memories were derived from careful experimentation in animals.[64,68] Animal studies have also elucidated the potential value of disruption of reconsolidation in the treatment of substance abuse or dependence.[69] Ongoing animal work is examining pharmacological drugs that regulate the stress response via inhibition of the renin–angiotensin system (eg, losartan) as another method for enhancing consolidation of extinction learning.[70] Furthermore, advances in understanding the neurobiology of rodent self-grooming could identify potential treatment mechanisms for repetitive behaviours such as compulsions.[71]

In reverse-translation approaches, clinical research informs models to be tested in animals—eg, paradigms for assessing depressive cognitive styles, such as pessimism, that have been validated in human studies have now been reverse translated into paradigms that measure judgment bias in rodents.[72] Similarly, drawing from human-based studies on reward systems, paradigms have been developed to assess decision making in rodents between cues that predict reward versus cues that predict punishment.[73]

Despite these examples of the iterative flow of reciprocal information between experimental studies in human beings and animals, for the most part a huge gap exists between basic and clinical researchers. This gap hinders the development of more refined animal models of psychopathology and treatment and their translation to clinical populations. The reverse and forward translation of advances in basic science and clinical science is essential.

Assessment of mechanisms

Once a mechanism has been identified through careful experimentation, it can be assessed within the context of adequately powered clinical trials. To reach this stage requires measures of the purported mechanisms that are reliable, valid, and sensitive to change, since these measures will become the mediators that are assessed statistically. A major contribution to this effort will be funding to establish a list of candidate mechanisms that explain therapeutic change (based on evidence that the experimental manipulation influences only selected outcomes in animal or human studies) and a list of measures for each candidate mechanism. The RDoC notion of units of analysis provides a helpful framework for choosing measures from multiple modalities.

Kazdin[27] has carefully outlined the steps necessary to establish that a measure is a mediator of a psychological treatment. As an initial step, a strong association must be shown between the psychological treatment and the hypothesised mediator (ie, the mediator changes over the course of treatment), and between the mediator and therapeutic outcome (ie, change in the mediator is related to clinical outcomes). Kazdin lists several methods that allow greater attribution of causality to the mediator—ie, the underlying mechanism. One method is temporal precedence, since mediation cannot be presumed unless changes in the purported mediators occur before, and then predict changes in, the outcomes. Temporal precedence necessitates repeated measurement of mediators and of outcome variables throughout treatment, ideally in every treatment session.

Causality can be attributed to a mechanism more confidently when a single mechanism is specifically associated with a single outcome. Even more convincing than the identification of a single mediator is when the purported mediator of a specific psychological treatment can predict patient outcomes more accurately than a mediator of a different mechanism that has no theoretical association with the treatment. Specificity can also be shown by a stronger mediation via a proposed mediator for a treatment with which it has a theoretical association, compared with a treatment to which it is not theoretically relevant. Evidence for dose–response effects, in which stronger doses of the proposed mediator are associated with greater changes in symptoms than weaker doses, also strengthens the argument for a causal link. The consistency of the associations observed across independent replications is another validator. Although for some mechanistic questions appropriately powered experimental studies of small samples can be informative, validation of the mechanism will require large samples. Collaborative multisite studies will be needed, which will require a strong investment from funders and collaboration among researchers focusing on common goals.

Finally, the field would be advanced by listing the various therapeutic elements that constitute psychological therapies; an effort that has already been initiated.[74] Psychological treatments are mostly packages of different elements, such as cognitive restructuring, self-monitoring, problem solving, relaxation training, or assertiveness training. The more elements that are combined in a psychological treatment, the harder mechanistic specificity is to establish. Improved precision is likely to come from assessing the mechanisms of particular procedural elements rather than combinations of elements (panel 4).[75] Increased collaboration between clinical researchers and basic scientists, combined with new methods and technologies, will help the field of psychopathology to make substantial progress in understanding the mechanisms of change in evidence-based psychological treatments.

Part 2: Where can psychological treatments be deployed? Research to improve mental health worldwide

Introduction

Little or no access to efficacious psychological treatments is not only a major problem for people in low-income and middle-income countries, but is also problematic for many people in high-income countries. Brief, flexible, modular, and efficacious treatments that are derived from mechanistic research could enable the efficient adaptation of such treatments to different cultural contexts. Furthermore, the adaptation of treatments could be of help in the training of lay people who could implement such interventions within a framework of low-intensity treatment using modern techniques on a large scale in low-income, middle-income, and high-income countries. To achieve this goal further work is needed, including: the development of such treatments and adapting them to the local needs, priorities, traditions, and cultural norms of different environments; education and training for lay people to acquire proficiency to deliver such treatments as counsellors in a sustainable way; and the development of delivery models for mental health care with long-term sustainability.

Psychological treatments from an international perspective

As discussed in Part 1, mental disorders constitute a substantial part of the burden of disease worldwide.[7,76] Mental disorders also interact with other serious health conditions—eg, cardiovascular diseases, ischaemic stroke, and HIV—increasing the risk of premature death.[77] Efficacious psychological treatments for a wide range of mental disorders have mainly been developed in North America or Europe, and are typically designed for delivery through one-to-one psychotherapy by highly trained professionals. However, at a global level, 90% of individuals with mental disorders do not receive treatment.[78] Little success will be achieved in decreasing the prevalence and incidence of mental illness without a major shift and expansion in clinical practice and intervention research.[22]

A scarcity of skilled human resources (ie, therapists) and low acceptability of psychological treatments across cultures have been suggested as the two major barriers to increasing access to evidence-based psychological treatments in low-income and middle-income countries.[79] WHO estimated a shortage of 1·18 million mental-health-care workers across 144 low-income and middle-income countries.[80] Other key barriers include prevailing public health priority agendas and inadequate investment in mental health care, stigma associated with accessing mental health care, and challenges in using primary-care settings for implementation of mental health care.[81]

Panel 4: **Recommendations for the assessment of mechanisms of psychological treatments**

- Assess within the context of adequately powered clinical trials
- Develop measures of mechanisms that are reliable, valid, and sensitive to change, and that represent multiple units of analysis (eg, genes, molecules, cells, circuits, physiology, behaviour, cognition, self-report); mechanisms are explanatory constructs, whereas measures are mediators that explain the statistical association between an intervention and an outcome
- Once a mechanism has been identified through experimental work, it can be assessed within clinical trials (see text)
- Establish mediation by showing change in the mediator over the course of treatment, and that change in the mediator precedes and predicts clinical outcomes
  - Temporal precedence (ie, change in the mediator precedes and predicts subsequent change in symptoms); value of repeated measurement
  - Specificity of mediation to a single or restricted number of mediators
  - Specificity of mediation to a theoretically relevant mediator versus an irrelevant mediator for a given treatment, or specificity of a theoretically relevant mediator versus one treatment relative to another treatment to which it does not have theoretical relevance
  - Dose–response relationship between degree of change in mediator and degree of clinical improvement
- Consistency in independent replication
- Assess mediation for elements or specific therapeutic strategies rather than packages of treatment elements

Research to improve worldwide access to psychological treatments

Global access to psychological treatments could become a reality if adequate global and local political support is given and a research agenda is compiled that includes, but is not limited to, the following conditions (panel 5). Psychological treatments that could be scaled up successfully would be brief, flexible, modular, efficacious, and streamlined to remove any unnecessary complexities. Such treatments should be aided by research into mechanisms of action in psychological treatments (see Part 1), and a consideration of the core psychopathology of mental disorders. Large and complicated psychological treatment packages can be delivered only by highly trained professionals and to the minority of people who can afford the high costs that are associated with such treatments. Simplified and clearly defined treatments could be more readily adapted to local needs and delivered by lay mental-health-care workers on a larger scale, and as low-intensity treatments—eg, via the internet. Mechanistically informed treatments could also afford flexibility—eg, shaping treatment to align with local cultural norms and conditions. For example, if one of the major maintaining factors in depression concerns a paucity of positive reinforcement in daily life (see Part 1) then treatment strategies to increase positive reinforcement can be formed in many different ways depending on what is the most relevant, acceptable, and affordable option in the specific context or culture—eg, via various cognitive, behavioural, or psychosocial

techniques. Such treatments could each have flexible forms, but be identical in function.

In low-income and middle-income countries, the development of psychological treatments has typically focused on improving availability and accessibility, and researchers have taken a pragmatic approach to treatment development itself; however, future research efforts should harness scientifically driven developments. Developing psychological treatments on the basis of sound psychological theories and empirical knowledge gained from research on the processes of action in treatment could afford opportunities for cultural adaptation and psychological treatment across international contexts. Research that has tested theories about the mechanisms of action of various exposure therapies for anxiety disorders has provided invaluable knowledge,[82] leading to the enhanced flexibility of exposure therapy, which in turn could be tailored for global adaptation. The findings of research on basic mechanisms will hopefully show the potential for brief and highly efficacious psychological treatments.[2] Future research will need to progress this work into the development of intervention formats and modules that are acceptable and efficacious cross-culturally, and that can be delivered on a wider scale.

The traditional models of one-to-one delivery of psychological treatments by skilled psychotherapists who have had many years of training need to be reconsidered, and new efficient methods of treatment delivery explored.[22,83] Given the small number of highly skilled and trained professionals internationally, a shift towards collaborative models of care delivery has been proposed in which novel strategies, such as task shifting (eg, educating lay people with no previous experience of the mental-health services to become lay counsellors; panel 5), have been successfully used to deliver streamlined treatment of mental disorders with promising results.[79,84,85] Nevertheless, empirical questions remain such as: how best to train people to become lay counsellors in a sustainable way? And what barriers might exist to such sustainability? One solution is the delivery of therapy to a group of patients rather than one-to-one.

Other research questions include: how many training, supervision, and booster sessions will be needed to ensure the high-quality delivery of treatments? Most studies in which potential treatment group leaders have received brief training (1–4 weeks) have shown effective outcomes,[86] but more research is needed in this context. These strategies of task shifting and training the trainer have been pioneering in the global context of mental health, as well as in developed countries. For example, the IAPT programme[24] resembles an advanced form of task shifting, rapidly educating a new category of mental-health professionals called psychological wellbeing practitioners, and the strengths and limitations of the programme can be of use to help in the improvement of future large-scale endeavours. How can technologies be used to train health-care workers on a large scale and maintain the reliability of treatment delivery? Primary-care clinics in the USA have used computerised guides to train inexperienced clinicians to give psychological treatments, albeit on a much smaller scale than IAPT.[87] The outcome and long-term follow-up data from such endeavours will yield many lessons on how to increase access to psychological treatments worldwide.

***Panel 5:* How can access to psychological treatments be increased worldwide?**

- Develop low cost, simple, specific, and effective treatments
- Task shifting: educate people who have not worked within the mental-health services to deliver psychological interventions
- Low-intensity intervention: self-help interventions comprising the most potent components of effective psychological treatments that can be provided through books, CDs or DVDs, the internet, or other media, combined with brief support—usually remote via e-mail or phone—over the course of a few weeks
- Cultural adaptation: rooting the treatment in the sociocultural context (eg, traditions, expectations, cultural norms, symbols) to make sure that it is perceived as intended

Technology is another important tool that can improve the availability of psychological treatments (see Part 5).[83] Providing psychological treatments via the internet or mobile phones, combined with minimal individual support through e-mail or telephone, has shown highly promising results in many studies in high-income countries;[88] however, few studies have tested such interventions in low-income and middle-income countries.[89] Further research is required, particularly since mobile phones are rapidly becoming available worldwide, and the availability of the internet is increasing.[90]

Low-intensity treatments delivered by computerised or mobile-based guided self-help technologies are an ideal early option in a stepped-care model of treatment. National guidelines are starting to propose the use of low-intensity treatments as a first option to improve the availability of efficacious treatments (eg, for bulimia nervosa and binge eating disorder[91]). Countries such as Sweden and Australia have led the way in research on internet-based treatment and the implementation of low-intensity treatments, with examples from eating disorders[92] to parent training[93] (for a meta-analysis of mental and somatic disorders see Anderson et al[94]). Work such as this provides models and lessons that can be used or developed to improve access to care worldwide—eg, the internet could offer enhanced possibilities for long-term follow-up after a standard course of psychological treatment has ended and the implementation of booster sessions.

Contextual factors have an essential role in any efforts to increase access to psychological treatments and are a topic for future implementation research. The involvement of all stakeholders is a key factor in scaling up services to ensure support and to facilitate sustainability.[95] Initiatives to improve mental health in low-income and middle-income countries need to be rooted in the local society to assure sustainability, and to inform ways to maximise and achieve this goal. Methods

to improve societal involvement could include engaging the local government, considering local legislations and traditions, involving patient organisations, and creating conditions for continued education and mutual exchange. One area that needs further research is the effort to help people who are refugees from war and persecution;[96] for these individuals, not only is the development of treatments essential, but particular contextual factors require investigation—eg, moving populations, multiple trauma experiences.

The stigma related to mental health problems is another barrier to improved access to treatment that requires further research. Understanding and addressing the association between religious or cultural beliefs and attitudes towards mental health is a crucial factor. The potential of media, such as radio and television, to combat the stigma related to mental health problems and seeking treatment for mental health problems warrants investigation. As an example, stigma is clearly associated with talking openly about family planning among people living in poor communities in some low-income and middle-income countries. The successful use of a well designed television series to improve family planning and to reduce fertility rates in Mexico is a good example of the effective application of such strategies to reduce stigma.[97] The Headspace initiative in Australia provides a model that could be adapted to different cultural contexts with the goal of decreasing the stigma of mental illness and facilitating access to treatment.

For the **Headspace initiative** see https://www.headspace.org.au

The economic aspects of international efforts to improve mental health should also be subject to more rigorous research. Evidence from the UK[98] suggests that psychological treatment approaches—eg, early intervention for psychosis, conduct disorder, and suicide prevention—can have a cost-effectiveness ratio higher than 10 (ie, for every £1 invested in such an intervention, there will be more than £10 of benefit). Future research designs should include cost-effectiveness analyses regarding the broader provision of psychological treatments in resource-limited settings, both in developed and developing countries.

Panel 6: **Example directions for future research to improve access to psychological treatments worldwide**

- Build brief, flexible, modular, and efficacious treatments that are streamlined on the basis of knowledge from research on mechanisms of action in psychological treatments
- With knowledge of the mechanisms of action of psychological treatments, derive treatments aligned with the local needs, priorities, traditions, and cultural factors, which will be specific to the environment in which the treatment will be given
- Investigate how much education and training is needed for people without or with little previous experience of work within mental health care to acquire proficiency to give basic psychological treatments as lay counsellors in a sustainable way
- Investigate how models of delivery of psychological treatments can be scaled up in a sustainable way
- Investigate the use of media such as television, radio, and the internet to combat the stigma related to mental disorders

Research collaboration and exchange between cultures

The best way to enable the improvement in psychological treatments would be by an international mutual exchange of knowledge, experience, and expertise between disciplines (panel 6). Opportunities for students and professionals—both scientific and clinical—from different parts of the world to visit one another and learn about conditions for, and challenges in, improving access to psychological treatments in different contexts could prove to be a key factor in creating the enthusiasm and lasting collaborations needed to develop sustainable interventions (see Part 7). Such exchanges could also facilitate cross-cultural comparisons that might contribute to understanding and more efficient prevention and treatment of mental disorders.

Work needs to continue towards increasing global access to psychological treatments, both for individuals in low-income and middle-income countries and those in high-income countries. Research into psychological treatments will allow the psychiatric community to continue to develop and assess the efficacy of brief and flexible interventions, which could be focussed on precise mechanisms of action, that could in turn be adapted to meet the needs of individuals in different cultural contexts. Training lay people to deliver such interventions, and scaling treatments for delivery in a manner that is sustainable in the long-term, are two key directions for future work.

Part 3: With what? The potential for synergistic treatment effects—using and developing cross-modal treatment approaches

Introduction

Both pharmacological and psychological interventions are commonly recommended as first-line treatments in psychiatry and the potential for enhancing treatment action through combination approaches has started to attract research interest. However, the optimal method for treatment combination is far from clear and requires dedicated research in preclinical studies, experimental medicine models, and randomised controlled trials. We advocate that such an approach should consider the potential for synergy between key mechanisms of action across different treatment modalities and consider these different treatment methods within the same research framework. The potential for negative effects from treatment combinations should be included in future research programmes.

Creating synergy and avoiding harm with combination treatments

An individual with a mental disorder or comorbid mental disorders is likely to receive a combination of different treatment approaches as part of his or her care, often

including psychological therapies, different types of medication, and social interventions (panel 7). However, clinical guidelines include little about combination treatments and the vast majority of research focuses on single treatments, often with the presence of another treatment as an exclusion criterion to participation in randomised controlled trials; although, some meta-analyses have been completed of existing studies on combination treatments.[101,102] The generalisation of research based on single treatments to the typical clinical reality of combination treatments is not always valid in practice. Therefore, exciting basic and clinical science questions arise about what happens when a psychological treatment is combined with other therapeutic approaches.

Empirical studies suggest that combination treatment might have small benefits over single treatments—eg, when a psychological treatment, such as CBT, and a pharmacological treatment, such as a selective serotonin-reuptake inhibitor (SSRI), are combined in the acute treatment of emotional disorders, including depression.[103] However, the longevity of effects after treatment discontinuation could actually be reduced in some cases compared with each single treatment alone. For example, in the treatment of anxiety disorders, post-treatment relapse has been reported to be higher in patients who also received benzodiazepine or antidepressant treatment during CBT than in those who received CBT alone or in combination with a placebo.[100,104] Findings such as these emphasise the importance of capturing clinical effects after treatment ends and during the acute response phase, and also of focusing on potential mechanisms that could underlie these differential outcomes (panel 7).

Mostly, combination treatments in the clinic are driven pragmatically—eg, an individual might receive two effective treatments, often with each from a different practitioner, such as a clinical psychologist and a psychiatrist. This sort of approach contrasts with attempts to combine treatments on the basis of a mechanistic understanding or model. The hope is that scientifically informed combination treatments have the potential to create synergy and to support a better therapeutic response than either treatment offered alone. This scientifically informed approach could be of use to potentiate the mechanisms that are hypothesised to support a therapeutic effect or to overcome the limitations or barriers to a particular mechanism applied on its own (see Part 1). Interventions that are given together with psychological treatments could include the addition of drugs, neuromodulation, social, nutritional, or other forms of psychological intervention such as computerised training (eg, cognitive bias modification).

Boosting psychological interventions by use of contemporary cognitive neuroscience research

Developments in neuroscience and experimental psychology[82] have been used by researchers who are focused on boosting the effects and retention of psychological treatments. Understanding the molecular basis of memory processes provides targets that might be manipulated to facilitate learning and the extinction and reconsolidation of memories, which are key components of many psychological treatments for a number of mental disorders.[64,105]

Augmentation of existing psychological treatments

A growing area of interest is the use of drugs that target the glutamatergic system (eg, d-cycloserine) to facilitate underlying processes of extinction and retention during exposure therapy for anxiety disorders such as agoraphobia, social anxiety, and PTSD.[63] However, identifying the factors that might moderate this benefit is challenging, and a 2015 Cochrane review[99] found no evidence that d-cycloserine versus placebo conferred any advantage overall when combined with CBT in the treatment of anxiety disorders. Techniques that directly stimulate the brain (eg, transcranial magnetic stimulation) applied over the medial prefrontal cortex have been reported to modulate conditioned fear learning and extinction in healthy volunteers.[106] Hopefully, add-on treatments that affect the underlying mechanisms of learning and memory might speed up overall treatment effects, reduce the number of treatment sessions needed, or even prolong treatment effects. However, better understanding is needed of the best methods to facilitate learning in an area about which much is still unknown. For example, the optimal parameters to support learning pharmacologically or through neuromodulatory devices are elusive and require dedicated strategic focus to support preclinical work in healthy volunteers and animal models (see Part 1).[63]

A focus on mechanistically derived combinations also requires an understanding of and the ability to predict the effects of a psychological treatment alone and in combination with other treatments—eg, enhancing learning by pharmacological means in an exposure

***Panel 7*: What is a combination treatment?**

Combination treatment

The application of two or more types of intervention that have been specifically assessed for efficacy in combination.

In this Commission, the combination of psychological treatments is referred to with other types of interventions across modalities, including the addition of drugs, neuromodulation, social, nutritional, or other forms of psychological intervention such as computerised training.

Synergistic *vs* harmful combination treatments

Some treatments might work well together and have greater efficacy than either applied on its own—eg, the use of a drug to improve learning has been hypothesised to enhance retention of the benefits of CBT;[63] however, no tested drugs exist that relaibly do this.[99]

By contrast, some treatments could impair efficacy in combination—eg, patients who receive benzodiazepines during psychological treatment can show reduced long-term benefits of CBT after drug discontinuation.[100]

CBT=cognitive behavioural therapy.

treatment that has failed, or in which extinction has not occurred, would be expected to have counterproductive effects, strengthening poor outcomes. These complexities underscore the necessity and potential effects of understanding the mechanisms of treatments in isolation and in combination.

The need for better preclinical models

These observations of the potential outcomes of combination treatment highlight the crucial role of preclinical and experimental medicine models in understanding both the key processes and mechanisms that are important for combination treatments and assessing early signals of efficacy for future clinical testing. Animal models are commonly of use in the pharmaceutical industry to screen novel drugs, but are rarely of use in a combination approach—ie, by testing the effect of a drug together with a psychological intervention. This single-treatment approach could lead to the early rejection of a drug that might have weak effects on its own, but which could be clinically useful in an adjunctive role with psychological treatments. Strategic focus and funding are needed for mechanistically informed approaches to treatment combination in animal and human models. The back translation of findings from the clinic to these models needs to be enhanced, and increased interest is needed in using combination models to assess novel treatments, including as part of drug development within the pharmaceutical industry. Research in this area needs to incorporate measures that can assess and predict when and for whom combination treatment will be helpful. Regulatory support for this approach from the US Food and Drug Association and the European Medicines Agency, linked to approval and licensing of drugs, will be required to allow pharmaceutical companies to develop and test these kinds of combined treatments, both to facilitate potentially beneficial combinations and to reduce potentially harmful ones.

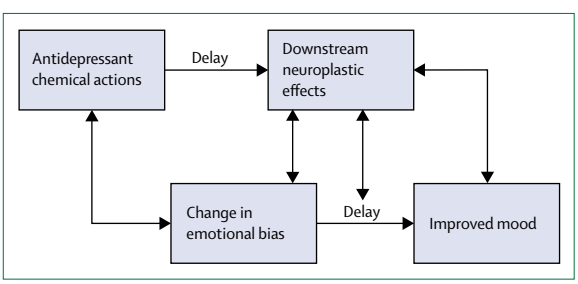

Figure 2: **Combining antidepressant drugs and psychological interventions to speed up the therapeutic effects**
Antidepressant drugs are hypothesised to work via early changes in negative affective bias—ie, by reducing the influence of this key maintaining factor in depression.[108] This theory raises the possibility that psychological treatments could be used in combination with chemical actions to boost the effect of antidepressants on negative affective bias, avoid delays in action, and facilitate the translation of effects on bias into clinical action—ie, improved mood. Reproduced from Harmer et al,[108] with permission from Elsevier.

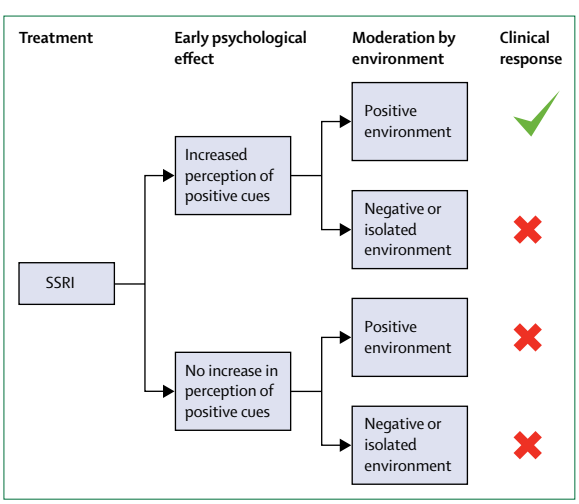

Figure 3: **Effect of patient environment on the clinical efficacy of antidepressant drugs**
Increased perception of positive cues has been associated with delayed clinical response with SSRI treatment, but this effect is moderated by environmental and social factors. Therefore, increased positive bias is only associated with improvements in depression in the context of a relatively supportive or positive environment. In the absence of changes in emotional bias, the patient's environment has little effect.[111] SSRI=selective serotonin-reuptake inhibitor.

Unifying approaches and measures across treatment research

Treatment combination across different treatment modalities can be restricted by barriers between researchers, clinicians, and funders. These barriers include different frameworks, languages, focus, and outcome measures, making it difficult to see natural synergy between the fields. However, exploring treatments using a common framework could help to overcome these barriers and lead to novel hypotheses that could not be predicted by a single approach alone. For example, studies have used measures across scientific fields to understand treatment effects, such as neuroimaging to understand and predict therapeutic response to psychological treatments,[107] and psychological outcome measures to explore the effects of drug treatment.[108]

As an example, efforts to understand the mechanism of an antidepressant drug usually focus on the molecular, cellular, or chemical interactions, but evidence is increasing that antidepressants affect core psychological processes that are important in depression before therapeutic effects are observed, which could help explain their delayed clinical actions in depression (figure 2).[108] Antidepressants increase the relative processing of positive versus negative information early in treatment, which could be important in the recovery process from depression since the patient has more positive feedback and reinforcement, countering the negative biases that are hypothesised to play a key role in maintaining the disorder.[109,110]

A key barrier to the successful translation of these effects into clinical benefit is the need for interaction with the environment. If a patient is socially isolated or in a socially detrimental environment, then increased

positive bias and processing would be expected to have only a small effect. Shiroma and colleagues[111] reported that increased positive bias, induced by treatment with antidepressant drugs, interacted with interpersonal support in the patients' environment to predict the therapeutic response (figure 3). This kind of interdisciplinary approach to treatment has the potential to generate new hypotheses concerning combination treatment that would not have been predicted from either approach alone. Using this example, the combination of early phase treatment with an antidepressant drug in combination with a psychological intervention is predicted to increase the patient's interaction with the environment (eg, behavioural activation), and could remove a barrier to successful treatment with an antidepressant drug (figure 2).[108]

To facilitate interdisciplinary combination approaches to treatment, increased communication and translation are key. Greater collaboration and joint meetings, the use of similar assessments and measures, and joint funding initiatives will help support this aim to improve combination treatments in the future. These improvements will require organisations, funding bodies, and researchers to work together, but the results will no doubt be exciting. An example of this collaborative approach to treatment occurred following a joint symposium and was presented at two very different meetings; the British Association for Psychopharmacology and the British Association for Behavioural and Cognitive Psychotherapies. The joint symposium, supported by the charity MQ: Transforming Mental Health, focused on the divide between psychological and biological treatment development and stimulated approaches to start to bridge the gap and align research strategies between psychopharmacology and psychotherapy.[112] Researchers in the field need to build on this exciting initiative, call researchers across all mental-health fields, and get strategic funding to strengthen this promising endeavour.

Testing the efficacy of combination treatments

Developing and assessing the efficacy of combination treatment also creates complexities in trial design and methodology (see Part 6). Treatment trials that compare active treatment with control treatment often require large sample sizes to have sufficient statistical power to isolate true effects from demand or placebo effects. Exploring interaction effects in comparison with individual treatments can require even larger sample sizes, depending on the study design. In particular, the effects of two treatments will often be assessed in isolation, as well as in combination, leading to a factorial design with four groups. Mechanistic studies also need to consider possible state dependency of learning—ie, that memory will be enhanced if tested in the same state versus a different state, including internal states produced by a drug.[113] The field of combination treatments will therefore benefit from a variety of approaches and from testing the effects of treatment at different time points and under multiple conditions.

Experimental medicine can be used to test hypotheses in smaller controlled studies and using surrogate markers of treatment success. This approach has revealed key effects of both pharmacological[114] and psychological[115] treatments that are used for anxiety disorders on the same underlying cognitive processes, and it has been used to explore the effects of combined treatment. For example, the effects of pairing computerised training for cognitive bias modification with brain stimulation of the dorsolateral prefrontal cortex were assessed using reactivity to a stressor as a proxy marker of efficacy in healthy volunteers.[116] The effects of cognitive bias modification and SSRI treatment alone and in combination have been explored by use of the same outcome measure, along with effects on negative memory bias. The results of this study showed that the combined effects could be worse than either applied in isolation in healthy volunteers.[117] Early changes in these measures are associated with delayed therapeutic benefit in patients[111] and can therefore be of use to guide initial proof-of-principle studies for treatment combinations and to reject those that have little therapeutic promise. Combinations that appear to be successful with these surrogate markers can be put forward for the next stage of clinical assessment, typically in a randomised controlled trial. This approach might be supported by big-data approaches in which the data are collected under more naturalistic conditions (eg, large-scale analysis of medical records or prescribing patterns; figure 4). Promising treatment combinations and timing of treatment combinations might be isolated by pattern analysis from large datasets. To facilitate this analysis, assessment and treatment elements must be standardised (see Part 8). The triangulation of experimental medicine, randomised controlled trials, and big-data analysis will be necessary to develop, assess, and understand combination approaches of the future.

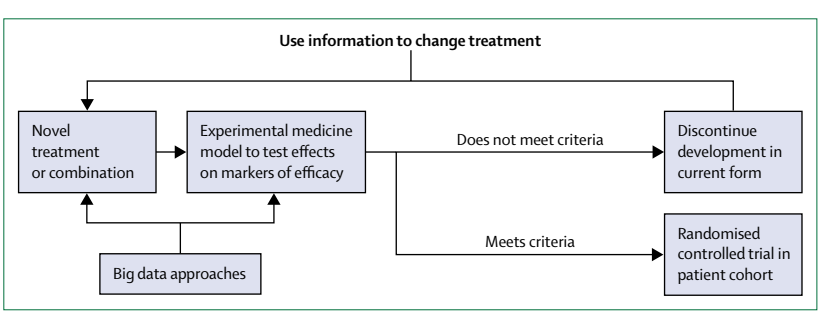

Figure 4: **Experimental medicine models for earlier assessment of efficacy of novel treatments and combinations**

Surrogate markers within experimental medicine models can be of use to screen new treatment combinations in small groups of patients or volunteers. This information is used to refine decision making for subsequent application in and design of randomised controlled trials. If insufficient evidence of efficacy is seen in the model, this information can be used to change treatment focus, the dose or duration, or the treatment target. If pre-set criteria are met, the efficacy of the treatment combination can be assessed using randomised trial designs. Approaches with big data can be useful to highlight particularly promising treatments or combinations and provide additional evidence of efficacy from naturalistic data-capture methods.

***Panel 8:* Potential future research directions in combination treatment**

- Development and validation of preclinical animal and human models for proof-of-principle studies and mechanistic focus in combination-treatment research
- Elucidating the optimal parameters for enhanced learning with drug-treatment approaches and the consideration of individual differences in this response
- Encouraging pharmaceutical companies to develop and assess novel drugs for a combinative role with psychological interventions; cultivate an understanding of this approach within the regulatory community
- Clinical studies informed by proof-of-principle work to test the efficacy of treatments alone and in combination across mental disorders
- Consideration of the potentially harmful effects of combination treatment for treatments that work well in isolation, including a focus on attribution bias and long-term outcomes
- Research the views and acceptability of combined treatments in mental disorders and the importance of patient preference and views about treatment for their clinical symptoms
- Patient preference needs to be considered in formal research programmes that attempt to bridge the psychological–pharmacological divide; the views, acceptance, and opinions of the individual receiving treatment can influence its effects
- Preclinical research using animal or human models is needed to understand key mechanisms and the effects of novel interventions before translation to clinical research programmes
- Back translation can be used to determine the success of translational research since success depends in large part on the validity of the experimental model that is used to mimic the disorder in the laboratory; back translation describes how evidence from clinical research and experience is used to drive, test, and refine the development and validation of animal and human preclinical models
- Experimental medicine and experimental psychopathology: investigators use models, typically human models in laboratory settings, to explore key mechanisms and processes that are hypothesised to be important for treatment action in psychiatry and psychology; these models can be of use for screening novel treatments and refining their application before full clinical testing

Breaking down barriers: from patient perspectives to research of the future

Finally, patient preference should be considered when assessing the effects of combination treatment. Individuals often express a preference for either psychological or pharmacological treatment, so the option of a combination of treatments might be a difficult choice for some. This view that a dichotomy exists between a psychological or biological view of mental disorders is challenged by evidence that psychological and biological treatments tap into the same core processes and represent different methods, rather than different concepts.[108] Challenging these assumptions and creating synergy at multiple levels (including among the public, clinicians, and scientists) will be a crucial step towards the optimal development of treatments. The ethical implications of combination treatments and their development should be incorporated within research strategies for these areas. Additionally, the attribution of treatment effects needs to be considered from the patient's perspective—eg, if any benefits from combined treatments are attributed to the medication, then the long-term advantage of CBT can be lessened.[118] Studies to characterise attribution bias in combined treatment approaches and consideration of the strategies that might be effective in reducing these effects are key priorities for future work (panel 8).

In summary, research to date that has tested the efficacy of combination treatments has shown great promise for the clinical utility of combining psychological and pharmacological approaches. However, many unanswered questions remain that need to be addressed regarding the optimal method for treatment combination in preclinical studies, experimental medicine models, and randomised controlled trials.

Part 4: When in life? Psychological science, prevention, and early intervention—getting the approach right from the start

Introduction

Opportunities for prevention and early intervention into mental health problems exist throughout a patient's lifespan; however, the early years of life are perhaps the best opportunity to set an individual on a path to good mental health. This process requires both population-based change and the accurate identification of those at risk, and for both approaches effective and safe interventions are needed. Many approaches have little or no scientific underpinning, and so the rigorous and sustained application of approaches that are based on psychological science to this area of practice is crucial and offers enormous promise. The focus of this section is primarily on children and young people.

Prevention and early intervention

The prevention of mental disorders is one of the main challenges for the future of mental health care because of their high burden of disease for individuals and societies, the relatively small effect of treatments to date, and the enormous societal costs of mental disorders once they have emerged.[119] The imperative to reduce risk factors across the population and to intervene at the earliest point when symptoms or precursors of mental distress occur makes sense on a human, societal, and economic level.[120,121] Psychological science can inform and underpin the development of early preventive interventions, even if the risk factors are social in origin.

The early years of life, from conception through to childhood and adolescence, are a good opportunity to set an individual on a path to good mental health. Most mental disorders have their origin or onset before the age of 18 years.[122] The greater plasticity of the brain during childhood and the nature of the emotional and behavioural responses of a child mean that the potential to intervene successfully and powerfully could be greater than at any other point in life. Nowadays, the potential role in early life for psychological approaches is greater than that of pharmacological and other physical interventions; however, many interventions remain under-researched, such as nutritional approaches. For psychological interventions to make progress into the

effective prevention of mental disorders, some key requirements and scientific and clinical challenges have to be met.[2]

Requirements and challenges for prevention and early intervention

Preventive approaches in childhood and adolescence (panel 9) require the identification of risk factors or at-risk groups (unless an intervention is going to be delivered to the whole population).[120] Key risk factors in early life include exposure to severe adversities, such as maltreatment, disturbed parenting, parental substance misuse, exposure to domestic and other violence, and loss events—eg, serious parental illness or death of a parent.[126] However, further research is needed into these and additional risk factors, as well as into the interactive effect of risk factors.

For change to occur, effective and acceptable interventions should be available. These interventions might target modifiable risk factors or use other theoretical approaches to affect change, including tackling key psychological mechanisms. However, many early interventions do not have sufficient evidence to be considered as effective. Developing and testing early interventions that might reduce the risk of psychological illness is a fundamental and largely unmet challenge.

Current research limitations regarding early interventions

Any kind of early intervention is often implicitly assumed to be better than no intervention, but this assumption is not correct. Almost any intervention that can do or change something has the potential to cause harm if applied in the wrong circumstances, as discussed by Carter and colleagues[127] regarding eating disorders. The possibility for harm is often overlooked and is probably one of the key blind spots in the field of prevention of psychological problems, particularly when translated into policy. Crucially, clincians and researchers need to acknowledge that not all interventions are the same; even those interventions that overlap in appearance or content can have different effects.[128]

A paucity of evidence on the effectiveness of psychological treatments exists in many areas of child and adolescent mental health practice, particularly for very young children. However, this area does hold promise since the differences in effectiveness for different treatments can be seen where high-quality evidence exists.[60,129] A related consideration is that an intervention might not have the same treatment effect in every setting or with all individuals equally (eg, the apparently contradictory findings for the Family Nurse Partnership intervention[130]). Disentangling these challenging problems is made more difficult if the components of a psychological intervention are not clearly specified or publicly available, perhaps because of some commercial or other protective reason.

***Panel 9:* Psychological treatments: what are preventive and early interventions?**

Prevention is often defined as those interventions that are done before people meet formal criteria for a disorder.[123]

Three types are described:

- Universal prevention, which is aimed at the general population or parts of the general population regardless of whether they have a higher than average risk of developing a disorder (eg, school programmes or mass media campaigns).
- Selective prevention, which is aimed at high-risk groups who have not yet developed a mental disorder (eg, the Nurse Family Partnership programme developed in the USA that initially aimed to prevent later adverse psychosocial outcomes for women and their children in socioeconomically deprived areas).[124]
- Indicated prevention, which is aimed at individuals who have some symptoms of a mental disorder but do not meet diagnostic criteria (eg, the intervention developed by Rapee[125] for parents of preschool-aged children who are at risk of anxiety disorders).

A further challenge is the paucity of understanding of the mechanisms by which an intervention occurs in many preventive and early interventions. As set out in Part 1, an understanding of the mechanism of action is crucial to the development of new and more effective methods of successful treatment. However, the mechanisms of action are likely to be more changeable in early life than at other points in life, complicating efforts to understand them in a preventive and developmental context. For example, different mechanisms could operate at different points in childhood, and each of these mechanisms could be different from those operating in adulthood, even for the same condition or problem that is presented (see Part 8). Although few well studied examples of this divergence between childhood and adult mechanisms seem to exist, studies are emerging—eg, Ewing and colleagues[131] found that children at risk of anxiety disorders do not have the specific cognitive biases for emotional stimuli that are seen in adults at risk of anixety disorders. For patients in early childhood, clinicians and researchers will need to go beyond the individualised mechanisms suggested in the RDoC explanatory constructs (see Part 1). Instead, other mechanisms existing in the social world of young children might open crucial pathways to help change precursors of psychopathology—eg, via the early relationships or attachments that children form to their parents or carers. Parental sensitivity has been shown to be a key mechanism of change (eg, in the context of attachment),[132] although the detailed processes which might then lead to the development of psychopathology remain to be elucidated.

Making interventions stick—persistence of effects

Another challenge for preventive and early intervention approaches, which is shared with many other forms of psychological intervention, is how to make interventions stick—ie, not only how to make the effects of psychological treatment last beyond the end of the treatment, but also how to make them generalise to other areas of functioning. Few psychological interventions have convincing evidence of sustained benefit.

Panel 10: **Examples of promising preventive and early intervention approaches**

Example 1: video feedback to promote positive parenting

During infancy, brief and focussed interventions, such as video feedback to promote positive parenting,[135] can improve parental sensitivity and the child's attachment relationship with their primary carer or parent; this technique draws on both attachment theory and social learning theory; some evidence of effects on child behaviour exist for this intervention, which are largely lacking for other video feedback parent-focused approaches to date.

Example 2: parental interventions for childhood anxiety

An intervention for parents of children aged 3-5 years who have an increased risk of anxiety disorders (identified by having high levels of behavioural inhibition) has been shown to reduce the risk of subsequent anxiety disorders within the child; this intervention was brief (six sessions), and used an educational approach with some behavioural components focussed on exposure; effects from the treatment were still seen 11 years later, although only convincingly in girls, and were shown to be cost-effective using Australian criteria for cost-effectiveness.[125]

Example 3: parenting programmes for child behavioural problems

Among school-age children (aged 3–7 years), consistent evidence has shown the benefit of parenting groups based on social learning theory, such as Scott and colleagues' Parenting Programmes to improve child behaviour;[136] longer-lasting benefits have been shown, and economic modelling studies point to societal, financial, and individual health gains.[137]

Panel 11: **Research questions in prevention and early interventions**

- When are the optimal times to intervene to prevent mental disorders?
- Who are the key at-risk groups that will most effectively respond to early or preventive treatment?
- What are the potential harmful effects of specific early-intervention approaches?
- How do we increase the so-called stickiness of treatment effects? How do we make them last beyond the end of treatment?
- How can we deliver interventions on the scale needed (including internationally) to reach at-risk children and young people?
- How can insights from mechanisms of change help prevent or delay disorders and reduce the recurrence of episodes?
- How can insights about prevention be applied across the human lifespan?

Developments are needed in psychological science to inform how to take psychological interventions outside of the therapy room—which could make interventions more widely available and acceptable, and make the effects of interventions more generaliseable to everyday life functioning. Technologies could help in this regard (see Part 5)—eg, by use of gaming and other technologies to prevent or treat early signs of depression.[133] A further approach is to take interventions into schools.[134] To date, both of these approaches have utilised primarily cognitive behavioural interventions, although other approaches, such as interpersonal therapy, also show promise for the treatment of depression in children and young people.

Positive examples for the future

Panel 10 contains three examples of intervention types for young children and their parents that have shown that preventive and early interventions are possible from very early in life, and that longer-lasting benefits are possible. All three interventions are derived from scientifically rigorous and sustained approaches to intervention development and are informed by theory. Other preventive or early interventions do exist, with varying levels of research evidence to support them, for a range of psychological and psychiatric conditions.

Prevention of mental disorders in adults

In the past two decades, randomised controlled trials have shown that preventing or at least delaying the onset of mental disorders is possible in adolescents and young adults, especially depression and psychotic disorders. Psychosocial preventive interventions, typically based on psychological treatments such as CBT or interpersonal psychotherapy, have been tested in at-risk populations and in people with subthreshold symptoms of depression or psychosis. Meta-analyses[138,139] confirm that these interventions effectively reduce the incidence of new cases of depressive disorders by about 20–25%, and prevent or delay the onset of about 50% of psychotic disorders in those at high risk for developing a psychotic disorder.[140,141] Preventing the onset of mental disorders is one of the most promising areas in which research on psychological interventions can help to reduce the disease burden of mental disorders.

The challenges ahead

Clearly, more research is needed to expand the repertoire of approaches and the range of mental disorders that can be treated. These approaches need to be theory driven and rigorously trialled (see Part 1 and Part 6).

Particular attention should be given to ensuring that interventions can produce effects with lasting benefits for children and adolescents, and substantial efforts need to be made to develop or adapt interventions so that they can be of use across a range of settings and accessible internationally (see Part 2).[142] Although preventive and early intervention approaches for mental disorders potentially have huge health benefits, they face particular challenges in terms of showing reliable efficacy and being applied consistently and thoughtfully in everyday practice in health care. The examples considered in this section provide optimism for future developments, but health-care professionals and researchers need to look carefully at the limits of effectiveness, and at the potential to cause harm (eg, potential negative effects of screening and classifying high-risk groups, offering unnecessary treatment to young people with only temporary distress or symptoms, or harmful side-effects of individual psychological treatments; panel 11). Knowledge of these benefits and harms should be pooled from patients of all ages. Although a lot of work still has to be done before effective methods of prevention for mental disorders are widely available, the rigorous and sustained application of psychological-science approaches to these areas of practice offers enormous promise.

Part 5: Technology—can we transform the availability and efficacy of psychological treatment through new technologies?

Introduction

Internet-based psychological treatments have been applied across a broad range of mental disorders. The rise of eHealth and mHealth approaches that use information technology (eg, the internet, virtual reality, serious gaming) and mobile and wireless applications (eg, text messaging, apps) marks a new era for psychological assessment and treatments. Technological innovations offer considerable possibilities to innovate psychological treatments, adjust them to daily life and the people using them, and improve access to treatment. Such knowledge could be of use to better understand how therapies work, make them easier to use, and enable more people to benefit from psychological treatments. Developments in technology-based treatments should be theory driven and properly assessed.

Internet-based psychological treatments

Most research into psychological treatments has been done with somewhat traditional internet interventions. In these interventions, patients work through self-help materials on a computer, learning how to apply a psychological treatment to themselves with the help of a coach or psychologist.[143] Such self-help materials have often been very close in content to face-to-face psychological therapy (eg, CBT). Accordingly, the materials are as if a hard-copy paper manual has been converted into a computerised form, sometimes with simple additional content such as video clips. Direct comparisons between face-to-face interventions and guided internet interventions suggest that no major differences are apparent in efficacy between the two treatment formats.[94] The efficacy of internet-based therapies (see appendix) has been shown for a broad range of mental disorders, including depression,[144] anxiety disorders,[145] sleep problems,[146] bulimia,[147] and alcohol problems.[148]

Internet interventions have many advantages, including saving time for therapists, reducing waiting lists, allowing patients to work at their own pace, removing the need to schedule appointments with a therapist, saving travelling time, reducing the stigma of going to a therapist, and facilitating psychological help for individuals who are hard of hearing.[149] Furthermore, internet interventions might reach patients who cannot be reached with more traditional forms of treatment (eg, because of distance or stigma). Interventions can be quite easily adapted to specific patient groups, with a wide range of attractive audiovisual information with voices giving instructions via a character of whichever gender or age, with whichever accent or language, or perhaps game format, the patient prefers. Internet interventions are probably more cost-effective than face-to-face treatments, but further economic research is needed to verify this.

From a research perspective, internet interventions have many advantages. One major advantage is that recruiting patients for randomised controlled trials of internet interventions is much easier and more cost-effective and efficient than doing trials of traditional face-to-face psychotherapies (see Part 6). Research into these interventions should stimulate further development of personalised treatments for mental disorders by allowing large-scale trials that are powered to examine complex questions (see Part 8) or test for weaker effects (eg, prevention trials).

However, internet interventions have limitations. The quality of interventions that are offered through the internet is not clear, and despite portals for evidence-based internet therapies, such as Beacon, the possibility that low-quality therapies are being offered remains a threat. Beacon is a webservice through which a panel of health experts categorise, review, and rate websites and mobile applications for internet-based psychological treatments. It is part of a suite of self-help programmes that have been developed and delivered by the National Institute for Mental Health Research at the Australian National University, although it is unfortunately not being updated. Drop-out rates are higher in internet-based interventions than in face-to-face therapies,[150] and it is unknown whether the condition of these patients gets worse as a result of the intervention, or in general, since they cannot be followed-up. Internet interventions might affect the therapeutic alliance between therapists and patients, but most evidence suggests that internet-based therapies are at least equivalent to face-to-face therapies in terms of therapeutic alliance.[151] Little research has focused on the long-term effects of internet interventions; however, the same is true for face-to-face psychological treatments. Furthermore, we acknowledge that internet interventions might have unknown disadvantages, such as misunderstandings due to reduced communication channels in unguided interventions and the potentially confusing depiction of content as graphs and schemes. Additionally, data security and privacy should be guarded for any intervention that is offered through the internet.

For **Beacon** website see https://beacon.anu.edu.au

See **Online** for appendix

Finally, despite increasing access, the internet is not yet accessible to many potential users around the world, and dissemination will depend on the attitudes of possible users and health-care professionals. However, even in low-income and middle-income countries, access to the internet and mobile phones is expanding (see Part 2), although creative solutions (eg, regarding literacy) might need to be taken into consideration where applicable.

Other technological opportunities

Interventions can increasingly be offered through smart phones and watches, Google glasses, virtual-reality headsets, and other kinds of innovative devices. Many of these devices have the advantage that they can be worn by the patient and collect information during daily life (ecological momentary assessment;[152] see Part 8). The

Panel 12: **Potential directions for future research with new technologies for psychological treatments**

- Treatment and theory development: health behaviour theory can be of use to inform technological treatment innovation across all areas of psychological treatments
- Treatment evaluation: trials to assess the effectiveness of new products such as apps
- Learning: maximising and innovating learning methods during psychological treatment by fresh means—eg, skills learning, habit change—such as via serious gaming
- Devices: the incorporation of new technologies—eg, avatars , smart watches, and other devices—into existing psychological treatments to facilitate delivery and improve outcomes
- Harnessing new technologies to advance methods of examining causal mechanisms, refine treatments, and derive treatment approaches that are mechanistically driven
- Health monitoring: enable large-scale data mining and data interpretation to predict the onset and course of mental disorders
- Personalisation of technology-based interventions
- Technologically aided preventive treatment approaches adapted across all age ranges and globally

information collected might considerably improve prediction models for individual patients and thus potentially improve and increase the effect sizes of existing treatments. Computerised adaptive-testing techniques assess symptoms online with greater sensitivity and specificity from fewer items than traditional forms of outcome monitoring—ie, pen and paper questionnaires.[153] Several virtual-reality treatments have been developed, mainly for anxiety disorders. Patients are not confronted with the real stimuli that provoke their anxiety but with their virtual counterparts using real-time computer graphics, body-tracking devices, and other sensory input devices.[154] This form of treatment has shown some effectiveness;[155] however, many of the trials have been small and of suboptimal quality. Many studies have shown that telephone-supported therapies are effective in the treatment of common mental disorders.[156]

The range of mental-health applications (ie, apps) available is rapidly growing, offering a range of psychological interventions;[157] however, most apps are not based on health behaviour theory and little evidence supports their effectiveness.[158] Future researchers should develop theory-driven interventions and assess their effectiveness, since only a few interventions have been tested in randomised controlled trials.[159,160] Specific adaptations to the design of a randomised trial might be needed because of rapid technological developments.[161] Widely available and untested products pose a risk to the public. Although the field of technology-based interventions is still young, and efforts to progress treatment development have started, international approaches are needed to develop regulated approaches and procedures.

The format of new technologies could allow new treatment techniques to be developed that are not part of existing face-to-face psychological treatments, offering novel information processing options (eg, virtual-reality exposure, and possibly interpretation of bias training). Serious gaming, such as the SPARX program, also opens opportunities for interdisciplinary research and new methods of treatment delivery.[133] Serious games refer to games with a purpose other than providing entertainment, which in this case is the delivery of a psychological treatment using game principles. SPARX is an interactive fantasy game designed to give CBT to adolescents seeking help for depression.

At some point, the automated support of these new technologies might replace the therapist altogether (ie, therapist-free therapy[162]), and lead to improved, personalised treatments (see Part 8). New technologies can also be of use in predicting the development and outcome of mental disorders. For example, mobile phone apps are available to monitor associations between psychological risk and suicidal ideation,[163] and evidence exists that the use of specific phrases and personal pronouns can, for example, predict an individual's depression status from their blog posts (see Part 9), although we acknowledge that such monitoring could raise ethical concerns.[163] Because of the huge quantities of data can be collected through mobile phones and other devices that can be connected with existing databases, data-mining techniques could be helpful to predict the onset and course of mental disorders. This data accumulation could aid the development of innovative psychological interventions that could be integrated into new technologies that become part of the daily lives of patients. However, to increase the likelihood of success, new technology and data accumulation alone will not suffice. A sound theoretical framework should be incorporated to drive hypothesis alongside clinical knowledge.

Finally, eHealth and mHealth approaches that use information technology and mobile and wireless applications are examples of ways that technology has been harnessed to innovate psychological treatments, their availability, and their assessment. Technology-based treatments need to improve with advances in psychological theory and understanding of mechanisms of change. Future technological innovations offer considerable possibilities to innovate psychological treatments (panel 12), including adjusting treatments to patients' daily lives and using the information gained to better understand how therapies work, improve the treatments, and improve the technology's ease of use, so that people across all age ranges and worldwide can benefit from psychological treatments.

Part 6: Trials to assess psychological therapies

Introduction

Several key issues in the design and conduct of clinical trials to assess psychological therapies must be addressed to develop therapies that are evidence based. These issues offer several opportunities for improvement and

some specific challenges, given the complexities of both the therapies being assessed and the populations who are receiving them. The challenges include more accurate reporting of clinical trials, eg, specification of therapy protocols and inclusion and exclusion criteria, choice of outcome measures, measurement of adverse effects, and prevention of bias in trial design and analysis. The opportunities include the increasing role of service users and carers in all aspects of trial design and conduct, the development of methodologies for achieving a consensus regarding research questions and outcome measures, the development of new methods for analysis of mediators and mechanisms, and innovations in the design of clinical trials (eg, adaptive trial designs and mixed methods approaches that incorporate nested qualitative studies).

These challenges and opportunities will be considered in this section of the Commission in the context of a feasibility study (the COMPARE trial, ISRCTN06022197) and the potential for a subsequent trial to assess CBT for people with psychosis. This subsequent trial would be a direct comparison of CBT, an antipsychotic medication, and as a combined treatment, which is a research recommendation in the UK National Institute for Health and Care Excellence guideline for the treatment of psychosis in children and young people (for additional information see appendix).[164]

The need to improve clinical trial methodology

Clinical trials are the cornerstone of evidence-based approaches to decisions about access to health care, but in the field of mental health such trials often have substantial methodological shortcomings that result in low-quality evidence. Many psychotherapy trials are not registered in an international database before recruitment starts,[165] therefore other researchers cannot be sure whether the outcomes that are reported were those originally intended, and raises the possibility of selective reporting of outcomes (ie, focusing on those results that were statistically significant), or that negative trials remain unpublished. A systematic review[166] found that many psychotherapy trials did not attempt to maintain blinding (ie, masking) in the people rating the treatment outcomes increasing the likelihood of bias. Additionally, treatment protocols were broad and not based on a specific model, which makes assessment of fidelity and replication problematic. These limitations could be overcome by ensuring linkage between experts in trial design and methodology and statisticians and innovators in psychological therapy development. Accredited clinical trials units, with their extensive experience of trial design and conduct, could coordinate with academic methodologists who are at the forefront of developments in trial statistics and methodologies.[167] In the past decade, substantial improvements in psychological treatment trials have been made, with more studies adopting clinical trial registration and pre-specification of primary outcomes, including application of Consolidated Standards of Reporting Trials (CONSORT) criteria (appendix). Such procedures are increasingly required by leading journals and ethical review boards. However, to apply these procedures to psychotherapy trials particular adaptations of both trial design and reporting guidelines will need to be developed—eg, around issues such as double-blinded studies, a trial design that cannot be maintained with a therapist-delivered psychological treatment. However, double-blinded studies can also be problematic for pharmacological treatments, since aspects of the treatments can become apparent despite the investigators' best intentions—eg, the rapid and dramatic weight gain and parkinsonian side-effects found with both first-generation and second-generation antipsychotics. Another possibility is that subjective cognitive effects[168] unmask participants.

Additionally, the potential negative effects of psychotherapy are increasingly being recognised, and unwanted effects and serious adverse events need to be documented and reported to ethics committees as part of safety monitoring. Historically, psychological therapy trials have been poor at both monitoring hypothesised side-effects and deterioration, and reporting serious adverse events.[169] Negative effects and adverse events that require documenting range from the worsening of existing symptoms, to issues such as novel symptoms, poor therapeutic relationship, and perceived coercion.[170] Such adverse events are possible in both traditional psychotherapy and internet-based interventions.[171] A procedural model and checklist are available for clinicians and researchers,[172] and the detection and management of adverse events in treatment trials is considered a sign of good practice. Formalised measures of possible harms (ie, side-effects) caused by trials should be the rule, rather than the exception, in psychotherapy research.[169]

To ensure that psychological therapy trials are credible, the minimum standards expected in other fields should be met (eg, those standards in pharmaceutical trials). However, psychotherapy researchers have an opportunity to develop their own standards, which could ensure superior trial design, conduct, and reporting, which other fields could aspire to meet.

A set of reporting standards specifically tailored to psychological therapy trials are being developed as an extension of the original CONSORT guidelines.[173] These reporting standards include recommendations to improve internal and external validity, address measurement issues (psychological therapy trials often have many measures, of which many assess latent constructs), improve reporting of recruitment processes and representativeness of participant groups, and increase contextual information—eg, factors that helped or hindered the interventions. Additionally, research on general trial methodology (eg, on how to deal with the issue of masking participants) will be an important area of future inquiry.

Conflicts of interest

Management of a clinical trial by the developer of a psychological therapy could be considered equivalent in terms of bias to a pharmaceutical company managing a drug trial, and investigator allegiance effects have been observed in psychological therapy trials.[174,175] The focus of investigations into this bias has been more on allegiance to a given type of psychotherapy than on financial interests. Steps can be taken to reduce bias, including the declaration of interests (ie, personal financial interests such as training fees, book royalties, and non-financial interests), registration of protocols, prespecification of plans for statistical analysis, and involvement of independent methodologists in the trial design and data analysis. Trial steering committees and data-monitoring committees with independent clinical, statistical, and service-user representation also increase study confidence and minimise bias. These committees can provide constructive criticism and protect the safety of participants and scientific integrity of the trial. Expertise in all relevant approaches is important for trials that compare two or more therapies—eg, the team for the COMPARE trial includes researchers with expertise in both CBT and antipsychotic medication.

Inclusion and exclusion criteria

The selection and justification of inclusion and exclusion criteria are crucial to good trial design. The criteria should be specific enough to allow the identification of suitable participants and replication of a trial, but broad enough to reflect real-world clinical settings and permit generalisability according to the purpose of the trial. Historically, many psychological therapy trials require a single diagnostic category or symptom as an entry criterion, not allowing those with several or at least specific comorbidities (eg, other mental disorders, physical health issues, drug or alcohol use). These exclusion criteria are difficult to justify when the clinical reality of a mental health difficulties is complex and comorbidities are the norm (see Part 8). Trials in the past two decades that have assessed CBT for psychosis have typically been good in terms of generalisability, allowing for inclusion of participants who meet broad criteria (which is also true for trials of psychological therapy for depression[176]). Even trials that have focused on mechanisms of change—eg, whether reducing worry processes results in a reduction in paranoid thinking—have allowed participants with comorbidities.[177] However, in these situations compromises might have been made between clinical pragmatism (ie, having broad entry criteria) and the ability to scrutinise specific mechanisms within the trial. Trials that attempt to address transdiagnostic processes by targeting a specific mechanism (eg, modification of attention biases or extended perseverative processing) or problem (eg, sleep difficulties or irritability) across diagnostic groups offer potential advantages in terms of recruitment, generalisability, and implementation in mental health care (for further discussion of these issues see Part 8).

Improved integration of research trials within clinical settings would facilitate the generalisability of results to the real world. One goal is for every individual who attends a hospital clinic because of a mental health problem, or engages with a community mental health team, or attends an appointment in primary care, to be offered participation in psychological therapy research (if willing and able to provide consent). For example, for interventions for which genuine uncertainties in treatment exist (eg, what dose of CBT for psychosis is required), all willing participants could be randomised into groups with different treatment durations.

Choice of control condition

Appropriate control conditions for psychological therapy trials are a matter of considerable debate—eg many argue that so-called treatment as usual is not appropriate since such conditions can be highly variable and at times include access to the treatment that is being provided in the experimental group. The use of an active control condition is often recommended, which reduces confounds such as non-specific factors (eg, attention, warmth, human relationships); however, inclusion of an active control condition could oversimplify the issue of therapeutic relationship—itself a topic of research and debate about its importance. The provision of an alternative therapy can raise other confounds, such as the so-called match between therapist and participant, and the ability of a therapist to switch between, and adhere to, different treatment protocols even though they probably have greater skill and allegiance to one protocol over another. Ways to deal with such issues include having multiple therapists who can provide each active condition, perhaps across trial sites, so that different trial sites can have different expertise but can provide all therapies (eg, a trial of CBT for psychosis compared with befriending).[178] Furthermore, mental health problems might differ in their response to psychological placebos—eg, the effects of non-directive supportive therapy are similar to CBT and interpersonal psychotherapy for depression,[179] although CBT is superior for patients with psychosis.[180]

Experts in clinical psychology trials, such as Alan Kazdin, have formulated models to guide the type of trial needed to address the type of question asked. In part, design solutions will depend on the specific research question. For example, if the pragmatic question is whether an intervention works better than the current provision, then a two-arm trial design would allow the comparison of the new intervention with a specified and defined treatment as usual that follows best practice—eg, CBT plus monthly engagement and monitoring of the participant's daily difficulties compared with monthly engagement and monitoring alone.[181] If the question is whether one form of psychotherapy is better than another, then a direct comparison might be required.

However, if the question is why a treatment works, or whether a specific element is necessary, then the comparator treatment should be a therapy that controls for specified factors (eg, human contact) but in which the active ingredient has been removed. Findings from meta-analyses suggest that wait-list controls should be avoided, since they can lead to inflated effects sizes for the experimental treatment, possibly because people abandon their efforts to solve their mental health problems or recover independently because they are waiting for therapy.[48]

Outcome measures

Most trial methodologists would recommend a single primary outcome and a single prespecified timepoint at which this main outcome should be measured (eg, total symptoms at final follow-up assessment). This method can sit uncomfortably with basic aspects of psychological assessment—eg, the need for multiple assessments of a construct for validity, and multiple timepoints for reliability, as well as tracking the time course of the response. Having more than one primary outcome is justified in some situations (eg, in psychosis studies clinicians prefer psychiatric symptoms whereas service users tend to prefer social outcomes).[182] However, multiple primary outcomes require larger sample sizes. Additionally, the use of data obtained at multiple timepoints can give the most accurate estimate of treatment effects over the full follow-up duration. This process can be done by specifying an analysis involving all available data for a particular measure, which might be preferable to anchoring judgements regarding efficacy to a single assessment timepoint.

The most important outcome can be a subject of debate. Clinicians often prefer clinical outcomes (eg, psychiatric symptoms) whereas service users might prefer social outcomes (eg, recovery, social functioning, and quality of life).[182] Consensus regarding outcome measures for a specific condition would enable individual participant data meta-analyses,[183–185] which could hopefully provide information about the moderators and mediators of the treatment response. Integration with and adoption of routinely collected service user outcome data would also facilitate understanding of mediators and moderators. As part of a UK initiative that aims to establish agreement about sets of core outcomes for particular health conditions (Core Outcome Measures in Effectiveness Trials [COMET]), work is underway to establish consensus about a set of core outcomes for assessments of interventions for people with psychosis.[186] Regarding reporting outcome measures, it is unclear whether having a detailed interviewer-administered rating scale, which could provide rich data and be more engaging for participants than self-administered rating, is preferable to a self-report measure, which could be more reliable since inter-rater reliability is not needed across sites and staff and it avoids rater bias. A combination of both approaches could be a reasonable solution that maximises the benefits of both, so long as they are clearly prespecified as dual primary outcomes. If a trial with dual primary outcomes shows consistency across these outcomes, then the confidence in the findings would be increased.

Another important consideration when selecting outcomes is the time required to complete all assessments. Psychological therapy trials often include numerous secondary outcome measures, which might be of substantial interest. However, a large assessment burden on participants is more likely to impair retention in the trial, subsequently resulting in missing outcome data and reducing the internal validity of the trial. Limiting the number of outcome measures is likely to minimise attrition, but it restricts opportunities for understanding the processes of change. Similarly, agreement on the frequency of assessments and the length of follow-up would facilitate the pooling of data and the capacity for comparisons across trials. A compromise usually needs to be made between collecting meaningful data that will permit identification of what approaches work for whom across a broad range of outcomes and that facilitate mediation and moderation analyses, and not jeopardising participant retention. The involvement of service users who would be eligible for trial participation in the design of the trial, and ensuring pilot and feasibility work has been done, are both likely to be useful strategies in achieving a balance between these factors. Another possibility for minimising the assessment burden and maximising ecological validity and multiple measurements of outcomes is by use of experience sampling methods or ecological momentary assessment data as outcomes. This approach would allow reporting of symptoms, emotions, and indicators of functioning (eg, use of time in daily life—how many hours are spent engaged in constructive activity such as employment, education, parenting, housework, and leisue) as primary outcomes in clinical trials (see Part 8).

In addition to the measurement of wanted effects, such as improvements in symptoms or quality of life, measuring unwanted effects and reporting serious adverse events to ethics committees are important to safety monitoring. Historically, trials of psychological therapies have been poor at both monitoring hypothesised side effects and deterioration and reporting serious adverse events.[169] Several trials[181,187] of CBT for psychosis have attempted to measure adverse effects via qualitative and quantitative approaches. Some critics have suggested an association between CBT for psychosis and increasing stigma, encouraging deterioration or destabilisation, leading to serious adverse events such as admissions to hospital. However, these trials[181,187] also showed the opposite effect when compared with control conditions. This result is surprising when the inbuilt detection bias inherent in the design and implementation of these studies is taken into account (ie, therapists might have

For **COMET** website see http://www.comet-initiative.org/about/overview

weekly contact with a participant, whereas raters might only have contact at baseline, end of treatment, and follow-up, which clearly reduces the likelihood of detection of serious adverse events).

Public and patient involvement

Public and patient involvement is another area that can help to improve how psychological therapy trials are run.[188,189] People with mental disorders can provide unique insights into clinical trials, including identification of the most important and relevant research questions and thus outcome measures. For example, a definitive trial comparing CBT with antipsychotic medication would need to decide whether the most important question is one of superiority (ie, is combination treatment superior to monotherapy), equivalence (which would enable choice), or non-inferiority (in which case choice might depend on adverse-effect profiles). The assessment of acceptability of psychological therapies and the exploration of potential adverse effects can be informed by embedded qualitative interviews and analyses that can be led by service users (eg, the COMPARE trial is incorporating such a study). Finally, the involvement of service users as staff and, ideally, coapplicants, and investigators, should ensure meaningful participation in all phases of the design of the trial, running the trial, and reporting (eg, COMPARE has two service users as co-investigators and two as grant holders).

Public and patient involvement can be via consultancy groups (which is the case for the COMPARE trial), via priority setting partnerships that identify and prioritise the top ten unanswered questions (the James Lind Alliance facilitate the development of such partnerships in the UK), which has been done for the treatment uncertainties related to a diagnosis of schizophrenia,[190] or by the use of Delphi methods to establish consensus on topics with experts with experience (the COMPARE trial is also informed by Delphi studies of people with psychosis for both defining recovery[191] and identifying treatment priorities and preferences[192]).

For the **James Lind Alliance** website see http://www.jla.nihr.ac.uk/

Mechanisms and mediators of change

Trial design should also attempt to facilitate the identification of potential mechanisms, mediators of change (see Part 1), and moderators of treatment effects to inform on how a treatment works, what components are necessary and sufficient, and what treatments work for whom. The identification of mechanisms could be built into all clinical trials, which would also allow pooling of data, although this pooling would require consensus among researchers about the instruments that should be included in the trials. When a specific research question involves testing a mechanism, the trial must have sufficient statistical power for the mechanistic hypotheses and any between-group predictions.

The identification of mediators and moderators requires considerable thought at the planning stage to ensure that the appropriate factors are measured at the appropriate timepoints. The development of new statistical methods for the analysis of mediation and moderation should help with the accurate identification of mechanisms of change and mediators of treatment outcome. Traditional approaches to mediation analysis[193] assume the absence of confounding due to an unmeasured variable being responsible for changes in both the mechanism and outcome. These approaches are problematic because the assumptions made are unrealistic in many instances, especially given the complexity of potential influences on mental health. Subsequent developments that might be better suited to mediation analysis include attempting to measure and adjust for all important confounders,[194] or attempting to adjust effectively for unmeasured confounders (hidden confounding) by use of instrumental variable-based methods analysed on the basis of principal stratification.[195] Examples that are relevant to CBT for psychosis include the finding that participants with a psychosocial causal explanation of their difficulties could be more likely to engage with and benefit from CBT than those with a biological explanation,[196] and that participants with a good therapeutic alliance with their therapist are likely to benefit from a high number of CBT sessions, whereas participants with a poor alliance might be more likely to be harmed as the number of sessions increase.[197]

Innovation in trial design and methodology

The wider context of an individual trial should be considered. The reliability and validity of the findings from meta-analyses that are used to inform policy, guidelines, and service recommendations are largely dependent upon the quality of the trials that are included and the suitability of the selection criteria (ie, whether the included trials were designed to answer equivalent questions). Designing high-quality trials with a long-term perspective provides an opportunity to improve such meta-analyses. Collaboration between research groups, investigators, and methodologists with regard to future pooling of data could be facilitated by establishing collective research groups that would be recognised by group authorship, which would incentivise such involvement and cooperation.

Sometimes, alternative approaches to the traditional two-arm randomised controlled trial are needed, such as multiarm multistage trials.[198]

New methodologies, including adaptive designs, preference trials, and sequential multiple assignment randomised trials (SMARTs), will permit better generalisability to routine practice and more ethical and efficient trial conduct than traditional approaches. For example, a SMART that permits investigators to re-randomise patients who do not respond to CBT or antipsychotic medication after a relatively short period of time into the other monotherapy group or the combination group would confer future clinical

advantages—eg, arriving at a suitable treatment for an individual faster than with traditional trial designs. A preference trial would maximise recruitment in a field in which both service users and clinicians can have strong treatment preferences and opinions about psychological therapy or medication that could jeopardise recruitment, generalisability, or adherence to allocation in a standard randomised controlled trial. An adaptive design with a planned and prespecified interim analysis could permit the early abandonment of a treatment group that proved to be inferior. The cohort multiple randomised controlled trial design[199] allows several randomised controlled trials to be done simultaneously within a large patient cohort. For each randomised trial, all people who are eligible in the cohort are identified, then some are randomly selected to be offered the experimental intervention. The outcomes in the randomly selected participants are compared with the outcomes in those who were eligible but not selected (ie, receiving standard care or treatment as usual). Such designs could overcome recruitment difficulties and increase statistical power, efficiency, representativeness of samples, and comparability between trials, as well as increasing knowledge about the natural course of mental disorders and the likelihood of collecting data on long-term outcomes. This approach would be ideally suited to mental disorders that are seen within specialist teams (eg, eating disorders or first-episode psychosis), especially when the teams are linked within a national or international network and routinely monitor outcomes in a standardised way.

Improvements in the detection of patients who can be classified as responders and non-responders could be achieved by the selection of appropriate measures, incorporation of experience sampling or momentary assessment in the early phases of a trial (see Part 5), use of improved inclusion and exclusion criteria, and the development of statistical methods for mediation, moderation, and consideration of individual response trajectories rather than aggregate effects.

Notably, researchers should recognise that identifying successful interventions is not just about randomised trials, and clinical trials should complement other types of research questions and evidence. For example, randomised trials need to include embedded qualitative studies to obtain rich data alongside quantitative outcomes to inform understanding of active treatment processes and generate new hypotheses that can be tested empirically. The COMPARE trial involves interviewing participants about their experiences of both CBT and medication, focusing on acceptability, credibility, and wanted and unwanted effects (these interviews are designed, completed, and analysed by researchers with lived experience of psychosis). The results of these interviews have the potential to inform the design of a definitive trial related to the selection and recruitment of participants, inclusion and exclusion criteria, outcome measures, and treatment protocols.

If all of the above improvements can be achieved, the ability of researchers to identify and answer the most important questions will improve, trials will be run with greater reliability and validity, and confidence in and acceptance of the findings of these trials will increase (panel 13). Meaningful involvement of service users and carers will allow the identification of appropriate research questions and methods, ensure the relevance of outcomes (including adverse effects), and improve the retention of participants. Additionally, creation of large-scale datasets will enhance the credibility of the results of clinical trials, either by consensus regarding design considerations and measures that enable pooling of data, developments in individual participant data meta-analyses, or by use of routinely collected service data. Psychological treatment trials should also benefit from advances in trials in other areas of medicine.

Part 7: Training—can we cultivate a vision for interdisciplinary training across mental health sciences to improve psychological treatments?

Introduction

In this section, we discuss why the field of mental health science should endeavour to improve links between

Panel 13: **Directions and priorities for future research in clinical trials of psychological treatments**

- Establish a consensus among stakeholders (ie, the innovators and developers of psychological treatments, service users, and methodologists) regarding outcome measures, appropriate scheduling of assessments, and the length of follow-ups
- Routinely build into the design of clinical trials the ability to analyse for mechanisms of treatment
- Engage with commissioners and providers of psychological services to maximise the likelihood that such services can facilitate the routine collection of data to contribute to the evidence base and include clinical trials as part of service delivery when uncertainty exists
- Ensure quality trial design and valid, reliable analysis of data by routine and early engagement with clinical trials units, registration for all trials (including production of prespecified statistical analysis plans), and ensure that data analysis adheres to plans and is done by independent specialists in trial statistics
- Involve service users in all aspects of trial design and conduct, from decisions regarding research questions and methods, through to involvement in trial management and governance, research administration, and interpretation and dissemination of findings
- Carefully match comparators to the specific research questions that trials are seeking to answer
- Measure unwanted and wanted effects and arrive at a consensus about how to measure and report adverse effects
- Increase the use of innovative trial designs that maximise value for money, value for participant input, and reflect clinical practice; such designs include adaptive trials, multiple trials within cohorts, SMARTs, and preference trials; different designs will be suited to different research questions and clinical contexts
- Encourage career paths for those focused on advancing methods in the methodology of psychological treatment trial design, statistics, and other areas that will aid in future research

clinical psychology, psychiatry, and basic research training, and make some proposals about how this aim might be achieved. We review some early successes in innovation in psychological treatments in which basic researchers and clinicians have worked together, and discuss the reasons that such productive interaction has decreased in the past several decades. We offer some recommendations to bridge the gap between clinical practice and basic research into psychological interventions.

Historical shifts in interdisciplinary training

In 1949, in Colorado, the American Psychological Association held the Boulder Conference on Graduate Education in Clinical Psychology to agree on a standard model for clinical psychology training in the USA. Heavily influenced by the ideas of David Shakow, the conference adopted a scientist–practitioner training framework that encouraged clinical psychologists to use scientific research to inform their practice.[200] This proposal facilitated the development of effective new psychological interventions, which was catalysed by clinicians who did basic research, and basic researchers who understood the principles of psychological treatments (see appendix). This confluence of expertise resulted in crucial insights into the mechanisms of onset, maintenance, and treatment of symptoms of mental disorders, and, in some cases, completely revolutionised the psychological treatments available.

By taking a scientist–practitioner approach, training in psychological treatment becomes far more than just learning how to deliver a treatment described in a manual. Understanding the principles on which a treatment was derived can help the practitioner to deliver the treatment well and adapt the treatment to a given situation or patient. An example of a situation in which basic training was important was the development of various types of exposure therapy (incorporating response prevention) for anxiety disorders, including phobias, PTSD, and obsessive compulsive disorder. This treatment was initially derived from research on fear extinction in rodents, which showed a reduction in Pavlovian responses to negatively conditioned stimuli when the aversive outcome was omitted (see Part 1).[201,202] Notably, the focus on response prevention—ie, encouraging patients with anxiety not to engage in their usual coping strategies when confronted with an anxiety-provoking stimulus (eg, avoidance for phobias, rituals for obsessive compulsive disorder)—came from the insight that these behaviours can maintain the conditioned association through preventing extinction.[203] This approach might seem counterintuitive to the patient because, acutely, the prevention of coping behaviours increases their anxiety in the short term, but leads to a reduction in anxiety in the long term. Since this approach can also be counterintuitive from the perspective of some other therapeutic approaches, understanding the principles behind exposure techniques is important. Another example of practitioners benefiting from understanding the underlying science via their training is in the context of depression—namely, the influential learned helplessness model,[204] and its later modifications associated with hopelessness.[205] The learned helplessness model originated from the finding that animals that were exposed to inescapable aversive stimuli subsequently failed to escape when they had the option to do so.[206] Learned helplessness theory has made notable contributions to the understanding of risk factors for depression, especially associated with the roles of attributional style and perceived controllability.[207] Moreover, this theory has inspired numerous animal models that remain the mainstay of testing procedures for new antidepressant drugs in preclinical research, and translational research in this field has yielded valuable insights into the basic cognitive and brain changes that underlie depressive symptoms and their response to treatment.[208]

Over the past several decades, the links between basic research, clinical psychology, and psychiatry have become weaker, the reasons for which could be numerous. One simple fact is that because of the rapid expansion of psychology, basic researchers and practitioners rarely work in the same building. This distance reduces opportunities for interaction and the sharing of ideas between researchers and practitioners. Another important issue is that basic researchers and clinical psychologists often do not read the same journals, or even attend the same conferences, meaning that opportunities for interaction are few.[2]

Renewing the links between basic research and psychological treatments

Clinicians providing psychological treatments need training in basic research

In most countries, little teaching of contemporary basic research (eg, experimental psychology, neuroscience, genetics, physiology, pharmacology, data science, social science, economics) is incorporated into the clinical syllabuses of clinical psychology or psychiatry, or of allied professional training in the treatment of mental disorders. Canada and the USA are notable exceptions, since many clinical psychologists in these countries complete a doctoral training programme lasting at least 5 years, which includes substantial teaching in basic research together with an extensive research-based thesis and clinical training. The basic science content of training courses for psychiatry trainees in the USA has been emphasised,[209] although professionals within the field recognise that further training in basic science would be desirable.[210,211] Other than these examples, the basic research content included in clinical psychology programmes is small, even at the doctoral level (eg, PsyD in Canada and the USA, which is completed by approximately half of all qualified clinical psychologists in these countries; DClinPsy in the UK). In other countries, in which a master's degree is the standard educational

qualification required to become a clinical psychologist (including most of the European Union, Australia, New Zealand, and South Africa), very little basic research is in the curriculum.

This paucity of basic research content in clinical psychology programmes raises a serious concern about the training of clinical mental health researchers of the future and the risk that they will not be equipped with the tools to understand, critically assess, and use basic research that might be relevant to the development of new treatments or preventive strategies. Psychological interventions might become stuck in the past—relying on outdated models that are not supported by contemporary research or theory. This disconnect between basic researchers and clinical psychologists hinders innovation, and slows the emergence of effective and truly novel psychological treatments. Unless clinical psychologists and psychiatrists have the skills to assess research on both risk factors (eg, genetic and socioeconomic influences) and proximal mechanisms (eg, cognitive and neural processing of information), improving preventive strategies and treatments will be difficult.

Basic researchers need training in clinical conditions and psychological treatments

Although most basic researchers are enthusiastic that their research might contribute to improved treatments for mental disorders, they tend to have only a vague idea of what standard psychological interventions entail, since clinical practice is not generally taught even in undergraduate psychology degrees. Specifically, many basic researchers have little knowledge of the evidence base that supports standard psychological treatments, and have little opportunity to interact with clinical psychologists, see therapy in action, or find out what the common techniques comprise. Indeed, in our experience, the view that psychological treatments are primarily given in the context of an antiempirical psychoanalytical couch tradition, and that they are not derived from solid scientific theory or supported by robust evidence from clinical trials, is worryingly prevalent among basic researchers.[2] To formulate relevant research questions, basic researchers who are interested in contributing to the development of psychological treatments need to understand what the symptoms of mental disorders are (and are not), what the most common evidence-based psychological interventions entail and how theoretical models guided their development, and what the key questions are that need to be solved in the future.

The future of interdisciplinary training

Training clinicians in basic research

How can we ensure that the next generation of research leaders, both clinical and basic, are able to bridge the growing divide between their fields? One priority is to provide extra opportunities for academic training to trainees and qualified practitioners, and to attract those with a strong aptitude for research. In the UK, although competition for places on professional doctoral courses in clinical psychology is intense, and they recruit students who are highly academically able, very few graduates subsequently have a career in clinical research. Funding opportunities for the academic training of qualified clinical psychologists are highly competitive. That said, some major UK research funding bodies, such as the National Institute for Health Research (NIHR) and the Medical Research Council, offer academic training pathways for clinicians. These training pathways offer clinically qualified, non-medical health-care professionals the chance to undertake a PhD, while covering a clinical-level salary, tuition, travel, training costs, and research consumables. This training provides a valuable springboard for a career in clinical research, but there is scope for uptake by more clinical psychologists than at present, in part because they might not be aware of these opportunities or have sufficient support or research experience to develop a strong application. Another way of improving academic training in clinical psychology would be to create longer training programmes specifically for those trainees with a strong aptitude for research. These courses could be similar to the North American PhD model, providing students with sufficient time to complete an extensive research project and teaching relevant scientific material alongside clinical skills. The Psychological Clinical Science Accreditation System model that has been developed in the USA, which emphasises the science of clinical psychology in training and internships, would also be an effective way of increasing opportunities for research training. A similar training model is offered at The University of New South Wales (UNSW), Sydney, Australia, in which students are enrolled in a clinical training programme and a PhD programme concurrently, and they are awarded both degrees at the conclusion of their course (eg, Master of Psychology [Clinical] and PhD).

Training pathways also need to be developed for mental health researchers that cultivate an interdisciplinary approach both between clinical psychology and psychiatry, and between disciplines of clinical mental health and a variety of relevant basic research. One possible way to achieve this interdisciplinary approach would be to encourage clinical psychologists to undertake internships or placements in basic-research settings across a range of relevant disciplines, from economics and social science, to neuroscience and genetics. Psychiatrists in the UK already have such an opportunity through the NIHR Academic Clinical Fellowships scheme, but no equivalent programmes seem to be available for clinical psychologists, in either the UK or other European countries. Multiskilled clinical academics, trained in an interdisciplinary environment, would have the advantage of being able to speak the languages of both clinical and basic research. They would also be best placed to develop the metaprofessional skills needed to do truly interdisciplinary

For more on the **UK National Institute for Health Research fellowship for research** see https://www.nihr.ac.uk/funding-and-support/funding-for-training-and-career-development/training-programmes/nihr-hee-ica-programme/nihr-hee-ica-programme-cdrf.htm

For more on the **UK Medical Research Council Clinical Research Training Fellowship** see http://www.mrc.ac.uk/skills-careers/fellowships/clinical-fellowships/clinical-research-training-fellowship-crtf/

translational research, and to use the knowledge derived from basic research to drive innovation in the development of psychological treatments.

Training basic researchers in psychological interventions

Basic researchers with an interest in understanding and contributing to the development of new psychological treatments need to be provided with the opportunities to do so. In the same way that a first-year neuroscience PhD student might learn about the principles and practice of neuroimaging analysis, and therefore be able to assess neuroimaging evidence more effectively because they understand the potential pitfalls (even though they might never use the technique), basic researchers need a route through which they can learn about what psychological treatments are used in practice and how they are hypothesised to work. This knowledge would provide a new generation of researchers who understand the basic principles underlying psychological interventions and could bring a fresh perspective on driving innovation. Even sitting in the same lectures and tutorials as clinical trainees would increase the opportunities for meaningful interaction, and encourage clinical and non-clinical students to value input from each other when developing collaborations. Although neuroscience and cognitive or experimental psychology students are obvious candidates for such an approach, students with backgrounds in a whole range of disciplines—from social science and economics, to computer science and mathematics, and molecular biology and genetics—might have an interest in psychological interventions and could contribute important ideas.

A culture change is needed to accept more crossover

To address these problems that are hindering interdisciplinary interaction several obstacles will need to be overcome, which will require bold changes in thinking within the health-care system. These obstacles exist for both clinical accreditation and funding. A huge number of mental health practitioners have research talents that are being underutilised, and perverse disincentives often discourage clinicians from entering academia, including a possible reduction in salary and a perception that research will not help in their career progression. Additionally, the procedures for obtaining funding for a research doctorate are not widely understood among trainees, and the opportunities to gain the research experience that would contribute to a competitive application are sporadic and invariably depend on locally available supervisors; therefore, the trainees with the most research potential might be overlooked. Furthermore, unlike for clinical training (at least in the UK), an absence of national recruitment is apparent for research training in clinical psychology.

These obstacles could be addressed through longer, targeted clinical academic programmes (like the PhD programme in North America) that include a substantial research component in the professional doctorate, alongside standard clinical training, and national recruitment to attract trainees with the greatest research potential. More substantial research projects than are completed nowadays in most clinical psychology courses would also help to address the concern that learning about techniques could be forgotten if they are not put into practice. Many European training programmes for clinical psychology successfully blend clinical training with basic research; however, the courses are at a master's level, and so do not have the requirement of a doctoral-level thesis, and therefore trainees do not receive the same quality of research training as those in the North American PhD model. For example, in the past decade a pioneering model for training clinical psychologists has been adopted by the Karolinska Institutet in Stockholm, Sweden. In this model, teaching is based within the Division of Psychology in the Department of Clinical Neuroscience, and within a medical university. This design has resulted in the students being exposed to both psychology and neuroscience, and encouraged awareness of the rich links between clinical psychology, neuroscience, psychiatry, and physical medicine. Almost all of the instructors are involved in research, and the majority have at least 50% of their time devoted to research. Although only a master's level qualification is required to become a clinical psychologist in Sweden, Karolinska students are poised as members of the new scientist–practitioner generation. The development of similar programmes elsewhere would be a positive step toward interdisciplinary training, as would an examination of the outcomes of different international models. To our knowledge, such an investigation has not been done to date, but would be extremely valuable.

Models of shared research supervision

Another major factor that restricts access to interdisciplinary training is that those trainees who do enter research training are often supervised only by clinicians, rather than by basic researchers. As discussed, this separation between clinical training and basic research affects both fields with very few opportunities available for trainees in basic research who are keen to understand psychological treatments, to find out what they entail, and the diverse approaches that they adopt. Such exposure to ideas, and understanding of how psychological interventions are actually administered, is an important first step for basic researchers to start to formulate valuable research questions. Therefore, allowing basic researchers to have an active part in the supervision of research projects of clinical psychology trainees would be desirable when possible, and vice versa. Encouraging joint doctoral supervision (whether for research or clinical students) between principal investigators within basic research and clinical

psychology would be a simple and valuable step in the right direction in this regard. Returning to the Australian example, at UNSW Sydney, students who are studying for a combined clinical and PhD degree often do their PhD research under the supervision of a basic researcher (eg, behavioural neuroscientists) and test questions with clear clinical relevance (eg, on topics such as fear extinction, and drug addiction), alongside their clinical training programme. Such a model of supervision facilitates a broad training experience and a unique opportunity for mentorship from both clinical supervisors and basic researchers.

Mixing and mingling—the role of conferences

Finally, even among those clinical psychologists who do enter academia, few forums exist for exchanging ideas with researchers from other disciplines, since the journals they read and the conferences they attend are typically discipline specific (with some notable exceptions—eg, the MQ: Transforming Mental Health annual science meeting; the meeting on neuroscientific research into psychological treatments arranged by the European College of Neuropsychopharmacology;[212] and the annual meeting of the German Association for Psychiatry, Psychotherapy and Psychosomatics). Some clinical psychologists and neuroscience researchers have started to work together to produce new ideas for intervention. A good example is the adoption of ideas from the literature on the neuroscience of reconsolidation—the modification of old memories during their reactivation—in the formulation of new treatment approaches for PTSD.[213] Several studies have tested the possibility that reactivated memories could be disrupted through pharmacological intervention with propranolol,[214,215] with some preliminary indications of positive effects. Other studies[65,216,217] have tested whether the reconsolidation of established memories can be disrupted by use of simple psychological interventions based on cognitive science, with promising results. Engagement with a simple visuospatial task (the computer game Tetris) following memory reactivation was shown to substantially reduce subsequent intrusive memories of experimental trauma.[65] Although this line of research requires considerable further work to show robust clinical efficacy (see Part 6),[216,217] it is an intriguing example of the type of interdisciplinary innovation between basic and clinical research that holds promise for improved treatments in the future. Other good examples of interdisciplinary innovations have been found in the development of new psychological interventions for anhedonia (panel 14).

In the 1950s and 1960s, the development of new psychological interventions transformed the treatment of mental disorders, with the creation of effective treatments on the basis of novel, empirically testable models. Inspired by ideas that were drawn from cognitive psychology and behavioural neuroscience, interventions that were developed through collaborations between previous generations of basic researchers and clinicians have become the treatments of choice. Despite these successes, improvements in treatments are still needed since patient responses to psychological interventions are highly variable. However, in the past few decades the productive interaction between those who deliver psychological interventions and basic researchers has waned. The gap between these

For the **German Association for Psychiatry, Psychotherapy and Psychosomatics** website see https://www.dgppn.de/

***Panel 14:* Could understanding reward processing in the brain help in the development of new treatments for anhedonia?**

Over the past decade, interest has been renewed in a core symptom of depression, anhedonia, which is the loss of interest or pleasure in previously enjoyable activities; anhedonia is also an important component of many other mental disorders, including schizophrenia and addiction, as well as a prominent symptom in neurological disorders, such as Parkinson's disease.

In depression, anhedonia is associated with a more severe course of illness and poorer response to standard antidepressant drugs[218] and psychological treatments[15] than depression without anhedonia; clinicians appreciate that this symptom is an area in which treatments are inadequate.

Given that anhedonia is intrinsically related to an absence of motivation and hedonic response, researchers have proposed that this symptom could arise because of a disruption of the brain's reward circuits,[219] which have been characterised in extensive detail by neuroscience research over the past 30 years.

This idea is not new; in the 1970s Jeffrey Gray first proposed that symptoms of depression might be explained by changes in a behavioural activation system and a behavioural inhibition system,[220] although most researchers focused on the behavioural inhibition system and its association with neuroticism.

An important conceptual advance in this theory has been the notion that the reward system (the behavioural activation system) comprises several relevant cognitive processes: hedonic response to reward delivery, valuation of rewards, reward learning, propensity to exert effort, and decision making; these components at least partially dissociate, and are linked with activation in different brain circuits and neurochemical systems.[221]

This knowledge from neuroscience research has been exploited by clinical psychologists seeking to develop treatments specifically targeted at anhedonia—eg, positive affect treatment;[221] this treatment builds on behavioural activation therapy and positive event scheduling, which are both effective treatments for depression[222] that were originally motivated by ideas derived from behaviourism,[45] and that are known to increase responsivity in the brain's reward system.[223]

Drawing on the finding that reward processing comprises a diverse set of processes, the aim of positive affective treatment is to increase engagement in, attention to, and anticipation of enjoyable activities.[17]

From a complementary angle, another novel approach based on cognitive science (ie, the processes of mental imagery and interpretation bias) has been via positive imagery training; in trials with individuals with depression, post-hoc analyses show early indication of an effect on anhedonia;[224,225] this type of focussed approach could be developed into the wider package of positive affective training.

Although these novel interventions require further assessment, specifically in groups of individuals with anhedonia and depression, the research so far provides examples of how scientific discoveries are of use to fuel development of innovative psychological interventions.

Panel 15: **Example directions for the future of training and links between clinical and basic science**

- Opportunities for integrated clinical and academic training in psychology, through extended programmes that are targeted at those clinicians with the greatest research potential
- Training for basic researchers in psychological treatments, including hands-on experience of techniques and interactions with clinicians, so that they can formulate research questions that are relevant to psychological interventions
- An expectation of interdisciplinary research for psychological treatment researchers, including cosupervision of the research component of professional qualifications by clinical and non-clinical principal investigators
- The provision of seminars on the next steps, focused on academic training as a standard part of programmes for clinical training in mental disorders
- Improved dissemination of research internship and doctoral funding opportunities for clinical psychologists, such as that provided by the Society for a Science of Clinical Psychology
- Training programmes in which trainees in clinical psychology, psychiatry, and basic research can learn alongside each other
- High-level interdisciplinary meetings between basic researchers, clinical psychologists, psychiatrists, and others, including forums in which practitioners can propose questions that they think are important to basic scientists; with tangible outcomes such as papers, grant applications, and implementation work
- Use of the continuing professional development framework to enhance the understanding of basic science among psychological treatment practitioners

For **Society for a Science of Clinical Psychology** website see http://www.sscpweb.org/

disciplines impedes innovation in the development of new psychological treatments, both because basic researchers do not understand what psychological interventions entail, and because clinicians are not familiar with relevant advances. In this section, we have outlined a number of proposals for how to bridge this gap; these proposals should promote a much more extensive interdisciplinary interaction and dialogue than exists nowadays (panel 15).

Part 8: Whom should we treat, for what, and with what? Embracing the complexity of mental disorders from personalised models to universal approaches

Introduction

Most theoretical models and evidence-based psychological treatments have typically been designed for specific, categorically defined mental disorders—eg, major depressive disorder, social phobia, or PTSD. Leading clinical guidelines recommend specific treatments for each mental disorder, usually categorically defined by symptomatology.[226,227] However, mental disorders are more complex than these guidelines take into account, and are characterised by huge varieties between individuals with a given disorder.Heterogeneity in symptomatology across mental disorders is very common,[228] and many individuals have more than one mental disorder.[229,230] Additionally, many individuals have subsyndromal symptoms of other disorders, and could have symptoms that shift between disorders over time. Mental health researchers—and those in psychological treatment research specifically—need to embrace the complexity of mental disorders to make progress in reducing the burden of these disabling conditions. The complexity of mental disorders is a challenge for research and clinical practice. Treatment solutions to deal with this complexity include both highly individualised (ie, personalised) approaches, and so-called universal or transdiagnostic approaches that target common mechanisms. More studies are needed to examine whether these approaches improve the effectiveness of treatments for mental disorders.

Why are mental disorders so complex?

Unlike most areas of medicine, mental disorders are defined predominantly by their symptoms. A paucity of knowledge about the causes of mental disorders contributes to this approach. Symptoms are often considered as manifestations of an underlying latent factor (eg, sad mood and loss of interest are caused by an underlying major depressive disorder). However, these symptoms might not only serve as an output from so-called underlying processes, but could also mutually reinforce one another, as presumed by the network approach.[231] For example, in depression, insomnia might lead to concentration problems, which in turn might cause sadness and loss of pleasure, which in turn might lead to fatigue, feelings of guilt, and suicidal ideation, resulting in the full syndrome of major depressive disorder. Thus, whether these symptoms are indeed manifestations of an underlying factor is still uncertain.[231]

Mental disorders are dimensional, and yet most mental health researchers use a categorical model to study the effects of treatments. The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM–5)[227] is a categorical nosology for classification, to identify, for instance, a depressive episode, and to study the effects of a disorder-specific treatment for depression, such as behavioural activation. In the past few years, initiatives have been taken—eg, the RDoC initiative[29]—to stimulate research on the dimensions of observable behaviour and neurobiological measures of mental disorders, instead of categorical diagnostic criteria (see Part 1).

An additional complicating factor is the differences between individuals and the specific characteristics of their psychopathology. Studies using network analyses have given new insights into the variation of psychopathology between patients.[228,232] These studies show that, although for some people—eg, those with a strongly connected network of symptomatology—the transition from feeling healthy to being fully depressed can be abrupt (categorical), for others—eg, individuals with a weakly connected network of symptoms—external stressors (such as not being able to pay rent) could lead to an increase in symptomatology; although these symptoms gradually decrease after the stressor is gone.[233] These differences in psychopathology could be explained

by a dimensional model of psychopathology—ie, that the individuals with strongly connected networks might be those with increased neuroticism. However, whether these differences between individuals can be explained by an underlying dimensional mechanism or categorical disorder remains unclear.

Mental disorders are complex to study because of the interplay between an individual's emotions, cognitions, physiology, and other factors, as well as how they interact with the environment, which can change over time or as a consequence of having a mental disorder (for the differentiation of mechanisms responsible for onset *vs* mechanisms that are responsible for maintenance of psychopathology see Part 1). For instance, for individuals with depression, major life events (eg, the death of a loved one) are consistent risk factors for the onset of the first episode, whereas for those who have had one or two previous depressive episodes, comparatively less stressful events (eg, getting a minor traffic ticket) are sufficient to trigger a subsequent depressive episode.[234] Huge differences have been found between individuals in how their emotions fluctuate—an important part of many mental disorders—and huge differences over time.[235]

Furthermore, at least 45% of people with mental disorders have more than one disorder (for definitions see appendix), while over half of people with a mental disorder have subsyndromal symptoms of other mental conditions.[229] The lifetime comorbidity of common mental disorders (ie, anxiety disorders with major depressive disorder) can be as high as 73%.[230] The Global Burden of Disease Study[236] estimated that comorbidities for mental disorders for 188 countries between 1990 and 2016 had risen substantially. Comorbid disorders are consistently associated with a greater demand for professional help, poorer prognosis, greater interference with everyday life, and a higher incidence of suicide than disorders without comorbidities.[237,238] An improved understanding of comorbid mental disorders is crucial to give insight into their causes and to improve psychological treatments for all mental disorders and other conditions.

Heterogeneity and comorbidity have been studied in some fields of mental health to explain the causes of mental disorders, including comorbid disorders.[239,240] Dimensional models have been proposed to explain the cause of comorbid disorders; most suggest shared factors for the concurrent disorders (eg, neuroticism),[241] and some add specific factors that differentiate among mental disorders.[242] For instance, the dimensional tri-level hierarchical model of anxiety and depression includes the following levels: a shared higher level factor for anxiety and depression (ie, general distress); two additional factors that are at an intermediate level in terms of specificity for anxiety and depression (ie, anxious misery; fears that explain covariation in positive affect, anhedonia, and sad mood; social fears and fears to explain covariation in social fears; and fears of specific stimuli and interoceptive sensations, and agoraphobic fears); and five further specific unique factors for depression and anxiety disorders (ie, depression, fears of specific stimuli, anxious arousal, social fears, and interoceptive or agoraphobic fears; figure 5).[243]

Alternatively, a network approach can be of use to explain comorbidities through spreading symptom activations. Comorbidities are hypothesised to result from direct associations between the symptoms of multiple disorders—ie, a symptom of one diagnostic category (eg, major depressive disorder) can evoke other symptoms that in turn evoke symptoms of another diagnostic category (eg, anxiety about several events, chronic anxiety or worry).[231] Thus, a comorbidity might be the result of shared symptoms across mental disorders, so-called bridge symptoms.

Figure 6 is an example of a dynamic network of symptoms of major depressive disorder that mutually reinforce other symptoms of the disorder and comorbid symptoms of generalised anxiety disorder.[228,231] For example, disturbed sleeping, which is a symptom of depression, could lead to fatigue, concentration problems, and irritability or agitation (bridge symptoms), as well as other specific generalised anxiety disorder symptomatology. The bridge symptoms are criteria of major depressive disorder and generalised anxiety disorder.[231,244] Additionally, between different individuals comorbidities can develop in different ways, resulting in many different paths to the comorbidity depending on the individual and their environment. However, the network approach does not explain why some individuals are more prone to developing comorbidities (ie, having more symptoms) than others.

Both the network model and the dimensional (hierarchical) model could contribute to the explanation of mental disorders, including comorbidities. These models emphasise the necessity of translating findings from group studies to specific individuals struggling with mental health problems. The role of symptoms, individual differences in symptoms and emotions, and potential underlying mechanisms as maintenance factors in mental disorders, are key elements that require further study.

Personalised models of mental disorders

Although some disorder-specific treatments have positive effects on comorbid disorders in addition to the specific presenting disorder (eg, CBT for specific anxiety disorders also reduces depressive symptomatology),[245] improvements in treatment outcomes are still needed for people with mental disorders, including those with comorbid mental disorders.

Research should embrace the complexity of mental disorders to make progress in psychological treatment research (panel 16). One way forward is to study both interindividual and intraindividual differences. An experience sampling method or ecological momentary assessment can be of use to develop personalised models of psychopathology.[246] The experience sampling method

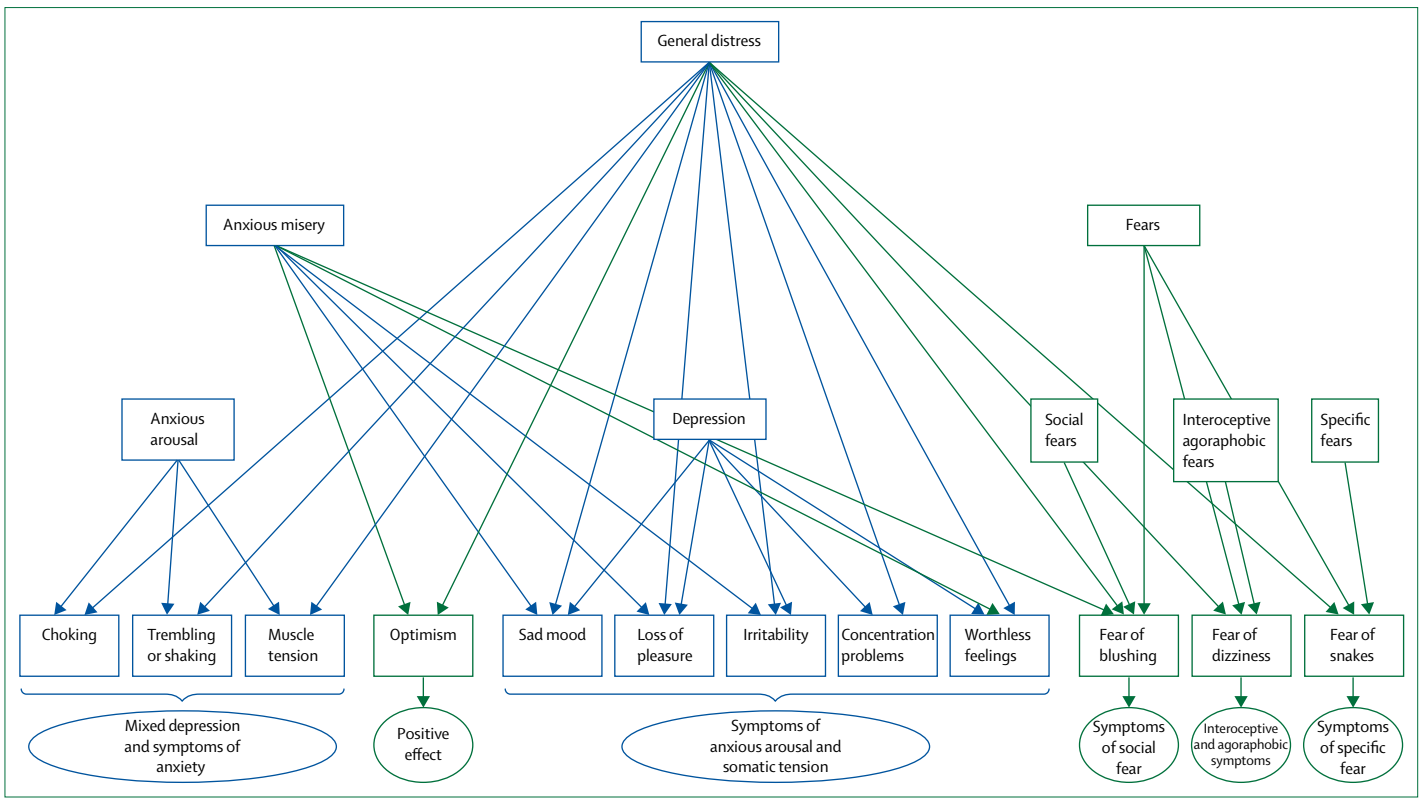

Figure 5: **Tri-level hierarchical model of the comorbidities associated with major depressive disorder and generalised anxiety disorder**
Blue and green boxes and lines show how factors and symptoms are associated with the major comorbidities. Adapted from Prenoveau et al,[243] with permission from Elsevier.

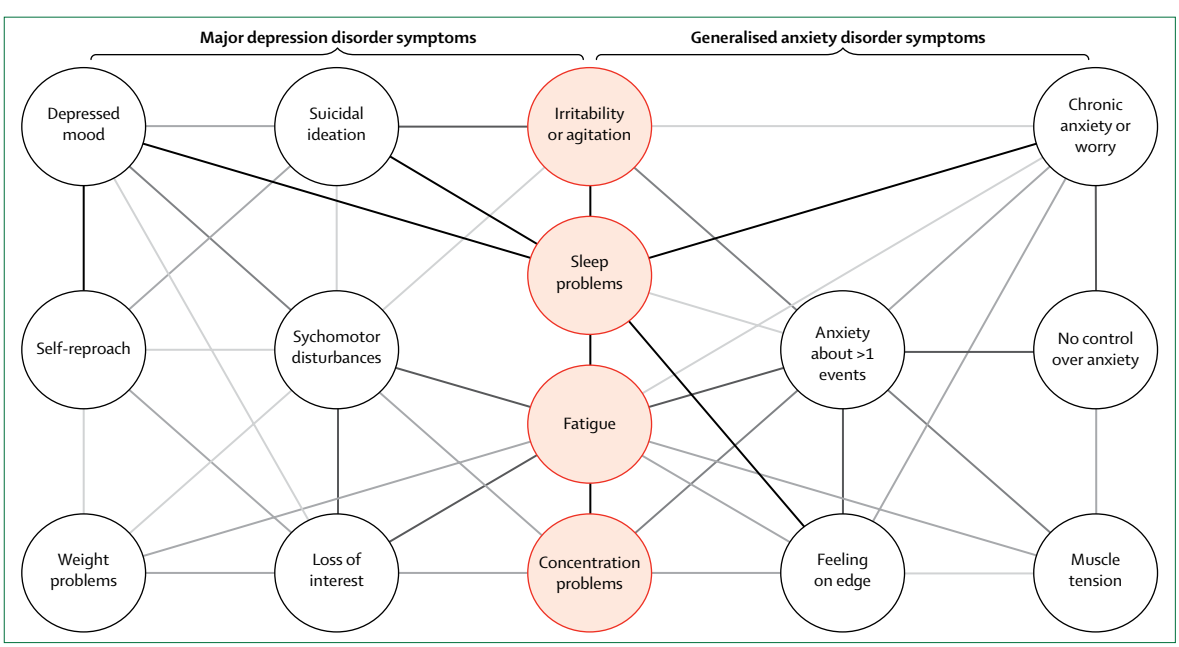

Figure 6: **Hypothetical dynamic network of the symptoms of major depressive disorder that mutually reinforce other symptoms of the disorder and comorbid generalised anxiety disorder symptoms**
Circles contain symptoms and the lines show the causal relationship between those symptoms. Darker lines indicate a stronger relationship between the symptoms. Red circles are bridge symptoms of major depressive disorder and generalised anxiety disorder. Adapted from findings in Borsboom et al[231] and Cramer et al.[228]

is a collection of research methods by which a service user reports on symptoms, affect, behaviour, and cognitions close to when they occurred in the service user's daily life—eg via an application on a mobile phone (see Part 5). Given that the experience sampling method can gather extensive data for each individual, individualised analyses can generate personalised models on the dynamics of each patient's network of psychopathology. Therefore, for instance, the centrality (or the strength) of a specific symptom or mechanism for a specific person can be defined—eg, a loss of interest might be a central symptom for one person with major depressive disorder, whereas the central symptom for another person with the same disorder could be sad mood.[246] This experience sampling method would offer new insights into mental disorders and personalised models of psychopathology. Systematic reviews have emphasised the value of the experience sampling method for assessing symptom fluctuations and interactions over time in anxiety disorders,[247] depressive disorders,[248] and substance use.[249] Studying the transient processes of emotions, cognitions, symptoms, and stress (and other relevant factors) in daily life can be done in prospective and experimental studies—eg, in a randomised controlled trial (see Part 6). In one study,[250] alongside a randomised trial of the effectiveness of three relapse-prevention treatments for depression, an ecological momentary assessment study was incorporated for a subset of patients who had remitted from recurrent depression. This momentary assessment study assessed the participants' emotions, cognitions, symptoms, and imagery-based processing ten times a day, 3 days a week, for 8 weeks, using the *Imagine your mood* application on a mobile phone.[250] Given these ecological momentary assessment studies involve self-reporting questionnaires, addition of physiological and behavioural measures might be useful for such investigations.

Personalised treatment approaches

Research on personalised models might disentangle the complexity of mental disorders, including comorbidities, and enable the optimisation of psychological treatments (appendix). The goal of the personalised medicine approach is to optimise the patient's response to treatment on the basis of their unique characteristics (ranging from genetic and neurobiological factors to symptoms) and underlying mechanisms (appendix). Ecological momentary assessment might improve insight into specific diagnoses[251,252] and offer valuable information that might improve matching treatments to patients. For instance, assessing daily fluctuations in positive and negative emotions by use of an experience sampling method for patients with depression predicts their response to treatment.[253] Assessing an individual's change in emotions (and other processes) over time as they are undergoing therapy might offer valuable empirical information on patterns and mechanisms of change during treatment.

An alternative route to improve the matching of patients to treatment is to use a machine-learning approach to identify the characteristics of an individual on the basis of group studies, which predict the patient's differential responses to existing treatments. An example of this technique is the calculation of a personalised advantage index score,[254] generated by comparing psychological treatments with pharmacological treatments for depression. Future studies should examine whether treatment matching can be improved for individuals with comorbid mental disorders. Similar approaches include clinical-risk scoring,[255] as is used in the field of medicine—eg, treatments for lung cancer are improved by molecular testing for targeted therapies that can overcome resistance to first-generation drugs.[256] Within the field of mental disorders, further studies are needed to examine the relevant variables of these index scores to optimise treatment matching and incorporate, for instance, machine learning.

Additionally, as discussed in Part 1, research on the mechanisms of psychological treatments might reveal crucial moderators of treatment outcomes that lead to better matching of patients to treatment, such as cognitive and biological markers.

Apart from enhancing treatment matching, feedback to the clinician and the patient on daily fluctuations might be of use to adapt treatment and thereby improve the treatment outcomes. Feedback on daily fluctuations via momentary assessment might enable clinicians to adapt interventions immediately—ie, within the session—by

***Panel 16:* Potential directions for future research regarding the complexities of mental disorders**

- Embrace the complexity of mental disorders, including comorbidities, by studying interindividual and intraindividual differences in daily life, and investigate individual dynamics of emotions, cognitions, symptoms, and stress (and other relevant mechanisms) in prospective studies, and in experimental studies, such as randomised controlled trials
- Study models that explain comorbidities in mental disorders and treatment approaches for comorbid disorders
- Investigate whether psychopathological models can be personalised to the extent that treatments can be adjusted, and thereby improve treatment outcomes
- Investigate which patients should be treated, and with what; a disorder-specific treatment, a personalised treatment, or a transdiagnostic or universal treatment, or a combination of these approaches
- Examine the effects of transdiagnostic or universal treatments for several mental disorders, including the comorbid conditions, in comparison with evidence-based disorder-specific treatments

giving real-time feedback on progress to the clinician and the patient.[234] A randomised controlled trial[257] of 102 patients with depression showed that the efficacy of pharmacological treatment could be enhanced by the addition of feedback to the clinician and patient on the personalised patterns of positive affect via an experience sampling method. The collection of data from ecological momentary assessments, with comparable assessments within clinical settings on a patient's patterns of daily fluctuation of change over time while undergoing treatment, would be of great value in a large population with mental disorders (including outcomes after treatment; see Part 6). Mobile devices and applications could increasingly be of use for personalised and immediate interventions. In the future, researchers could make empirical data available to clinicians and patients, which could help them to work together on improving treatment outcomes. Close collaboration will be needed with computer scientists and mathematicians, drawing on advances in these fields (eg, areas of complexity, dynamical systems, and handling big data). Further research is needed on the dynamics of symptom outcomes, rather than just static assessments—eg, time-series analysis of data on mood in patients with bipolar disorder.[258] For now, studies are needed to examine whether personalised treatments are indeed more effective than traditional treatments. A crucial question is, can psychopathological models be personalised to the extent that treatments can be adjusted for the individual, and thereby improve outcomes (see Part 6)?

One size fits all or a universal approach?

Most traditional disorder-specific psychological treatments contain a package of several interventions that target underlying mechanisms of psychopathology (see Part 1). Another, approach is to consider common features between mental disorders via a so-called universal approach (appendix; panel 9)—eg, adverse life events are consistent predictors for the onset of most mental disorders.[259] A risk factor—eg, stress sensitisation—might prove to be a valuable target for treatment, since changing sensitisation might also influence other symptoms in the network, such as rumination or sleeping problems.[260] Alternatively, changing stress sensitisation might reduce a latent factor (eg, neuroticism) and thereby reduce symptomatology. Research efforts could be focussed on trying to identify universal underlying mechanisms across numerous mental disorders, and targeting these mechanisms by universal interventions (panel 16; see Part 4). This transdiagnostic approach has begun to give very promising results—eg, in the treatment of eating disorders.[261,262]

Another example of a transdiagnostic approach to psychological treatment is Barlow's unified protocol for the treatment of emotional disorders.[263] This approach targets transdiagnostic mechanisms that are hypothesised to be responsible for the development and maintenance of psychopathology broadly, rather than addressing disorder-specific mechanisms or symptomatology (especially studied in patients with a principal anxiety disorder). A more personalised approach is taken as part of this protocol than in most treatment protocols, including an assessment of how each patient's dysfunction is associated with the underlying mechanisms of their disorder. The patient's personal profile can then be used by a clinician to select additional interventions that are specific to the mechanisms underlying their symptomatology.[264] Further studies are needed that examine whether these unified approaches are indeed more effective than traditional disorder-specific treatments.

Finally, despite the apparent contrast between a personalised and a universal approach, we suggest that future research agendas embrace the complexity of mental disorders, including comorbidities, and consider both ends of the treatment spectrum—ie, examine approaches that could offer universal treatment and, if necessary, add disorder-specific interventions alongside personalised treatment solutions (panel 16). Solutions to the problems regarding the complexity of mental disorders need to consider both highly individualised approaches and universal or transdiagnostic approaches to target common mechanisms.

Part 9: Target: suicidal behaviour—protecting lives

Introduction

In this section, we discuss how many of the principles outlined earlier in the Commission could be applied to the development, assessment, and implementation of treatments to reduce suicidal behaviour. Although the causes of suicide and suicidal behaviour are complex, they are psychological at their core, since an individual who attempts suicide makes a decision to end their life. In the past 25 years, substantial advances have been made in understanding who is most at risk of death by suicide and what factors increase this risk in some individuals but not in others. Moving forward, the growing evidence base for psychological treatments can be built on to reduce the risk of suicidal behaviour. However, despite these advances, key gaps are apparent in the understanding of suicidal behaviour that require urgent attention. Addressing these gaps is an excellent opportunity to develop more effective treatments that can be replicated, are more precise than treatments to date, and can reach those who are most vulnerable irrespective of who they are or where they live.

Suicide and suicide attempts are the most tragic outcomes that result from an inability to effectively treat those with mental disorders. Suicide is a major public health concern, with at least 804 000 people dying by suicide globally each year.[265] Since suicidal behaviour is a transdiagnostic occurrence that is

associated with many mental disorders, we believe that it is an ideal test case of how the methods that have been discussed elsewhere in this Commission can be applied to a specific problem.

In addition to the personal tragedy associated with death by suicide, the economic cost of suicide is huge. For example, in countries in the European Union, the average lifetime cost associated with a suicide is approximately €2 million.[266] Although the science of suicide research is still relatively new compared with other mental health sciences, in the past few decades several welcome advances in the understanding, treatment, and prevention of suicidal behaviour have been made.[267] These advances include a better understanding of the common risk factors for suicidal behaviour,[268–271] evidence that some psychological treatments reduce suicidal ideation and behaviour,[272–279] and growing evidence that public health interventions are associated with reductions in suicide.[278,279] In this section, we discuss the advances that relate to psychological treatments for suicidal behaviour in more detail and identify a number of urgent calls to action (panel 17). We focus on psychological treatments, but clinicians and researchers should keep in mind how the principles outlined in this Commission can be applied to the primary prevention of suicide.

Although suicide most often occurs in the context of mental disorders,[280,281] the need to move beyond diagnostic categories to explain and treat suicidal behaviour is widely recognised,[282] as is the central role of psychological factors in the cause and course of suicidal behaviour.[271] Arguably, suicide is the cause of death that is most closely associated with psychological factors, given that an individual makes a decision to end their own life.[271] Despite advances in the knowledge of the risk factors associated with suicidal behaviour, the ability to predict who is most likely to die by suicide is poor because no markers of suicide risk are sufficiently specific—eg, although depression is the mental disorder most associated with suicide risk, less than 5% of people with depression die by suicide.[271,283]

New psychological models of suicide have been developed that have identified more proximal and specific markers for risk of suicide than previous models.[284–290] In addition to the theoretical importance of identifying proximal markers of the final common pathway to suicidal behaviour, proximal markers are crucially important for clinical practice and should be treatment targets. Specifically, constructs that are among the key predictors of suicide attempts include feelings of defeat, entrapment, not belonging, and being a burden, as well as future thinking, goal adjustment, reasons for living, and fearlessness of death;[271,286–288,291,292] therefore, these constructs should be targeted in psychological treatments and suicide prevention activities. To date, insufficient focus has been on these suicide-specific psychological proximal markers. Moreover, little is known about which factors are responsible for the observed effectiveness of approaches to suicide prevention (see Part 1). Trials of psychological treatments for suicidal behaviour should routinely assess theoretically derived mechanisms (both psychological and biological) that could explain the treatment effect. A concerted focus on potential biomarkers—eg, salivary cortisol or the serotonin metabolite 5-hydroxyindoleacetic acid—is also required, ideally tested in combination with other factors.[293,294]

Evidence for psychological treatments and their effect on suicidal ideation and behaviour

Psychological treatments reduce suicidal ideation and the frequency of suicide attempts,[272,274,295] although little evidence is available that such treatments have a marked effect on subsequent incidences of death by suicide.[296] Indeed, in 86 (50%) of the 172 WHO member states, between 2000 and 2012, the incidence of death by suicide either remained approximately the same, or increased by more than 10%.[265] Most people who die by suicide are not in contact with clinical services in the 12 months before death, so until the reach of psychological treatments can be expanded beyond those already in contact with clinical

***Panel 17*: Calls to action for research into psychological treatments for suicidal behaviour**

- More large-scale psychological treatment trials (including psychotherapeutic and brief-contact interventions) targeting suicidal ideation and behaviour are urgently required
- Establish whether psychological treatments work for different sociodemographic populations (eg, men *vs* women, adolescents *vs* older adults, individuals from different ethnic backgrounds) and in different settings (eg, primary or secondary care *vs* acute settings), patient groups (eg, treatment as an inpatient *vs* as an outpatient) and countries (eg, low-income and middle-income countries *vs* high-income countries)
- Rigorous investigation of those individuals at imminent risk of suicide
- Replication of psychological treatments by independent research groups
- Agree on common measures of core outcomes (ie, suicidal ideation and behaviour) and complete multicentre treatment studies and harness so-called big-data techniques to establish whether psychological treatments can prevent suicide
- Assess potential mechanisms derived from psychological theories that are hypothesised to account for treatment effects in all trials (risk and protective mechanisms) and moderators of the effects
- Use techniques derived from experimental psychopathology to establish whether hypothesised mechanisms account for changes in symptoms or wellbeing (see Part 1)
- Establish the active ingredients of psychological treatments, including the role of therapeutic alliance
- All psychological and social treatments trials (irrespective of whether suicidal ideation or behaviour is the target) should routinely include a measure of suicidal ideation or behaviour (even as a secondary outcome) that could be harvested in big-data analyses
- Ascertain the barriers to seeking treatment—particularly for males
- Investigate the extent to which new technologies might be of use to engage difficult to reach populations (eg, men, adolescents)
- Those with lived experience of suicidal behaviour (eg, bereaved by suicide or with personal experience) should be involved in all stages of psychological treatment research

services, these services are unlikely to have a direct effect on national suicide rates. Given the complexity of the risk factors for suicide, multilevel interventions offer the most promise.[279,297]

Nonetheless, meta-analyses show that CBT is effective in reducing suicidal behaviour in adults, although not in adolescents.[275] A systematic review and meta-analysis[275] of psychosocial interventions following self-harm in adults concluded that CBT "seems to be effective in patients after self-harm", and specific studies (which require replication) provide support for dialectical behaviour therapy (for individuals with borderline personality disorder),[298] psychodynamic interpersonal therapy,[299] and mentalisation-based therapy.[300] Efforts have also been made to establish whether the Collaborative Assessment and Management of Suicidal ideation and behaviour (CAMS) is feasible and clinically effective.[301] The Attempted Suicide Short Intervention Program (ASSIP), a brief intervention consisting of integrated therapy and personalised letters, showed encouraging findings in patients who have attempted suicide.[302]

A meta-analysis[303] of therapeutic interventions for attempted suicide and self-harm in adolescents found that therapeutic interventions are effective in reducing self-harm when it is treated as a global category that includes suicidal and non-suicidal self-harm, but that the effects are weaker when suicidal and non-suicidal behaviour are examined separately. This weaker effect when separately analysing suicidal and non-suicidal behaviour is consistent with the findings of a Cochrane review of interventions for children and adolescents who self-harm.[277] The authors of the review found only 11 trials, most of which were single trials, from which they concluded that therapeutic assessment, mentalisation, and dialectical behaviour therapy "warrant further evaluation"(see also Part 4).[277] Treatments that target depression are not effective in reducing suicidal thoughts or suicide attempts.[304] A marked heterogeneity is notable across treatment studies in the field, and many studies have small sample sizes and evidence of publication bias is clear since no published studies seem to report negative findings.[275] Replication of the existing treatments by independent groups is needed, as is the development of evidence-based assessment measures that are clinically useful in the field of treatment research for suicidal behaviour (see Part 6).

The development, assessment, and implementation of psychological treatments for suicidal behaviour should be prioritised. Moreover, the extent to which psychological treatments are effective for different sociodemographic populations needs to be established (eg, men *vs* women, adolescents *vs* older adults, individuals from different ethnic backgrounds), as well as in different health-care settings (eg, primary or secondary care *vs* acute settings) and patient groups (eg, psychiatric inpatients *vs* outpatients; see Part 8). The sex-specific research is especially important, because more men die by suicide than women in all countries worldwide,[265] but many more women participate in treatment trials for suicidal behaviour.[276] Additionally, the optimal time to give treatment interventions to reduce the risk of future suicidal behaviour among those who have attempted suicide is still unclear.

Psychological treatments are not a panacea. For those psychological treatments that are effective, the overall effect sizes are small.[276,305,306] Also, for many reasons, including access and suitability, psychological treatments reach only a minority of people who die by suicide or who are suicidal. Given the inequality gradient for suicide (ie, people from lower socioeconomic backgrounds are substantially more likely to die by suicide than people in a higher socioeconomic situation[307]), the structural inequalities (eg, poverty) that contribute to the excess in suicide mortality among those from low socioeconomic backgrounds needs to be challenged.

Most suicides occur in low-income and middle-income countries,[265] so the extent to which treatments that are developed in high-income countries are generalisable worldwide needs careful consideration (see Part 2). When developing and assessing treatment trials, consideration should be given to whether a tailored or modular approach is desirable and feasible, whether the treatment is based on principles or manualised (eg, a person-centered approach or an approach with a specified session plan), and whether the interventions account for different risk profiles and inequalities (see Part 8). Furthermore, as noted in Part 1, efforts need to be re-focussed to ensure that when treatment successes occur, the mechanisms responsible for them are understood (eg, does prevention of suicide depend on changes in reward sensitivity?). An appreciation of mechanisms will help explain why treatments that are expected to be effective are not.

Challenges and opportunities for research

Panel 17 highlights the key challenges and opportunities for treatment research for suicidal behaviour in the next decade and beyond. Since individuals who are at imminent risk of death by suicide are usually excluded from treatment trials, little is known about which treatments might be effective in this patient group. Similarly, most people who are suicidal do not receive treatment;[308] therefore, an understanding is needed of the barriers to seeking help and accessing treatment. One reason some people in distress are reluctant to seek psychological or psychiatric treatment could be for fear of stigma. Organisations such as Headspace in Australia (see Part 2) offer promising stepped-care treatment models that aim to remove the stigma of mental disorders, are set in the community, and provide people with a way to seek help for relatives and friends. Another challenge is that patients with suicidal behaviour or ideation are difficult to keep in treatment;[309] an understanding of the factors associated with

disengagement is needed, so that the treatment given can be maximised when patients are in health-care settings—eg, innovative brief-contact interventions have been shown to offer some promise in acute settings.[273,310–312] Maximised treatment approaches should be considered as adjuncts to existing treatments and could be effective in reducing the likelihood that individuals act on their suicidal thoughts.[310,311] Although some public health interventions for suicide prevention have a multilevel approach and explored synergies through a combination of interventions,[297,313] few examples exist in which interventions for suicide prevention have explored combining different psychological treatments (see Part 3). Given the heterogeneity of individuals who attempt suicide or die by suicide, exploring the efficacy of treatment combinations is likely to be a rewarding approach. However, potential iatrogenic effects should be monitored in such studies, as well as in monotreatment studies (see Part 6). The potential for harm during psychological treatments research has been highlighted in the Royal Australian and New Zealand College of Psychiatrists guidelines for deliberate self-harm.[305]

To facilitate the pooling of findings across treatment studies, we urge researchers of suicidal behaviour and ideation to agree on a common set of core outcome measures (see Part 6). In the USA, some movement has been made in this regard;[273] however, an international consensus would be ideal. Agreement on such a set of measures would be aided by the gathering of an international, interdisciplinary working group. We also call for all psychological treatment trials to include a measures of suicidal ideation and behaviour as an outcome measure. Although suicidal behaviour occurs transdiagnostically, the differential prevalence of suicidal ideation and behaviour across psychiatric categories needs to be considered to understand why, for example, individuals with bipolar disorder are at particularly high risk of suicide.[314] Research into psychological treatments needs to embrace the assessment of potential mechanisms to account for treatment efficacy, and establish the active ingredients of effective treatments for suicidal ideation and behaviour (see Part 1).

The extent to which new technologies could be useful to engage so-called difficult to reach populations (eg, men, adolescents) needs to be investigated.[315,316] For example, could gaming technology be harnessed to engage young people in seeking help and treatment? Mobile applications offer opportunities to monitor suicidal ideation and mood in real time and have the potential to enhance the ability to identify (and intervene) when individuals are at their most vulnerable; however, these applications should be developed with the same rigor as traditional methods of psychological treatment (see Part 5). Arguably, the field of suicide prevention has not given sufficient consideration to the cultural influences and pressures on men, women, and adolescents (eg, depictions of masculinity). Given the high incidence of death by suicide among male individuals, the improved integration of such factors into the understanding of suicide risk and suicide prevention efforts is crucial.[317–319]

Those with lived experience of suicidal behaviour (eg, individuals bereaved by suicide, and those with personal experience) should be involved in all stages of treatment development.[320] Since little is known about what protects vulnerable people from engaging in suicidal behaviour, research into potential buffering factors should be central to the development of treatment protocols (see Part 4).

Finally, multidisciplinary collaboration is key to the success of developing, assessing, and implementing psychological treatments to prevent suicide. Since suicide is an end product of the interplay between psychological, social, biological, clinical, and cultural factors, an interdisciplinary approach should be the norm in psychological treatment research (see Part 7). However, since an individual who attempts suicide makes a decision to end their life, in the context of a range of different risk factors, psychology needs to be at the centre of future developments in the field.

Now is an exciting time to be working in research for psychological treatments for suicidal behaviour, since the theoretical and empirical foundations are available for promising treatments. However, in the next decade and beyond, innovative thinking and practice will be needed to ensure that the promise of research into psychological treatments is realised and leads to a reduction in suicidal ideation and suicide attempts.

Part 10: Active innovation and scrutiny of future psychological treatments research

Inspecting ideas and making space for future ideas

Psychological treatments are highly effective for many patients, but a large proportion of patients either do not respond to existing therapies, or the therapies are inaccessible to them. New ideas are needed, and they should be critically inspected, with the progression and rejection of ideas via rigorous and high-quality research.

In the Introduction, we used the metaphor of the fourth plinth in London's Trafalgar Square. The plinth is a metaphor to make contemporary ideas visible and to give them critical consideration. Although some pieces that are displayed on the plinth will be preserved for posterity, others might not be. Some psychological treatments or research ideas should not stand on the plinth forever, whereas some might stand the test of time. Ideas for the plinth need to be generated, inspected, and replaced over time, all within the context of a science-driven framework. Psychological treatment is a relatively young field compared with some medical treatment fields, and the notion of innovation and turnover are crucial parts of its future.

How might this innovation work for psychological treatments? The wide range of potential topics would need to be considered, as well as how these topics could

be selected, where they would be used, how they could achieve visibility, in addition to the need for a repeated cycle of this endeavour, the ultimate aim of which would be to improve the discussion and debate of the pertinent issues to make a difference for mental health. Topics could include both longstanding challenges and novel ideas such as new findings that would benefit from constructive and rapid scrutiny (eg, therapeutic approaches that emerge from the findings of preclinical studies, new ideas from sister disciplines, and new technology and ethical issues). Exciting new directions that emerge in these and other contexts should be clearly formulated, considered, and reflected upon. The ideas would need to undergo rigorous debate within and beyond the field of mental health science, and empirical assessment in the context of scientifically sound studies—eg, well controlled randomised trials.

Open and constructive debate needs to be encouraged, without new ideas being too swiftly quashed by tradition and vested interests in maintaining a status quo. However, new ideas and trends in thinking must be scrutinised before being accepted into clinical practice. One problem for the field of psychological therapy is the need to promote the use of evidence-based treatments by practitioners, who might prefer to ignore the evidence and use techniques for which they have a personal preference. For example, exposure is a treatment technique that is theoretically driven with an excellent evidence base and there is a strong scientific understanding of the mechanisms that underlie its effectiveness;[82] however, in practice, a substantial proportion of therapists do not use this technique.[321] This reluctance and sparse uptake of empirically supported interventions, or aspects of them, among practitioners is an issue that needs to be understood and rectified.

The plinth metaphor also provides a way to question older ideas that are now taken for granted, but that would benefit from further examination. Many broad issues that affect the whole field of psychological treatment require discussion (eg, the diagnostic systems, the quantity of academic publications *vs* their capacity to affect patients, and funding issues specific to psychological treatments), in addition to many issues that are relevant to science generally—from reproducibility to open data. Psychological science is a young discipline compared with many other fields, and emphasis on the progression of psychological treatments over the past century could be beneficial to stimulate innovation. Parallels exist between some of our suggestions in this Commission and the Science in Transition initiative in the Netherlands, which calls for several key reforms in science with the goal of achieving reproducible outcomes.[322,323]

For the **Science in Transition** website see http://scienceintransition.nl/

How can topics be selected? In the art world, the Fourth Plinth Initiative is an open competition to artists and is subject to a review panel. For research into psychological treatments, an equivalent competition or selection process could be held, with specific calls for people to raise challenging ideas that can catalyse progress. This process would generate topics outside what can be imagined now, and potentially create a way to capture the concerns and questions of younger generations in the field (eg, why is neuroscience not being used in treatment research more?), or those of researchers with several decades of experience (eg, why have effect sizes for psychological treatments not improved?).

Such debates and discussions could be included in a dedicated session at conferences and cross-disciplinary meetings, in a specific type of journal article, and in electronic media and areas and settings that allow debate and scrutiny. The metaphor could be adapted to fit a range of outlets, and journal editors and conference organisers could be encouraged to provide space for it. To bring attention to the resulting ideas, an annual prize could be awarded for topics that have attracted attention and made constructive progress.

The empty plinth metaphor highlights the need for repetition in the process of innovation, so that novel ideas for psychological treatment would constantly be generated, tested, and disseminated. This iterative process would not only encourage innovation, but would also enable differentiation of the new treatments and ideas that can stand the test of time, and allow long-held assumptions to be questioned to bring about progress. Essentially, these processes all occur throughout the scientific process, but—as we have discussed throughout this Commission—because of the huge scale of mental disorders globally, progress needs to speed up within psychological treatments research. Borrowing an idea from the arts gives a metaphor for one way (among many needed) to start achieving this goal.

Mental disorders and psychological treatments provide crucial and demanding targets for research enquiry. Creative but realistic solutions require communication and meaningful multidisciplinary collaborations among researchers and funding agencies, and some so-called blue skies thinking from outside the field. Additional researchers from across all disciplines are needed within the psychological treatment field, since a vast range of important questions remain that need to be addressed. This need within the field poses a great opportunity for many early career scientists to make landmark contributions, and other researchers should be encouraged into the field.

Debatably, research has stagnated in some areas of psychological treatment. Outcomes for many mental disorders (ie, depression, obsessive compulsive disorder, schizophrenia, and bipolar disorders) have not improved since the original interventions were developed, and might even be declining.[324] Understandably, an emphasis has been put on increasing access to psychological treatments,[24] given the large unmet need and changing models of service delivery.[22,83,325,326] However, an equally

strong need exists for the development of innovative new psychological treatments for the large proportion of people who do not engage with or respond to existing interventions, or who relapse after a seemingly successful course of treatment. The proportion of people who are in one of these categories varies by disorder, age group, and research study, but it can be considered to be at least 50%.[327,328] We also see a pressing need for multiple solutions, given the scale of the challenge ahead. A range of approaches could be valuable in this endeavour, including the dissemination of evidence-based therapies and increasing the accessibility of evidence-based psychotherapies. Therefore, although we see the need for a multipronged approach to tackling mental disorders worldwide, we argue that the development of new psychological treatments is one of the most promising approaches, especially given the scale of the problem of mental disorders from a public health perspective.

What factors might encourage stagnation or innovation? Branding, communication, and funding

One obstacle to innovation in the field of psychological treatment research is branding of psychological interventions, with the accompanying restrictions due to intellectual property issues. Such branding prevents the dissemination and implementation of psychological therapies, and stifles innovation by implying ownership.[329] A sustainable, not-for-profit model for the development of psychological interventions is an alternative and potentially better model than the branding model. Some research groups are under increasing pressure from so-called knowledge transfer departments at universities to brand their work for uniqueness—this pressure needs to be resisted. Instead, departments and research groups should be in favour of developments in psychological therapies that are more open, that highlight shared common components, and that are described to an extent that they can benefit from examination by the wider psychological treatment community. The issue of sharing knowledge is clearly complex because of concerns regarding incent-ivising investment in psychological treatments from a range of sources, and the need for quality control within some interventions. The development of citizen science has the potential to counteract branding and provide a fertile ground for innovation.

Noticeably, as discussed in Part 7 about training, the majority of psychological treatment researchers stick to what they know. Such adherence is rewarded by strong CVs, grant funding, and in-depth knowledge of a specific field. However, this approach can also lead to insularity. Input from fields such as neuroscience, maths, pharmacology, and more diverse disciplines, such as medical geography,[330] could help clinical researchers and practitioners think differently. Jointly reviewing advances in areas such as cognitive and social science to identify which innovations might be relevant to improving psychological therapies is entirely feasible. Such an approach has substantial potential to facilitate the introduction of new, scientifically sound ideas into psychological treatment. Innovation can benefit from creativity, including taking ideas from one area and seeing if they apply to another for treatment benefits.

Improvements are needed in communication between service users, clinicians, and across the health services. Mental and physical health-care services are typically entirely separate services, with minimal overlap despite their close relationship in terms of pathology, service use, and cost to the health services around the world.[331] Improving communication between providers of these two health-care services via shared training, resources, or even co-location would be a fundamental step toward innovation, with scope to give substantial benefits to the entire health-care system. Drawing on multiple areas of expertise will be important—particularly, obtaining input from patients and carers, which is a topic that is receiving increasing attention,[188] but which requires further consideration.

The issues of innovation and improvement cannot be dissociated from those of dissemination and implementation. Innovations that stay localised will benefit some patients but the effect will be minimal (see Part 2). Furthermore, the time taken for a treatment to get from bench to bedside will continue to be unacceptably high (estimated to be 17 years, although some argue the development of psychological treatments is quicker than pharmacological treatments[3,332]) unless dissemination and implementation are part of the development plan from the outset. Communication between stakeholders is essential to ensuring the effects of innovations are as anticipated. Only through the development of meaningful networks can genuine collaborations be built—eg, joint training, conferences, and funding. Such joint networks need to be funded appropriately for the stage of development, with basic researchers and clinicians having a bidirectional conversation, initially by email but then face to face in a relaxed atmosphere with time to think creatively, discuss constructively, and develop testable hypotheses.

The role of funders in promoting or stifling innovation cannot be overemphasised. The NIMH's influence on funding has been profound, and inclusion of a category on the RDoC entitled "Other"—so that researchers are not restricted to only studying established research domains—encourages new ideas.[333] Although researchers understand that funding agencies tend to want to avoid risks, the funding of high-risk studies is fundamental to the development of new treatments. Agency support to fund proof-of-concept studies in psychological therapies could be especially important to the field. The extent of funding for international research into mental disorders, and psychological treatments in particular, is far too low;[334,335] increased funding is essential for progress and to take risks in new areas.

Globally, within large funding organisations, mental health is often included with other diseases or with, for example, neuroscience. Representation within these funding organisations of people with experience in mental health research can be minimal and people with genuine expertise in mental health are needed within the decision-making bodies of the major funding organisations. Clearer representation of expertise in psychological treatments would also be of benefit. A review of the international funding organisations that address mental health would be useful, including the extent to which psychological treatment research is accommodated. Some charities fund research, which is of course welcomed, but unfortunately many smaller charities often do not have the capacity for a rigorous research review process. The quality and effect of studies that do not benefit from peer review and scientific support is often suboptimal. Funding models whereby smaller charities that support mental health research are themselves supported by larger charities, with regard to their commissioning and execution of research, are likely to improve both the quality of research and the value for money of the research projects. The creation of a framework for peer review for mental health in general, and psychological treatment in particular, or even a possible outsourcing model for such processes, might help many organisations with funding initiatives in this area.

How can the effectiveness of efforts toward new treatments be assessed?

Broadly, our aim in undertaking this Commission was to identify the scope of advancing research efforts to improve mental health globally via improvements in the effectiveness and the global reach of psychological treatments. We have outlined an agenda of some of the areas in which we see real scope to improve treatment research and treatment delivery to enable more effective interventions and greater accessibility of such treatments to individuals with mental disorders than have been available to date. Treatment protocols that effectively treat and prevent the onset of mental disorders will have a key role as one of the many contributions that are needed to relieve the substantial worldwide burden of mental disorders.

The ability to assess in a tangible and meaningful way whether the goal of improving treatments for mental disorders has been achieved remains a challenge for the field. The initial indicator of success is within the outcomes of the treatment trial—ie, whether the effect sizes indicate improved efficacy of novel and refined psychological interventions. In the longer term, meta-analyses will outline whether new treatment approaches have improved effectiveness, and thus, in turn, contribute to reducing the prevalence and the burden of mental disorders. In the future, the findings of epidemiological studies that show changes in the prevalence of mental disorders over time will reveal the success of scalable treatment and prevention approaches. We acknowledge, however, that measurement in this field can be complicated and ambitious—eg, changes in the diagnostic classification systems over time complicate comparisons. We therefore see a need for research on how to define and quantify the burden of mental disorders globally and over time. We see scope for progress to be made, not only by examining changes in prevalence, but also by investigating improvements in the functional effect of mental disorders—from impairments in social and occupational functioning, through to quality of life. Such a suggestion aligns with our acknowledgment of the value of expanding ideas of mental disorders beyond the notions of disease and infirmity, to outcomes with broad functional relevance (eg, an individual's capacity to adapt, and self-manage; see Introduction).

Innovation to create new treatments—what ideas can be put on the plinth in the first round?

Increasing access to effective psychological treatments is a priority, but investment in innovations that will energise the research field of psychological treatment and improve therapeutic outcomes is equally important.[22,83] Many books and journal articles have been dedicated to the issue of innovation, and even an entire journal is devoted to this topic (*Healthcare: The Journal of Delivery Science and Innovation*), which commenced in June 2013. Innovation is clearly a challenging area and what is presented as an innovation can often be seen as old wine in a new bottle. Innovation needs to be put into a historical context, so that existing ideas are not repackaged with enthusiasm as an innovation.[336] Engagement is needed in the critical inspection, progression, and rejection of ideas through research. One approach is to change the nature of the questions being asked; here we begin with two examples.

What matters to patients?

Most clinical research has tended to focus on single diagnoses, despite many patients having multiple coexisting disorders.[230] Clinicians have guidelines for the treatment of specific diagnoses but almost no data to guide them with regard to evidence-based decision making for patients who have common co-occurring disorders—eg, anxiety and depression. Patients' difficulties can alternatively be considered in terms of the problem they are having rather than in diagnostic terms—eg, loneliness or betrayal.[337] Linking with social psychology and having a problem-based approach to the development of psychological treatments, instead of a disorder-based approach, is likely to lead to new ways of thinking about and addressing mental disorders, which was partly the intention of the RDoC initiative.[333] Such approaches could increase engage-ment in and the acceptability of therapies, but challenges would still

exist for agreeing operationalised definitions of the problem, and ensuring that such difficulties were affecting people's lives in ways they value and that could be viewed within a psychological framework.

What matters to researchers?

Many things matter to researchers, but most scientists are curious about what does not work, as well as what does. Data that do not obey the expected rules are essential to scientific progress. For psychological treatments research, defining non-responders, identifying which people relapse, and those who do not engage in treatment, are all necessary and crucial steps.[328] A thorough and focused analysis of the characteristics of those individuals who do not respond to existing treatments, and having dedicated funding for such research, are priorities that would have a positive effect and bring generalisable benefits to existing and new treatments. Additionally, in areas in which no existing treatments work adequately, the generation of novel treatments is essential.

What next?

We see mental health as a substantial global challenge, but at the same time we recognise that nowadays we are faced with an array of pressing priorities that demand global attention and action, including, but in no way limited to: climate change, international conflicts, famine, and the displacement of millions of people from their home countries. Notwithstanding that many such substantial problems exist in the world, in the domain of mental health, we call for increased research efforts to advance psychological treatments, so that more effective interventions will serve as an essential part of our set of approaches that are needed to make an impact upon the burden of mental disorders worldwide and improve lives.

We acknowledge that our call for developments in psychological treatments for mental disorders is but one endeavour in the context other similar timely initiatives. For example, Wykes and colleagues[338] have laid out six key priorities for a mental health research agenda for Europe and worldwide. Mental health is increasingly being recognised as an area that needs to move forward on a global scale. Furthermore, psychological interventions can be applied not only to mental disorders, but have been increasingly of use across a range of areas—eg, in changing health behaviour, managing the psychological aspects and effects of physical health problems (ie, pain management and somatic concerns, psycho-oncology), and instituting organisational change.

Clinicians, researchers, patients, carers, funders, commissioners, managers, policy planners, change experts, and the general public all have a part to play in innovating psychological therapies, and a focus on any one of the ideas presented in this Commission has the potential to bring about substantial and much-needed improvements. More ideas will be needed than just those included here. This Commission is not a specific roadmap, all relevant areas of research and mental health science need to be considered to gain traction in this endeavour. Innovations arising from thoughtful effort have genuine potential to transform the science and practice of psychological therapies, and the lives of all of those who are affected by mental disorders.

Contributors

All authors contributed equally.

Declaration of interests

EAH reports her primary affiliation is the Division of Psychology, Department for Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden. She is an Honorary Professor of Clinical Psychology at the University of Oxford, Oxford, UK, in the Department of Psychiatry, and holds an honorary position at the Medical Research Council's (MRC's) Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, UK, and receives no renumeration for these roles. She serves on the board of the charity MQ: Transforming Mental Health and receives no remuneration for this role. She is on the board of overseers for the charity Children and War Foundation, Oslo, Norway, and receives no remuneration for this role. She is an associate editor for *Behaviour Research and Therapy*, for which she receives an honorarium, and was a founding associate editor for *Clinical Psychological Science*. She is on the editorial board of *Psychological Science* and *Cognitive Behaviour Therapy* and receives no remuneration for these roles. She has presented keynote addresses at conferences, such as European Association for Behavioural and Cognitive Therapies (EABCT), and received an honorarium for this. She has presented clinical training workshops, some of which include a fee. She receives royalties from her co-authored book *Oxford Guide to Imagery in Cognitive Therapy*. AG is a Professor of Clinical Psychology at the Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden. He is on the editorial board of *Behaviour Research and Therapy* and receives no remuneration for this role. He has presented clinical training workshops and provided supervision to clinicians at eating disorder treatment units, most of which include a fee, but are not related to the current contribution. He also receives royalties from his co-authored books on eating disorders and body image. CJH has received consultancy fees from P1vital, Lundbeck, and Servier. She has grant incomes from Johnson & Johnson, UCB Pharma, Lundbeck, and Sunovion. She is employed by the University Department of Psychiatry at Oxford University, Oxford, UK, and holds an associate Professorship at the Department of Psychology, University of Oslo, Oslo, Norway. She is an associate editor for *Psychological Medicine*, for which she receives an honorarium. PGR reports grants from the UK National Institute for Health Research (NIHR) outside the submitted work. He is employed by Imperial College London, London, UK, and Central and North West London Foundation National Health Service (NHS) Trust. He has been involved in the development and adaption of psychological interventions, but receives no payments from these. PC is Head of the Department of Clinical, Neuro and Developmental Psychology at the Vrije Universiteit, Amsterdam, for which he receives his annual salary. He is deputy editor of *Depression and Anxiety*, for which his university receives a fee. He is also leader of the Mental Health Program of the EMGO Institute for Health and Care Research at the Vrije Universiteit and Vrije Universiteit Medical Center in Amsterdam, Honorary President of the Canadian Psychological Association (until June, 2017), coordinator of the Global Consortium for Depression Prevention, a member of the Guideline Development Panel for Depressive Disorders of the American Psychological Association, Chair of the Sir Henry Wellcome Building for Mood Disorders Research Expert Advisory Board in Exeter, UK, adviser for several national and international research projects, and a member of the editorial board of several scientific journals; he receives no remuneration for any of these positions. He does receive expense allowances for his membership of the Board of Directors of the Fonds Psychische Gezondheid and Korrelatie, and for being Chair of the Parliamentary Assistance Coordination Office Committee of the Raad voor Civiel-militaire Zorg en Onderzoek of the Dutch Ministry of Defence. He also receives royalties for books he has authored or co-authored and

for occasional workshops and invited lectures. APM's primary affiliation is the School of Psychological Sciences, University of Manchester, Manchester, UK. He is also Director of the Psychosis Research Unit, Greater Manchester West NHS Trust, Manchester, UK. He serves on several editorial boards and receives no remuneration for these roles. He has presented keynote addresses at conferences and given clinical training workshops, some of which have included a fee. He receives royalties from several co-authored and edited books. He delivers cognitive behavioural therapy within the UK NHS and has received funding from both the MRC and UK NIHR to do evaluative research into the efficacy of psychological therapies. JPR is a consultant for Cambridge Cognition and Takeda. He is an associate editor for *Neuroimage: Clinical* and receives an honorarium for this role. He is a handling editor at *Royal Society Open Science* and is on the Editorial Board of *Computational Psychiatry*; he receives no renumeration for these roles. He has received the British Psychological Society's Spearman Medal, the British Association for Psychopharmacology's Senior Award, and a Philip Leverhulme Prize in Psychology. He has received renumeration for acting as a panel member for the Research Council of Norway. None of these positions or awards have any direct relation to this Commission. CLHB is Professor of Clinical Psychology at the Department of Psychiatry at the Academic Medical Center at the University of Amsterdam, Amsterdam, Netherlands, and at the University of Groningen, Groningen, Netherlands. She also has a Guest Professorship at the Faculty of Psychology and Pedagogy at Ghent University, Ghent, Belgium. She is co-editor of *PLoS ONE*, and receives no honorarium for this role. She serves on the board of the section for Affective Disorders at Dutch Cognitive Behavioural Association and is a boardmember of the Dutch multidisciplinary guideline for anxiety and depression; she receives no remuneration for this role. She is an adviser for the minister on National Health Care in the Netherlands on issues of care for inclusion in the statutory insured package (Advies Pakket Commissie, ZIN); she receives an honorarium for this role and it has no direct relation to the current contribution. She has received a fellowship at the Netherlands Institute of Advanced Sciences, supported by the Royal Netherlands Academy of Arts and Sciences and this is not directly related to the current contribution. She has given keynote addresses at conferences such as EABCT 2014 and the European Conference of Psychology and received an honorarium. She has given clinical training workshops, some of which included a fee. She receives royalties from her books and co-edited books. RCO'C's primary affiliation is the Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK, where he heads the Mental Health and Wellbeing Research Group. He is also Director of the Suicidal Behaviour Research Laboratory at the University of Glasgow. He is joint chief editor for *Archives of Suicide Research* and associate editor for *Suicide and Life-Threatening Behavior and Behavior Therapy*. He also serves on several editorial boards and is a current Vice President of the International Association for Suicide Prevention and past President of the International Academy of Sucide Research. He receives an honorarium for his role at *Behavior Therapy*, but does not receive a remuneration for any of the other roles. He was a member of the National Institute of Health and Care Excellence's guideline development group for the longer-term management of self-harm and he is a member of Health Education England's Self-Harm & Suicide Prevention Competence Framework Expert Reference Group. He sits on the Scottish Government's Suicide Prevention and Implementation Monitoring Group. He receives royalties from one co-authored and several co-edited books, occasional workshops, and invited addresses. RS served as a Senior Adviser for the MQ: PsyImpact programme from February, 2015, to February, 2016. She was a consultant for Big Health. She also receives royalties for books she has authored or co-authored (American Psychological Association Books, Elsevier Press) and occasional workshops and invited addresses. MLM's primary affiliation is the School of Psychology, UNSW, Sydney, NSW, Australia, where she is a Professor and PLuS Alliance Fellow. She is a consulting editor of the *Journal of Experimental Psychology: Applied* and *Clinical Psychological Science*, and a member of four additional editorial boards; she receives no remuneration for these roles. She has given keynote addresses at conferences and for some of these she has received honoraria. MGC's primary affiliation is the Department of Psychology, University of California, Los Angeles (UCLA), CA, USA, where she is Vice Chair, which provides her annual salary, supplemented by summer funds from grants from the US National Institute of Mental Health or the Defense Advanced Research Projects Agency. She is editor-in-chief of *Behaviour Research and Therapy* and associate editor of *Psychological Bulletin*, for which she receives remuneration. She is director of the UCLA Anxiety and Depression Center; co-director of the UCLA Staglin Family Music for Behavioral and Brain Health; former President of the Association for Behavior and Cognitive Therapy; co-chair of the Human Studies Section of the UCLA Grand Challenge for Depression; member of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) Steering Committee for the American Psychiatric Association; member of the Scientific Advisory Board for the Center of Excellence on Generalization Research at the University of Leuven, Leuven, Belgium; Honorary Member of the Experimental Psychopathology Group (Dutch-Flemish Postgraduate School for Research and Education); and Honorary Fellow of the Department of Psychiatry at Oxford University, Oxford, UK. She receives no remuneration for any of these positions. She received remuneration for her awards as Eleonore Trefftz Guest Professorship (Technical University of Dresden, Dresden Germany) and the International Francqui Professor (Univeristy of Leuven). She also receives royalties for books she has authored or co-authored (American Psychological Association Books, Elsevier Press) and occasional workshops and invited addresses.

Acknowledgments

Additional contributors who also attended The *Lancet Psychiatry* meeting in London, UK, in December, 2015 include: E Barley, N Balmer, S E Blackwell, M Browning, K Carroll, S Cartwright-Hatton, C Creswell, T Dalgleish, M Di Simplicio, S Dix, B Dunn, P Fearon, C Hirsch, J M Hooley, L Iyadurai, S Jones, S Kamboj, A Milton, A Reinecke, U Schmidt, and M Van Ommeren. We also thank C Fairburn and G Goodwin for helpful discussions. We thank R Emsley for his consultancy regarding clinical trial methodology, and we thank L Iyadurai and E L James for help preparing the manuscript. We are grateful for support from MQ: Transforming Mental Health for travel expenses to the Commission meeting held by The *Lancet Psychiatry*. EAH is supported by the Karolinska Institutet and the Lupina Foundation of Toronto. She has received support from the MRC intramural programme (MRC-A060–5PR50) and the NIHR Oxford Biomedical Research Centre Programme. AG is supported by the Swedish Foundation for Humanities and Social Sciences (Riksbankens Jubileumsfond). CJH has research funding from the Wellcome Trust, MRC, and the NIHR Oxford Health Biomedical Research Centre. PGR has funding from the NIHR to develop and evaluate early interventions in randomised controlled trials, and receives support from the Imperial NIHR Biomedical Research Centre. PC has funding from the European Union (FP7 and H2020 programmes), ZonMw (Dutch Health Research Council), and the Protestants Fonds Geestelijke Volksgezondheid (Protestant Foundation for Mental Health). APM has received funding from the NIHR. JPR is funded by the Wellcome Trust. CLHB is supported by the Department of Psychiatry at the Academic Medical Center of the University of Amsterdam, and the Netherlands Institute of Advanced Sciences (2017), which is supported by the Royal Netherlands Academy of Arts and Sciences. RCOC has received funding from the US Department of Defense, NIHR, NHS, NHS Greater Glasgow and Clyde, NHS Health Scotland, MRC, MQ: Transforming Mental Health Research, the Chief Scientist Office, and the Scottish Government. RS's research at Great Ormond Street Hospital, NHS Foundation Trust and Univeristy College London Great Ormond Street Institute of Child Health, London, UK, is supported by the NIHR Great Ormond Street Hospital Biomedical Research Centre. MLM is supported by the Australian National Health and Medical Research Council. She also receives support from the PLuS Alliance Fellows Funding Scheme (UNSW, Sydney, Australia). MGC is funded by the US National Institutes of Mental Health (R01 MH1001171, R01 MH1014531, R34 MH101359, R01 MH102274), the US Defense Advanced Research Projects Agency (R21 MH1010336), and the US National Aeronautics and Space Administration (NNX15AP57G). The views expressed in this Commission are those of the authors and are not necessarily those of any of the funding bodies or agencies.

References

1 James W. The principles of psychology. New York, NY: Henry Holt & Co, 1890.
2 Holmes EA, Craske MG, Graybiel AM. Psychological treatments: a call for mental-health science. *Nature* 2014; **511:** 287–89.
3 Joyce C. Transforming our approach to translational neuroscience: the role and impact of charitable nonprofits in research. *Neuron* 2014; **84:** 526–32.
4 McHugh RK, Whitton SW, Peckham AD, Welge JA, Otto MW. Patient preference for psychological vs pharmacologic treatment of psychiatric disorders: a meta-analytic review. *J Clin Psychiatry* 2013; **74:** 595–602.
5 Steel Z, Marnane C, Iranpour C, et al. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980–2013. *Int J Epidemiol* 2014; **43:** 476–93.
6 Värnik P. Suicide in the world. *Int J Environ Res Public Health* 2012; **9:** 760–71.
7 Whiteford HA, Degenhardt L, Rehm J, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; **382:** 1575–86.
8 Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. *Am J Psychiatry* 2014; **171:** 453–62.
9 Chisholm D, Sweeny K, Sheehan P, et al. Scaling-up treatment of depression and anxiety: a global return on investment analysis. *Lancet Psychiatry* 2016; **3:** 415–24.
10 Hu TW. Perspectives: an international review of the national cost estimates of mental illness, 1990–2003. *J Ment Health Policy Econ* 2006; **9:** 3–13.
11 Gustavsson A, Svensson M, Jacobi F, et al. Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011; **21:** 718–79.
12 Bloom DE, Cafiero ET, Jané-Llopis E, et al. The global economic burden of non-communicable diseases. Geneva: World Economic Forum, 2011.
13 Huber M, Knottnerus JA, Green L, et al. How should we define health? *BMJ* 2011; **343:** d4163.
14 Andrews G, Issakidis C, Sanderson K, Corry J, Lapsley H. Utilising survey data to inform public policy: comparison of the cost-effectiveness of treatment of ten mental disorders. *Br J Psychiatry* 2004; **184:** 526–33.
15 Baxter AJ, Patton G, Scott KM, Degenhardt L, Whiteford HA. Global epidemiology of mental disorders: what are we missing? *PLoS One* 2013; **8:** e65514.
16 Park-Lee E, Lipari RN, Hedden SL, Kroutil LA, Porter JD. Receipt of services for substance use and mental health issues among adults: results from the 2016 National Survey on Drug Use and Health. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2017. https://www.samhsa.gov/data/sites/default/files/NSDUH-DR-FFR2-2016/NSDUH-DR-FFR2-2016.htm (accessed Jan 5, 2018).
17 Appleby L, Asherson P, Ashtarikiani, et al. Mental health and wellbeing in England. Adult psychiatric morbidity survey 2014. Leeds: NHS Digital, 2016.
18 Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62:** 629–40.
19 Olfson M, Marcus SC. National trends in outpatient psychotherapy. *Am J Psychiatry* 2010; **167:** 1456–63.
20 Olfson M, Marcus SC. National patterns in antidepressant medication treatment. *Arch Gen Psychiatry* 2009; **66:** 848–56.
21 Gerhard T, Akincigil A, Correll CU, Foglio NJ, Crystal S, Olfson M. National trends in second-generation antipsychotic augmentation for nonpsychotic depression. *J Clin Psychiatry* 2014; **75:** 490–97.
22 Kazdin AE, Blase SL. Rebooting psychotherapy research and practice to reduce the burden of mental illness. *Perspect Psychol Sci* 2011; **6:** 21–37.
23 Fairburn CG, Patel V. The global dissemination of psychological treatments: a road map for research and practice. *Am J Psychiatry* 2014; **171:** 495–98.
24 Clark DM. Implementing NICE guidelines for the psychological treatment of depression and anxiety disorders: the IAPT experience. *Int Rev Psychiatry* 2011; **23:** 318–27.
25 Turnbull HW. Correspondence of Isaac Newton, volume 1: 1661–1675. Cambridge: Cambridge University Press, 1959.
26 Greater London Authority. What's on the Fourth Plinth now. https://www.london.gov.uk/what-we-do/arts-and-culture/art-and-design/fourth-plinth (accessed May 4, 2016).
27 Kazdin AE. Mediators and mechanisms of change in psychotherapy. *Annu Rev Clin Psychol* 2007; **3:** 1–27.
28 Brown LA, Wiley JF, Wolitzky-Taylor K, et al. Changes in self-efficacy and outcome expectancy as predictors of anxiety outcomes from the CALM study. *Depress Anxiety* 2014; **31:** 678–89.
29 Sanislow CA. Updating the research domain criteria. *World Psychiatry* 2016; **15:** 222–23.
30 Kozak MJ, Cuthbert BN. The NIMH research domain criteria initiative: background, issues and pragmatics. *Psychophysiology* 2016; **53:** 286–97.
31 Miller GE, Cole SW. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. *Biol Psychiatry* 2012; **72:** 34–40.
32 Dalgleish T, Werner-Seidler A. Disruptions in autobiographical memory processing in depression and the emergence of memory therapeutics. *Trends Cogn Sci* 2014; **18:** 596–604.
33 Roiser JP. What has neuroscience ever done for us? *Psychologist* 2015; **28:** 284–87.
34 Fox E, Zougkou K, Ashwin C, Cahill S. Investigating the efficacy of attention bias modification in reducing high spider fear: the role of individual differences in initial bias. *J Behav Ther Exp Psychiatry* 2015; **49:** 84–93.
35 Twamley EW, Vella L, Burton CZ, Heaton RK, Jeste DV. Compensatory cognitive training for psychosis: effects in a randomized controlled trial. *J Clin Psychiatry* 2012; **73:** 1212–19.
36 Smith T, Iadarola S. Evidence base update for autism spectrum disorder. *J Clin Child Adolesc Psychol* 2015; **44:** 897–922.
37 Barlow DH, Craske MG. The phenomenology of panic. In: Rachman SJ, Maser JD, eds. Panic: psychological perspectives. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988: 11–36
38 Bouton ME, Mineka S, Barlow DH. A modern learning theory perspective on the etiology of panic disorder. *Psychol Rev* 2001; **108:** 4–32.
39 Clark DM. A cognitive approach to panic. *Behav Res Ther* 1986; **24:** 461–70.
40 Barlow DH, Craske MG. Mastery of your anxiety and panic. Albany, NY: Graywind Publications, 1988.
41 Salkovskis PM, Clark DM, Hackmann A. Treatment of panic attacks using cognitive therapy without exposure or breathing retraining. *Behav Res Ther* 1991; **29:** 161–66.
42 Hofmann SG, Smits JA. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. *J Clin Psychiatry* 2008; **69:** 621–32.
43 Foa EB, Steketee G, Grayson JB, Turner RM, Latimer P. Deliberate exposure and blocking of obsessive-compulsive rituals: immediate and long-term effects. *Behav Ther* 1984; **15:** 450–72.
44 Öst LG, Havnen A, Hansen B, Kvale G. Cognitive behavioral treatments of obsessive-compulsive disorder. A systematic review and meta-analysis of studies published 1993–2014. *Clin Psychol Rev* 2015; **40:** 156–69.
45 Lewinsohn PM. A behavioral approach to depression. In: Friedman RM, Katz MM, eds. The psychology of depression: contemporary theory and research. New York, NY: Wiley, 1974: 157–85.
46 Jacobson NS, Martell CR, Dimidjian S. Behavioral activation treatment for depression: returning to contextual roots. *Clin Psychol Sci Pract* 2001; **8:** 255–70.
47 Cuijpers P, van Straten A, Warmerdam L. Behavioral activation treatments of depression: a meta-analysis. *Clin Psychol Rev* 2007; **27:** 318–26.
48 Mohr DC, Spring B, Freedland KE, et al. The selection and design of control conditions for randomized controlled trials of psychological interventions. *Psychother Psychosom* 2009; **78:** 275–84.
49 Cuijpers P, Cristea IA, Karyotaki E, Reijnders M, Huibers MJ. How effective are cognitive behavior therapies for major depression and anxiety disorders? A meta-analytic update of the evidence. *World Psychiatry* 2016; **15:** 245–58.

50 Wampold BE. How important are the common factors in psychotherapy? An update. *World Psychiatry* 2015; **14:** 270–77.

51 Kazdin AE. Evidence-based psychotherapies I: qualifiers and limitations in what we know. *S Afr J Psychol* 2014; **44:** 381–403.

52 Cristea IA, Kok RN, Cuijpers P. Efficacy of cognitive bias modification interventions in anxiety and depression: meta-analysis. *Br J Psychiatry* 2015; **206:** 7–16.

53 Fox E, Zougkou K, Ridgewell A, Garner K. The serotonin transporter gene alters sensitivity to attention bias modification: evidence for a plasticity gene. *Biol Psychiatry* 2011; **70:** 1049–54.

54 Milad MR, Rosenbaum BL, Simon NM. Neuroscience of fear extinction: implications for assessment and treatment of fear-based and anxiety related disorders. *Behav Res Ther* 2014; **62:** 17–23.

55 Lanius RA, Vermetten E, Loewenstein RJ, et al. Emotion modulation in PTSD: clinical and neurobiological evidence for a dissociative subtype. *Am J Psychiatry* 2010; **167:** 640–47.

56 van Vugt MK, Hitchcock P, Shahar B, Britton W. The effects of mindfulness-based cognitive therapy on affective memory recall dynamics in depression: a mechanistic model of rumination. *Front Hum Neurosci* 2012; **6:** 257.

57 Wiles NJ, Thomas L, Turner N, et al. Long-term effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: follow-up of the CoBalT randomised controlled trial. *Lancet Psychiatry* 2016; **3:** 137–44.

58 Bockting CL, Smid NH, Koeter MW, Spinhoven P, Beck AT, Schene AH. Enduring effects of preventive cognitive therapy in adults remitted from recurrent depression: a 10 year follow-up of a randomized controlled trial. *J Affect Disord* 2015; **185:** 188–94.

59 Wampold BE, Mondin GW, Moody M, Stich F, Benson K, Ahn H. A meta-analysis of outcome studies comparing bona fide psychotherapies: empirically, "all must have prizes". *Psychol Bull* 1997; **112:** 203–15.

60 Marcus DK, O'Connell D, Norris AL, Sawaqdeh A. Is the dodo bird endangered in the 21st century? A meta-analysis of treatment comparison studies. *Clin Psychol Rev* 2014; **34:** 519–30.

61 Lee KH, Siegle GJ, Dahl RE, Hooley JM, Silk JS. Neural responses to maternal criticism in healthy youth. *Soc Cogn Affect Neurosci* 2015; **10:** 902–12.

62 Ressler KJ, Rothbaum BO, Tannenbaum L, et al. Cognitive enhancers as adjuncts to psychotherapy: use of d-cycloserine in phobic individuals to facilitate extinction of fear. *Arch Gen Psychiatry* 2004; **61:** 1136–44.

63 Otto MW, Kredlow MA, Smits JA, et al. Enhancement of psychosocial treatment with d-cycloserine: models, moderators, and future directions. *Biol Psychiatry* 2016; **80:** 274–83.

64 Nader K, Schafe GE, Le Doux JE. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature* 2000; **406:** 722–26.

65 James EL, Bonsall MB, Hoppitt L, et al. Computer game play reduces intrusive memories of experimental trauma via reconsolidation-update mechanisms. *Psychol Sci* 2015; **26:** 1201–15.

66 Kindt M. A behavioural neuroscience perspective on the aetiology and treatment of anxiety disorders. *Behav Res Ther* 2014; **62:** 24–36.

67 Treanor M, Brown LA, Rissman J, Craske MG. Can memories of traumatic experiences or addiction be erased or modified? A critical review of research on the disruption of memory reconsolidation and its applications. *Perspect Psychol Sci* 2017; **12:** 290–305.

68 Davis M, Ressler K, Rothbaum BO, Richardson R. Effects of d-cycloserine on extinction: translation from preclinical to clinical work. *Biol Psychiatry* 2006; **60:** 369–75.

69 Schramm MJ, Everitt BJ, Milton AL. Bidirectional modulation of alcohol-associated memory reconsolidation through manipulation of adrenergic signaling. *Neuropsychopharmacology* 2016; **41:** 1103–11.

70 Marvar PJ, Goodman J, Fuchs S, Choi DC, Banerjee S, Ressler KJ. Angiotensin type 1 receptor inhibition enhances the extinction of fear memory. *Biol Psychiatry* 2014; **75:** 864–72.

71 Kalueff AV, Stewart AM, Song C, Berridge KC, Graybiel AM, Fentress JC. Neurobiology of rodent self-grooming and its value for translational neuroscience. *Nat Rev Neurosci* 2016; **17:** 45–59.

72 Hales CA, Stuart SA, Anderson MH, Robinson ES. Modelling cognitive affective biases in major depressive disorder using rodents. *Br J Pharmacol* 2014; **171:** 4524–38.

73 Parker RM, Paul ES, Burman OH, Browne WJ, Mendl M. Housing conditions affect rat responses to two types of ambiguity in a reward-reward discrimination cognitive bias task. *Behav Brain Res* 2014; **274:** 73–83.

74 Michie S, Richardson M, Johnston M, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Ann Behav Med* 2013; **46:** 81–95.

75 England MJ, Stith-Butler A, Gonzalez ML. Psychosocial interventions for mental and substance use disorders. A framework for establishing evidence-based standards. Washington, DC: National Academies Press (US), 2015.

76 Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380:** 2197–223.

77 Lawrence D, Kisely S, Pais J. The epidemiology of excess mortality in people with mental illness. *Can J Psychiatry* 2010; **55:** 752–60.

78 Wang PS, Angermeyer M, Borges G, et al. Delay and failure in treatment seeking after first onset of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry* 2007; **6:** 177–85.

79 Patel V, Chowdhary N, Rahman A, Verdeli H. Improving access to psychological treatments: lessons from developing countries. *Behav Res Ther* 2011; **49:** 523–28.

80 WHO. Mental health atlas: 2011. Geneva: World Health Organization, 2011.

81 Saraceno B, van Ommeren M, Batniji R, et al. Barriers to improvement of mental health services in low-income and middle-income countries. *Lancet* 2007; **370:** 1164–74.

82 Vervliet B, Craske MG, Hermans D. Fear extinction and relapse: state of the art. *Annu Rev Clin Psychol* 2013; **9:** 215–48.

83 Kazdin AE, Rabbitt SM. Novel models for delivering mental health services and reducing the burden of mental illness. *Clin Psychol Sci* 2013; **1:** 170–91.

84 Bass J, Neugebauer R, Clougherty KF, et al. Group interpersonal psychotherapy for depression in rural Uganda: 6-month outcomes: randomised controlled trial. *Br J Psychiatry* 2006; **188:** 567–73.

85 Rahman A, Malik A, Sikander S, Roberts C, Creed F. Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: a cluster-randomised controlled trial. *Lancet* 2008; **372:** 902–09.

86 Dawson KS, Bryant RA, Harper M, et al. Problem Management Plus (PM+): a WHO transdiagnostic psychological intervention for common mental health problems. *World Psychiatry* 2015; **14:** 354–57.

87 Craske MG, Rose RD, Lang A, et al. Computer-assisted delivery of cognitive behavioral therapy for anxiety disorders in primary-care settings. *Depress Anxiety* 2009; **26:** 235–42.

88 Andersson G, Titov N. Advantages and limitations of internet-based interventions for common mental disorders. *World Psychiatry* 2014; **13:** 4–11.

89 Arjadi R, Nauta MH, Chowdhary N, Bockting CLH. A systematic review of online interventions for mental health in low and middle income countries: a neglected field. *Glob Ment Health (Camb)* 2015; **2:** e12.

90 Poushter J. Smartphone ownership and internet usage continues to climb in emerging economies. Washington, DC: Pew Research Center, 2016. http://www.pewglobal.org/2016/02/22/smartphone-ownership-and-internet-usage-continues-to-climb-in-emerging-economies/ (accessed April 29, 2016).

91 Hay P, Chinn D, Forbes D, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of eating disorders. *Aust N Z J Psychiatry* 2014; **48:** 977–1008.

92 Ljotsson B, Lundin C, Mitsell K, Carlbring P, Ramklint M, Ghaderi A. Remote treatment of bulimia nervosa and binge eating disorder: a randomized trial of Internet-assisted cognitive behavioural therapy. *Behav Res Ther* 2007; **45:** 649–61.

93 Enebrink P, Högström J, Forster M, Ghaderi A. Internet-based parent management training: a randomized controlled study. *Behav Res Ther* 2012; **50:** 240–49.

94 Andersson G, Cuijpers P, Carlbring P, Riper H, Hedman E. Guided internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. *World Psychiatry* 2014; **13:** 288–95.

95 Eaton J, McCay L, Semrau M, et al. Scale up of services for mental health in low-income and middle-income countries. *Lancet* 2011; **378:** 1592–603.

96 Nickerson A, Bryant RA, Silove D, Steel Z. A critical review of psychological treatments of posttraumatic stress disorder in refugees. *Clin Psychol Rev* 2011; **31:** 399–417.

97 Singhal A, Rogers EM. Entertainment-education: a communication strategy for social change. Mahwah, NJ: Erlbaum, 1999.

98 Knapp M, McDaid D, Parsonage M. Mental health promotion and mental illness prevention: the economic case. London: Department of Health, 2011.

99 Ori R, Amos T, Bergman H, Soares-Weiser K, Ipser JC, Stein DJ. Augmentation of cognitive and behavioural therapies (CBT) with d-cycloserine for anxiety and related disorders. *Cochrane Database Syst Rev* 2015; **10:** CD007803.

100 Otto MW, Bruce SE, Deckersbach T. Benzodiazepine use, cognitive impairment, and cognitive-behavioral therapy for anxiety disorders: issues in the treatment of a patient in need. *J Clin Psychiatry* 2005; **66** (suppl 2)**:** 34–38.

101 Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, Reynolds CF 3rd. Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. *World Psychiatry* 2014; **13:** 56–67.

102 Cuijpers P, van Straten A, Warmerdam L, Andersson G. Psychotherapy versus the combination of psychotherapy and pharmacotherapy in the treatment of depression: a meta-analysis. *Depress Anxiety* 2009; **26:** 279–88.

103 Hollon SD, Jarrett RB, Nierenberg AA, Thase ME, Trivedi M, Rush AJ. Psychotherapy and medication in the treatment of adult and geriatric depression: which monotherapy or combined treatment? *J Clin Psychiatry* 2005; **66:** 455–68.

104 Barlow DH, Gorman JM, Shear MK, Woods SW. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. *JAMA* 2000; **283:** 2529–36.

105 Merlo E, Milton AL, Goozée ZY, Theobald DE, Everitt BJ. Reconsolidation and extinction are dissociable and mutually exclusive processes: behavioral and molecular evidence. *J Neurosci* 2014; **34:** 2422–31.

106 Guhn A, Dresler T, Andreatta M, et al. Medial prefrontal cortex stimulation modulates the processing of conditioned fear. *Front Behav Neurosci* 2014; **8:** 44.

107 Kennedy SH, Konarski JZ, Segal ZV, et al. Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. *Am J Psychiatry* 2007; **164:** 778–88.

108 Harmer CJ, Duman RS, Cowen PJ. How do antidepressants work? New perspective for refining future treatment approaches. *Lancet Psychiatry* 2017; **4:** 409–18.

109 Beck AT, Rush AJ, Shaw BF, Emery G. Cognitive therapy of depression. New York, NY: Guildford, 1979.

110 Disner SG, Beevers CG, Haigh EA, Beck AT. Neural mechanisms of the cognitive model of depression. *Nat Rev Neurosci* 2011; **12:** 467–77.

111 Shiroma PR, Thuras P, Johns B, Lim KO. Emotion recognition processing as early predictor of response to 8-week citalopram treatment in late-life depression. *Int J Geriatr Psychiatry* 2014; **29:** 1132–39.

112 Moss A, Freeman TP. Mind the gap: bringing together psychopharmacology and cognitive behavioural therapy. The British Psychological Society, 2015. https://thepsychologist.bps.org.uk/mind-gap-bringing-together-psychopharmacology-and-cognitive-behavioural-therapy (accessed Oct 5, 2017).

113 Bouton ME. Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. *Biol Psychiatry* 2002; **52:** 976–86.

114 Murphy SE, Downham C, Cowen PJ, Harmer CJ. Direct effects of diazepam on emotional processing in healthy volunteers. *Psychopharmacology (Berl)* 2008; **199:** 503–13.

115 Reinecke A, Waldenmaier L, Cooper MJ, Harmer CJ. Changes in automatic threat processing precede and predict clinical changes with exposure-based cognitive-behavior therapy for panic disorder. *Biol Psychiatry* 2013; **73:** 1064–70.

116 Clarke PJ, Browning M, Hammond G, Notebaert L, MacLeod C. The causal role of the dorsolateral prefrontal cortex in the modification of attentional bias: evidence from transcranial direct current stimulation. *Biol Psychiatry* 2014; **76:** 946–52.

117 Browning M, Grol M, Ly V, Goodwin GM, Holmes EA, Harmer CJ. Using an experimental medicine model to explore combination effects of pharmacological and cognitive interventions for depression and anxiety. *Neuropsychopharmacology* 2011; **36:** 2689–97.

118 Başoğlu M, Marks IM, Kiliç C, Brewin CR, Swinson RP. Alprazolam and exposure for panic disorder with agoraphobia. Attribution of improvement to medication predicts subsequent relapse. *Br J Psychiatry* 1994; **164:** 652–59.

119 Cuijpers P, Beekman ATF, Reynolds CF 3rd. Preventing depression: a global priority. *JAMA* 2012; **307:** 1033–34.

120 Campion J, Bhui K, Bhugra D, European Psychiatric Association. European Psychiatric Association (EPA) guidance on prevention of mental disorders. *Eur Psychiatry* 2012; **27:** 68–80.

121 Heckman JJ. Skill formation and the economics of investing in disadvantaged children. *Science* 2006; **312:** 1900–02.

122 Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. *Arch Gen Psychiatry* 2003; **60:** 709–17.

123 National Research Council (US) and Institute of Medicine (US) Committee on the Prevention of Mental Disorders and Substance Abuse Among Children, Youth, and Young Adults: Research Advances and Promising Interventions. Preventing mental, emotional, and behavioural disorders among young people: progress and possibilities. Washington, DC: National Academies Press; 2009.

124 Olds DL, Holmberg JR, Donelan-McCall N, Luckey DW, Knudtson MD, Robinson J. Effects of home visits by paraprofessionals and by nurses on children: follow-up of a randomized trial at ages 6 and 9 years. *JAMA Pediatr* 2014; **168:** 114–21.

125 Rapee RM. The preventative effects of a brief, early intervention for preschool-aged children at risk for internalising: follow-up into middle adolescence. *J Child Psychol Psychiatry* 2013; **54:** 780–88.

126 Stein A, Ramchandani P, Murray L. Impact of parental psychiatric disorder and physical illness. In: Rutter M, Bishop DVM, Pine DS, et al, eds. Rutter's child and adolescent psychiatry, 5th edn. Holboken, NJ: Blackwell Publishers, 2009: 407–20.

127 Carter JC, Stewart DA, Dunn VJ, Fairburn CG. Primary prevention of eating disorders: might it do more harm than good? *Int J Eat Disord* 1997; **22:** 167–72.

128 Fonagy P. Psychotherapy research: do we know what works for whom? *Br J Psychiatry* 2010; **197:** 83–85.

129 Zhou X, Hetrick SE, Cuijpers P, et al. Comparative efficacy and acceptability of psychotherapies for depression in children and adolescents: a systematic review and network meta-analysis. *World Psychiatry* 2015; **14:** 207–22.

130 Robling M, Bekkers MJ, Bell K, et al. Effectiveness of a nurse-led intensive home-visitation programme for first-time teenage mothers (Building Blocks): a pragmatic randomised controlled trial. *Lancet* 2016; **387:** 146–55.

131 Ewing DL, Dash S, Thompson EJ, et al. No significant evidence of cognitive biases for emotional stimuli in children at-risk of developing anxiety disorders. *J Abnorm Child Psychol* 2016; **44:** 1243–52.

132 Verhage ML, Schuengel C, Madigan S, et al. Narrowing the transmission gap: a synthesis of three decades of research on intergenerational transmission of attachment. *Psychol Bull* 2016; **142:** 337–66.

133 Merry SN, Stasiak K, Shepherd M, Frampton C, Fleming T, Lucassen MF. The effectiveness of SPARX, a computerised self help intervention for adolescents seeking help for depression: randomised controlled non-inferiority trial. *BMJ* 2012; **344:** e2598.

134 Araya R, Fritsch R, Spears M, et al. School intervention to improve mental health of students in Santiago, Chile: a randomized clinical trial. *JAMA Pediatr* 2013; **167:** 1004–10.

135 Juffer F, Bakermans-Kranenburg MJ, van IJzendoorn MH. Promoting positive parenting: an attachment-based intervention. New York, NY: Taylor & Francis Group, 2008.

136 Scott S, Briskman J, O'Connor TG. Early prevention of antisocial personality: long-term follow-up of two randomized controlled trials comparing indicated and selective approaches. *Am J Psychiatry* 2014; **171:** 649–57.

137 Dretzke J, Frew E, Davenport C, et al. The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children. *Health Technol Assess* 2005; **9:** 1–233.

138 Cuijpers P, van Straten A, Smit F, Mihalopoulos C, Beekman A. Preventing the onset of depressive disorders: a meta-analytic review of psychological interventions. *Am J Psychiatry* 2008; **165:** 1272–80.

139 van Zoonen K, Buntrock C, Ebert DD, et al. Preventing the onset of major depressive disorder: a meta-analytic review of psychological interventions. *Int J Epidemiol* 2014; **43:** 318–29.

140 van der Gaag M, Smit F, Bechdolf A, et al. Preventing a first episode of psychosis: meta-analysis of randomized controlled prevention trials of 12 month and longer-term follow-ups. *Schizophr Res* 2013; **149:** 56–62.

141 McGorry PD, Yung AR, Phillips LJ, et al. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Arch Gen Psychiatry* 2002; **59:** 921–28.

142 De Silva MJ, Ryan G. Global mental health in 2015: 95% implementation. *Lancet Psychiatry* 2016; **3:** 15–17.

143 Andersson G, Cuijpers P. Internet-based and other computerized psychological treatments for adult depression: a meta-analysis. *Cogn Behav Ther* 2009; **38:** 196–205.

144 Richards D, Richardson T. Computer-based psychological treatments for depression: a systematic review and meta-analysis. *Clin Psychol Rev* 2012; **32:** 329–42.

145 Andrews G, Cuijpers P, Craske MG, McEvoy P, Titov N. Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis. *PLoS One* 2010; **5:** e13196.

146 Cheng SK, Dizon J. Computerised cognitive behavioural therapy for insomnia: a systematic review and meta-analysis. *Psychother Psychosom* 2012; **81:** 206–16.

147 Beintner I, Jacobi C, Schmidt UH. Participation and outcome in manualized self-help for bulimia nervosa and binge eating disorder—a systematic review and metaregression analysis. *Clin Psychol Rev* 2014; **34:** 158–76.

148 Riper H, Blankers M, Hadiwijaya H, et al. Effectiveness of guided and unguided low-intensity internet interventions for adult alcohol misuse: a meta-analysis. *PLoS One* 2014; **9:** e99912.

149 Andersson G, Cuijpers P. Pros and cons of online cognitive-behavioural therapy. *Br J Psychiatry* 2008; **193:** 270–71.

150 van Ballegooijen W, Cuijpers P, van Straten A, et al. Adherence to Internet-based and face-to-face cognitive behavioural therapy for depression: a meta-analysis. *PLoS One* 2014; **9:** e100674.

151 Sucala M, Schnur JB, Constantino MJ, Miller SJ, Brackman EH, Montgomery GH. The therapeutic relationship in e-therapy for mental health: a systematic review. *J Med Internet Res* 2012; **14:** e110.

152 Wenze SJ, Miller IW. Use of ecological momentary assessment in mood disorders research. *Clin Psychol Rev* 2010; **30:** 794–804.

153 Smits N, Zitman FG, Cuijpers P, den Hollander-Gijsman ME, Carlier IV. A proof of principle for using adaptive testing in routine outcome monitoring: the efficiency of the mood and anxiety symptoms questionnaire—anhedonic depression CAT. *BMC Med Res Methodol* 2012; **12:** 4.

154 Powers MB, Emmelkamp PMG. Virtual reality exposure therapy for anxiety disorders: a meta-analysis. *J Anxiety Disord* 2008; **22:** 561–69.

155 Turner WA, Casey LM. Outcomes associated with virtual reality in psychological interventions: where are we now? *Clin Psychol Rev* 2014; **34:** 634–44.

156 Mohr DC, Vella L, Hart S, Heckman T, Simon G. The effect of telephone-administered psychotherapy on symptoms of depression and attrition: a meta-analysis. *Clin Psychol (New York)* 2008; **15:** 243–53.

157 Anthes E. Mental health: there's an app for that. *Nature* 2016; **532:** 20–23.

158 Donker T, Petrie K, Proudfoot J, Clarke J, Birch MR, Christensen H. Smartphones for smarter delivery of mental health programs: a systematic review. *J Med Internet Res* 2013; **15:** e247.

159 Espie CA, Kyle SD, Williams C, et al. A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. *Sleep* 2012; **35:** 769–81.

160 Bucci S, Barrowclough C, Ainsworth J, et al. Using mobile technology to deliver a cognitive behaviour therapy-informed intervention in early psychosis (Actissist): study protocol for a randomised controlled trial. *Trials* 2015; **16:** 404.

161 Mohr DC, Schueller SM, Riley WT, et al. Trials of intervention principles: evaluation methods for evolving behavioral intervention technologies. *J Med Internet Res* 2015; **17:** e166.

162 Therapist-free therapy. *The Economist* 2011; **398:** 82–83.

163 Christensen H, Cuijpers P, Reynolds CF 3rd. Changing the direction of suicide prevention research: a necessity for true population impact. *JAMA Psychiatry* 2016; **73:** 435–36.

164 National Institute for Heath and Care Excellence. Psychosis and schizophrenia in children and young people: recognition and management. National Institute for Heath and Care Excellence, 2013. https://www.nice.org.uk/guidance/cg155 (accessed Oct 5, 2017).

165 Bradley HA, Rucklidge JJ, Mulder RT. A systematic review of trial registration and selective outcome reporting in psychotherapy randomized controlled trials. *Acta Psychiatr Scand* 2017; **135:** 65–77.

166 Arnberg FK, Alaie I, Parling T, Jonsson U. Recent randomized controlled trials of psychological interventions in healthcare: a review of their quantity, scope, and characteristics. *J Psychosom Res* 2013; **75:** 401–08.

167 Dunn G, Emsley R, Liu H, et al. Evaluation and validation of social and psychological markers in randomised trials of complex interventions in mental health: a methodological research programme. *Health Technol Assess* 2015; **19:** 1–115.

168 Longden E, Read J. Assessing and reporting the adverse effects of antipsychotic medication: a systematic review of clinical studies, and prospective, retrospective, and cross-sectional research. *Clin Neuropharmacol* 2016; **39:** 29–39.

169 Jonsson U, Alaie I, Parling T, Arnberg FK. Reporting of harms in randomized controlled trials of psychological interventions for mental and behavioral disorders: a review of current practice. *Contemp Clin Trials* 2014; **38:** 1–8.

170 Rozental A, Kottorp A, Boettcher J, Andersson G, Carlbring P. Negative effects of psychological treatments: An exploratory factor analysis of the negative effects questionnaire for monitoring and reporting adverse and unwanted events. *PLoS One* 2016; **11:** e0157503.

171 Boettcher J, Rozental A, Andersson G, Carlbring P. Side effects in internet-based interventions for social anxiety disorder. *Internet Interv* 2014; **1:** 3–11.

172 Linden M. How to define, find and classify side effects in psychotherapy: from unwanted events to adverse treatment reactions. *Clin Psychol Psychother* 2013; **20:** 286–96.

173 Mayo-Wilson E, Montgomery P, Hopewell S, Macdonald G, Moher D, Grant S. Developing a reporting guideline for social and psychological intervention trials. *Br J Psychiatry* 2013; **203:** 250–54.

174 Munder T, Brütsch O, Leonhart R, Gerger H, Barth J. Researcher allegiance in psychotherapy outcome research: an overview of reviews. *Clin Psychol Rev* 2013; **33:** 501–11.

175 Lieb K, von der Osten-Sacken J, Stoffers-Winterling J, Reiss N, Barth J. Conflicts of interest and spin in reviews of psychological therapies: a systematic review. *BMJ Open* 2016; **6:** e010606.

176 van der Lem R, de Wever WW, van der Wee NJ, van Veen T, Cuijpers P, Zitman FG. The generalizability of psychotherapy efficacy trials in major depressive disorder: an analysis of the influence of patient selection in efficacy trials on symptom outcome in daily practice. *BMC Psychiatry* 2012; **12:** 192.

177 Freeman D, Dunn G, Startup H, et al. Effects of cognitive behaviour therapy for worry on persecutory delusions in patients with psychosis (WIT): a parallel, single-blind, randomised controlled trial with a mediation analysis. *Lancet Psychiatry* 2015; **2:** 305–13.

178 Sensky T, Turkington D, Kingdon D, et al. A randomized controlled trial of cognitive-behavioral therapy for persistent symptoms in schizophrenia resistant to medication. *Arch Gen Psychiatry* 2000; **57:** 165–72.

179 Cuijpers P, Driessen E, Hollon SD, van Oppen P, Barth J, Andersson G. The efficacy of non-directive supportive therapy for adult depression: a meta-analysis. *Clin Psychol Rev* 2012; **32:** 280–91.

180 Turner DT, van der Gaag M, Karyotaki E, Cuijpers P. Psychological interventions for psychosis: a meta-analysis of comparative outcome studies. *Am J Psychiatry* 2014; **171:** 523–38.

181 Morrison AP, French P, Stewart S, et al. Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial. *BMJ* 2012; **344:** e2233.

182 Morrison AP, Shryane N, Beck R, et al. Psychosocial and neuropsychiatric predictors of subjective recovery from psychosis. *Psychiatry Res* 2013; **208:** 203–09.

183 Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010; **340:** c221.

184 Vittengl JR, Jarrett RB, Weitz E, et al. Divergent outcomes in cognitive-behavioral therapy and pharmacotherapy for adult depression. *Am J Psychiatry* 2016; **173:** 481–90.

185 Weitz ES, Hollon SD, Twisk J, et al. Baseline depression severity as moderator of depression outcomes between cognitive behavioral therapy vs pharmacotherapy: an individual patient data meta-analysis. *JAMA Psychiatry* 2015; **72:** 1102–09.

186 Keeley T, Khan H, Pinfold V, et al. Core outcome sets for use in effectiveness trials involving people with bipolar and schizophrenia in a community-based setting (PARTNERS2): study protocol for the development of two core outcome sets. *Trials* 2015; **16:** 47.

187 Morrison AP, Turkington D, Pyle M, et al. Cognitive therapy for people with schizophrenia spectrum disorders not taking antipsychotic drugs: a single-blind randomised controlled trial. *Lancet* 2014; **383:** 1395–403.

188 Ennis L, Wykes T. Impact of patient involvement in mental health research: longitudinal study. *Br J Psychiatry* 2013; **203:** 381–86.

189 Brett J, Staniszewska S, Mockford C, et al. A systematic review of the impact of patient and public involvement on service users, researchers and communities. *Patient* 2014; **7:** 387–95.

190 Lloyd K, Rose D, Fenton M. Identifying uncertainties about the effects of treatments for schizophrenia. *J Ment Health* 2006; **15:** 263–68.

191 Law H, Morrison AP. Recovery in psychosis: a Delphi study with experts by experience. *Schizophr Bull* 2014; **40:** 1347–55.

192 Byrne R, Morrison AP. Service users' priorities and preferences for treatment of psychosis: a user-led Delphi study. *Psychiatr Serv* 2014; **65:** 1167–69.

193 Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986; **51:** 1173–82.

194 VanderWeele TJ. Marginal structural models for the estimation of direct and indirect effects. *Epidemiology* 2009; **20:** 18–26.

195 Emsley R, Dunn G, White IR. Mediation and moderation of treatment effects in randomised controlled trials of complex interventions. *Stat Methods Med Res* 2010; **19:** 237–70.

196 Freeman D, Dunn G, Garety P, et al. Patients' beliefs about the causes, persistence and control of psychotic experiences predict take-up of effective cognitive behaviour therapy for psychosis. *Psychol Med* 2013; **43:** 269–77.

197 Goldsmith LP, Lewis SW, Dunn G, Bentall RP. Psychological treatments for early psychosis can be beneficial or harmful, depending on the therapeutic alliance: an instrumental variable analysis. *Psychol Med* 2015; **45:** 2365–73.

198 Parmar MKB, Carpenter J, Sydes MR. More multiarm randomised trials of superiority are needed. *Lancet* 2014; **384:** 283–84.

199 Relton C, Torgerson D, O'Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. *BMJ* 2010; **340:** c1066.

200 Frank G. The Boulder Model: history, rationale, and critique. *Prof Psychol Res Pr* 1984; **15:** 417–35.

201 Abramowitz JS, Deacon BJ, Whiteside SPH. Exposure therapy for anxiety: principles and practice. New York, NY: Guilford Press, 2012.

202 Mowrer OH. Two-factor learning theory: versions one and two. Learning theory and behavior. Hoboken, NJ: John Wiley & Sons, 1960.

203 Foa EB. Cognitive behavioral therapy of obsessive-compulsive disorder. *Dialogues Clin Neurosci* 2010; **12:** 199–207.

204 Abramson LY, Seligman ME, Teasdale JD. Learned helplessness in humans: critique and reformulation. *J Abnorm Psychol* 1978; **87:** 49–74.

205 Abramson LY, Alloy LB, Metalsky GI. Hopelessness depression—a theory-based subtype of depression. *Psychol Rev* 1989; **96:** 358–72.

206 Seligman ME, Maier SF, Geer JH. Alleviation of learned helplessness in the dog. *J Abnorm Psychol* 1968; **73:** 256–62.

207 Liu RT, Kleiman EM, Nestor BA, Cheek SM. The hopelessness theory of depression: a quarter century in review. *Clin Psychol (New York)* 2015; **22:** 345–65.

208 Pryce CR, Azzinnari D, Spinelli S, Seifritz E, Tegethoff M, Meinlschmidt G. Helplessness: a systematic translational review of theory and evidence for its relevance to understanding and treating depression. *Pharmacol Ther* 2011; **132:** 242–67.

209 Roffman JL, Simon AB, Prasad KM, Truman CJ, Morrison J, Ernst CL. Neuroscience in psychiatry training: how much do residents need to know? *Am J Psychiatry* 2006; **163:** 919–26.

210 Fung LK, Akil M, Widge A, Roberts LW, Etkin A. Attitudes toward neuroscience education in psychiatry: a national multi-stakeholder survey. *Acad Psychiatry* 2015; **39:** 139–46.

211 The Academy of Medical Sciences. Strengthening academic psychiatry in the UK. London; The Academy of Medical Science, 2013.

212 Goodwin GM, Holmes EA, Andersson E, et al. From neuroscience to evidence based psychological treatments—the promise and the challenge, ECNP March 2016, Nice, France. *Eur Neuropsychopharmacol* 2018; **28:** 321–37.

213 Schwabe L, Nader K, Pruessner JC. Reconsolidation of human memory: brain mechanisms and clinical relevance. *Biol Psychiatry* 2014; **76:** 274–80.

214 Brunet A, Orr SP, Tremblay J, Robertson K, Nader K, Pitman RK. Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. *J Psychiatr Res* 2008; **42:** 503–06.

215 Brunet A, Poundja J, Tremblay J, et al. Trauma reactivation under the influence of propranolol decreases posttraumatic stress symptoms and disorder: 3 open-label trials. *J Clin Psychopharmacol* 2011; **31:** 547–50.

216 Iyadurai L, Blackwell SE, Meiser-Stedman R, et al. Preventing intrusive memories after trauma via a brief intervention involving Tetris computer game play in the emergency department: a proof-of-concept randomized controlled trial. *Mol Psychiatry* 2017; published online March 28. DOI:10.1038/mp.2017.23.

217 Horsch A, Vial Y, Favrod C, et al. Reducing intrusive traumatic memories after emergency caesarean section: a proof-of-principle randomized controlled study. *Behav Res Ther* 2017; **94:** 36–47.

218 Uher R, Perlis RH, Henigsberg N, et al. Depression symptom dimensions as predictors of antidepressant treatment outcome: replicable evidence for interest-activity symptoms. *Psychol Med* 2012; **42:** 967–80.

219 Eshel N, Roiser JP. Reward and punishment processing in depression. *Biol Psychiatry* 2010; **68:** 118–24.

220 Gray JA. The psychophysiological basis of introversion-extraversion. *Behav Res Ther* 1970; **8:** 249–66.

221 Craske MG, Meuret AE, Ritz T, Treanor M, Dour HJ. Treatment for anhedonia: a neuroscience driven approach. *Depress Anxiety* 2016; **33:** 927–38.

222 Dimidjian S, Barrera M Jr, Martell C, Muñoz RF, Lewinsohn PM. The origins and current status of behavioral activation treatments for depression. *Annu Rev Clin Psychol* 2011; **7:** 1–38.

223 Dichter GS, Felder JN, Petty C, Bizzell J, Ernst M, Smoski MJ. The effects of psychotherapy on neural responses to rewards in major depression. *Biol Psychiatry* 2009; **66:** 886–97.

224 Blackwell SE, Browning M, Mathews A, et al. Positive imagery-based cognitive bias modification as a web-based treatment tool for depressed adults: a randomized controlled trial. *Clin Psychol Sci* 2015; **3:** 91–111.

225 Williams AD, O'Moore K, Blackwell SE, Smith J, Holmes EA, Andrews G. Positive imagery cognitive bias modification (CBM) and internet-based cognitive behavioral therapy (iCBT): a randomized controlled trial. *J Affect Disord* 2015; **178:** 131–41.

226 National Collaborating Centre for Mental Health. Depression: the NICE guideline on the treatment and management of depression in adults, updated edition. Great Britain: The British Psychological Society and The Royal College of Psychiatrists, 2010.

227 American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder, 3rd edn. Washington, DC: American Psychiatric Association, 2010.

228 Cramer AO, Waldorp LJ, van der Maas HL, Borsboom D. Comorbidity: a network perspective. *Behav Brain Sci* 2010; **33:** 137–50.

229 Lewinsohn PM, Zinbarg R, Seeley JR, Lewinsohn M, Sack WH. Lifetime comorbidity among anxiety disorders and between anxiety disorders and other mental disorders in adolescents. *J Anxiety Disord* 1997; **11:** 377–94.

230 Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62:** 617–27.

231 Borsboom D, Cramer AO. Network analysis: an integrative approach to the structure of psychopathology. *Annu Rev Clin Psychol* 2013; **9:** 91–121.

232 van der Maas HL, Molenaar PC. Stagewise cognitive development: an application of catastrophe theory. *Psychol Rev* 1992; **99:** 395–417.

233 Borsboom D, Rhemtulla M, Cramer AO, van der Maas HL, Scheffer M, Dolan CV. Kinds versus continua: a review of psychometric approaches to uncover the structure of psychiatric constructs. *Psychol Med* 2016; **46:** 1567–79.

234 Bockting CLH. My optimism wears heavy boots: towards empirically driven tailored interventions, illustrated by depression research. Utrecht; Communicatie Service Centrum, Universiteit Utrecht, 2015 (in Dutch).

235 Kuppens P, Oravecz Z, Tuerlinckx F. Feelings change: accounting for individual differences in the temporal dynamics of affect. *J Pers Soc Psychol* 2010; **99:** 1042–60.

236 GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; **390:** 1211–59.

237 Merikangas KR, He JP, Burstein M, et al. Service utilization for lifetime mental disorders in U.S. adolescents: results of the National Comorbidity Survey-Adolescent Supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry* 2011; **50:** 32–45.

238 Nock MK, Hwang I, Sampson NA, Kessler RC. Mental disorders, comorbidity and suicidal behavior: results from the National Comorbidity Survey Replication. *Mol Psychiatry* 2010; **15:** 868–76.

239 Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62:** 593–602.

240 Moffitt TE, Harrington H, Caspi A, et al. Depression and generalized anxiety disorder: cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. *Arch Gen Psychiatry* 2007; **64:** 651–60.

241 Zinbarg RE, Mineka S, Craske MG, et al. The Northwestern-UCLA youth emotion project: associations of cognitive vulnerabilities, neuroticism and gender with past diagnoses of emotional disorders in adolescents. *Behav Res Ther* 2010; **48:** 347–58.

242 Caspi A, Houts RM, Belsky DW, et al. The p factor: one general psychopathology factor in the structure of psychiatric disorders? *Clin Psychol Sci* 2014; **2:** 119–37.

243 Prenoveau JM, Zinbarg RE, Craske MG, Mineka S, Griffith JW, Epstein AM. Testing a hierarchical model of anxiety and depression in adolescents: a tri-level model. *J Anxiety Disord* 2010; **24:** 334–44.

244 Borsboom D, Cramer AO, Schmittmann VD, Epskamp S, Waldorp LJ. The small world of psychopathology. *PLoS One* 2011; **6:** e27407.

245 Stewart RE, Chambless DL. Cognitive-behavioral therapy for adult anxiety disorders in clinical practice: a meta-analysis of effectiveness studies. *J Consult Clin Psychol* 2009; **77:** 595–606.

246 Wichers M. The dynamic nature of depression: a new micro-level perspective of mental disorder that meets current challenges. *Psychol Med* 2014; **44:** 1349–60.

247 Walz LC, Nauta MH, aan het Rot M. Experience sampling and ecological momentary assessment for studying the daily lives of patients with anxiety disorders: a systematic review. *J Anxiety Disord* 2014; **28:** 925–37.

248 aan het Rot M, Hogenelst K, Schoevers RA. Mood disorders in everyday life: a systematic review of experience sampling and ecological momentary assessment studies. *Clin Psychol Rev* 2012; **32:** 510–23.

249 Serre F, Fatseas M, Swendsen J, Auriacombe M. Ecological momentary assessment in the investigation of craving and substance use in daily life: a systematic review. *Drug Alcohol Depend* 2015; **148:** 1–20.

250 Bockting CL, Elgersma HJ, van Rijsbergen GD, et al. Disrupting the rhythm of depression: design and protocol of a randomized controlled trial on preventing relapse using brief cognitive therapy with or without antidepressants. *BMC Psychiatry* 2011; **11:** 8.

251 van Os J, Lataster T, Delespaul P, Wichers M, Myin-Germeys I. Evidence that a psychopathology interactome has diagnostic value, predicting clinical needs: an experience sampling study. *PLoS One* 2014; **9:** e86652.

252 Wigman JT, van Os J, Borsboom D, et al. Exploring the underlying structure of mental disorders: cross-diagnostic differences and similarities from a network perspective using both a top-down and a bottom-up approach. *Psychol Med* 2015; **45:** 2375–87.

253 Wichers M, Lothmann C, Simons CJP, Nicolson NA, Peeters F. The dynamic interplay between negative and positive emotions in daily life predicts response to treatment in depression: a momentary assessment study. *Br J Clin Psychol* 2012; **51:** 206–22.

254 DeRubeis RJ, Cohen ZD, Forand NR, Fournier JC, Gelfand LA, Lorenzo-Luaces L. The Personalized Advantage Index: translating research on prediction into individualized treatment recommendations. A demonstration. *PLoS One* 2014; **9:** e83875.

255 Barnett S, Moonesinghe SR. Clinical risk scores to guide perioperative management. *Postgrad Med J* 2011; **87:** 535–41.

256 Politi K, Herbst RS. Lung cancer in the era of precision medicine. *Clin Cancer Res* 2015; **21:** 2213–20.

257 Kramer I, Simons CJ, Hartmann JA, et al. A therapeutic application of the experience sampling method in the treatment of depression: a randomized controlled trial. *World Psychiatry* 2014; **13:** 68–77.

258 Holmes EA, Bonsall MB, Hales SA, et al. Applications of time-series analysis to mood fluctuations in bipolar disorder to promote treatment innovation: a case series. *Transl Psychiatry* 2016; **6:** e720.

259 Keller MC, Neale MC, Kendler KS. Association of different adverse life events with distinct patterns of depressive symptoms. *Am J Psychiatry* 2007; **164:** 1521–29.

260 Costantini G, Epskamp S, Borsboom D, et al. State of the aRt personality research: a tutorial on network analysis of personality data in R. *J Res Pers* 2015; **54:** 13–29.

261 Dalle Grave R, Calugi S, Sartirana M, Fairburn CG. Transdiagnostic cognitive behaviour therapy for adolescents with an eating disorder who are not underweight. *Behav Res Ther* 2015; **73:** 79–82.

262 Fairburn CG, Cooper Z, Doll HA, et al. Transdiagnostic cognitive-behavioral therapy for patients with eating disorders: a two-site trial with 60-week follow-up. *Am J Psychiatry* 2009; **166:** 311–19.

263 Farchione TJ, Fairholme CP, Ellard KK, et al. Unified protocol for transdiagnostic treatment of emotional disorders: a randomized controlled trial. *Behav Ther* 2012; **43:** 666–78.

264 Thompson-Hollands J, Sauer-Zavala S, Barlow DH. CBT and the future of personalized treatment: a proposal. *Depress Anxiety* 2014; **31:** 909–11.

265 WHO. Preventing suicide: a global imperative. Geneva: World Health Organization, 2014.

266 McDaid D, Bonin E, Park A, et al. Making the case for investing in suicide prevention interventions: estimating the economic impact of suicide and non-fatal self harm events. *Inj Prev* 2010; **16** (suppl 1)**:** A257–58.

267 O'Connor RC, Platt S, Gordon J. Achievements and challenges in suicidology: conclusions and future directions. In: O'Connor R, Platt S, Gordon J, eds. International handbook of suicide prevention: research, policy and practice. Chichester: Wiley Blackwell, 2011: 625–42.

268 Hawton K, van Heeringen K. Suicide. *Lancet* 2009; **373:** 1372–81.

269 Hawton K, Saunders KE, O'Connor RC. Self-harm and suicide in adolescents. *Lancet* 2012; **379:** 2373–82.

270 Turecki G, Brent DA. Suicide and suicidal behaviour. *Lancet* 2016; **387:** 1227–39.

271 O'Connor RC, Nock MK. The psychology of suicidal behaviour. *Lancet Psychiatry* 2014; **1:** 73–85.

272 Brown GK, Jager-Hyman S. Evidence-based psychotherapies for suicide prevention: future directions. *Am J Prev Med* 2014; **47** (suppl 2)**:** S186–94.

273 Inagaki M, Kawashima Y, Kawanishi C, et al. Interventions to prevent repeat suicidal behavior in patients admitted to an emergency department for a suicide attempt: a meta-analysis. *J Affect Disord* 2015; **175:** 66–78.

274 O'Connor E, Gaynes BN, Burda BU, Soh C, Whitlock EP. Screening for and treatment of suicide risk relevant to primary care: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2013; **158:** 741–54.

275 Tarrier N, Taylor K, Gooding P. Cognitive-behavioral interventions to reduce suicide behavior: a systematic review and meta-analysis. *Behav Modif* 2008; **32:** 77–108.

276 Hawton K, Witt KG, Taylor Salisbury TL, et al. Psychosocial interventions for self-harm in adults. *Cochrane Database Syst Rev* 2016; **5:** CD012189.

277 Hawton K, Witt KG, Taylor Salisbury TL, et al. Interventions for self-harm in children and adolescents. *Cochrane Database Syst Rev* 2015; **12:** CD012013.

278 Zalsman G, Hawton K, Wasserman D, et al. Suicide prevention strategies revisited: 10-year systematic review. *Lancet Psychiatry* 2016; **3:** 646–59.

279 van der Feltz-Cornelis CM, Sarchiapone M, Postuvan V, et al. Best practice elements of multilevel suicide prevention strategies: a review of systematic reviews. *Crisis* 2011; **32:** 319–33.

280 Cavanagh JT, Carson AJ, Sharpe M, Lawrie SM. Psychological autopsy studies of suicide: a systematic review. *Psychol Med* 2003; **33:** 395–405.

281 Hawton K, Saunders K, Topiwala A, Haw C. Psychiatric disorders in patients presenting to hospital following self-harm: a systematic review. *J Affect Disord* 2013; **151:** 821–30.

282 van Heeringen K. Towards a psychobiological model of the suicidal process. In: van Heeringen K, ed. Understanding suicidal behaviour: the suicidal process approach to research, treatment and prevention. Chichester: John Wiley & Sons, 2001: 136–59.

283 Bostwick JM, Pankratz VS. Affective disorders and suicide risk: a reexamination. *Am J Psychiatry* 2000; **157:** 1925–32.

284 O'Connor RC. Towards an integrated motivational–volitional model of suicidal behaviour. In: O'Connor RC, Platt S, Gordon J, eds. International handbook of suicide prevention: research, policy and practice. Chichester: Wiley Blackwell, 2011: 181–98.

285 Joiner TE. Why people die by suicide. Boston, MA: Harvard University Press, 2005.

286 Van Orden KA, Witte TK, Cukrowicz KC, Braithwaite SR, Selby EA, Joiner TE Jr. The interpersonal theory of suicide. *Psychol Rev* 2010; **117:** 575–600.

287 O'Connor RC, Smyth R, Ferguson E, Ryan C, Williams JMG. Psychological processes and repeat suicidal behavior: a four-year prospective study. *J Consult Clin Psychol* 2013; **81:** 1137–43.

288 O'Connor RC, Smyth R, Williams JMG. Intrapersonal positive future thinking predicts repeat suicide attempts in hospital-treated suicide attempters. *J Consult Clin Psychol* 2015; **83:** 169–76.

289 Klonsky ED, May AM. The Three-Step Theory (3ST): a new theory of suicide rooted in the "ideation-to-action" framework. *Int J Cogn Ther* 2015; **8:** 114–29.

290 Williams JMG. The cry of pain: understanding suicide and self-harm. London: Penguin, 2001.

291 Jobes DA. The Collaborative Assessment and Management of Suicidality (CAMS): an evolving evidence-based clinical approach to suicidal risk. *Suicide Life Threat Behav* 2012; **42:** 640–53.

292 O'Connor RC, O'Carroll RE, Ryan C, Smyth R. Self-regulation of unattainable goals in suicide attempters: a two year prospective study. *J Affect Disord* 2012; **142:** 248–55.

293 Blasco-Fontecilla H, Oquendo MA. Biomarkers of suicide: predicting the predictable? In: Courtet P (ed). Understanding suicide: from diagnosis to personalized treatment. Cham: Springer, 2016: 77–83.

294 O'Connor DB, Green JA, Ferguson E, O'Carroll RE, O'Connor RC. Cortisol reactivity and suicidal behavior: investigating the role of hypothalamic-pituitary-adrenal axis responses to stress in suicide attempters and ideators. *Psychoneuroendocrinology* 2017; **75:** 183–91.

295 Comtois KA, Linehan MM. Psychosocial treatments of suicidal behaviors: a practice-friendly review. *J Clin Psychol* 2006; **62:** 161–70.

296 Crawford MJ, Thomas O, Khan N, Kulinskaya E. Psychosocial interventions following self-harm: systematic review of their efficacy in preventing suicide. *Br J Psychiatry* 2007; **190:** 11–17.

297 Harris F, Maxwell M, O'Connor R, et al. Exploring synergistic interactions and catalysts in complex interventions: longitudinal, mixed methods case studies of an optimised multi-level suicide prevention intervention in four European countries (Ospi-Europe). *BMC Pub Health* 2016; **16:** 268.

298 Linehan MM, Comtois KA, Murray AM, et al. Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. *Arch Gen Psychiatry* 2006; **63:** 757–66.

299 Guthrie E, Kapur N, Mackway-Jones K, et al. Randomised controlled trial of brief psychological intervention after deliberate self poisoning. *BMJ* 2001; **323:** 135–38.

300 Rossouw TI, Fonagy P. Mentalization-based treatment for self-harm in adolescents: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry* 2012; **51:** 1304–13.

301 Ryberg W, Fosse R, Zahl PH, et al. Collaborative Assessment and Management of Suicidality (CAMS) compared to treatment as usual (TAU) for suicidal patients: study protocol for a randomized controlled trial. *Trials* 2016; **17:** 481.

302 Gysin-Maillart A, Schwab S, Soravia L, Megert M, Michel K. A novel brief therapy for patients who attempt suicide: a 24-months follow-up randomized controlled study of the attempted suicide short intervention program (ASSIP). *PLoS Med* 2016; **13:** e1001968.

303 Ougrin D, Tranah T, Stahl D, Moran P, Asarnow JR. Therapeutic interventions for suicide attempts and self-harm in adolescents: systematic review and meta-analysis. *J Am Acad Child Adolesc Psychiatry* 2015; **54:** 97–107.

304 Cuijpers P, de Beurs DP, van Spijker BA, Berking M, Andersson G, Kerkhof AJ. The effects of psychotherapy for adult depression on suicidality and hopelessness: a systematic review and meta-analysis. *J Affect Disord* 2013; **144:** 183–90.

305 Carter G, Page A, Large M, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guideline for the management of deliberate self-harm. *Aust N Z J Psychiatry* 2016; **50:** 939–1000.

306 Hawton K, Witt KG, Salisbury TLT, et al. Psychosocial interventions following self-harm in adults: a systematic review and meta-analysis. *Lancet Psychiatry* 2016; **3:** 740–50.

307 Platt S. Inequalities and suicidal behavior. In: O'Connor RC, Pirkis J, eds. International handbook of suicide prevention, 2nd edn. Chichester: Wiley Blackwell, 2016: 258–83.

308 Bruffaerts R, Demyttenaere K, Hwang I, et al. Treatment of suicidal people around the world. *Br J Psychiatry* 2011; **199:** 64–70.

309 Evans K, Tyrer P, Catalan J, et al. Manual-assisted cognitive-behaviour therapy (MACT): a randomized controlled trial of a brief intervention with bibliotherapy in the treatment of recurrent deliberate self-harm. *Psychol Med* 1999; **29:** 19–25.

310 Milner AJ, Carter G, Pirkis J, Robinson J, Spittal MJ. Letters, green cards, telephone calls and postcards: systematic and meta-analytic review of brief contact interventions for reducing self-harm, suicide attempts and suicide. *Br J Psychiatry* 2015; **206:** 184–90.

311 Armitage CJ, Rahim WA, Rowe R, O'Connor RC. An exploratory randomised trial of a simple, brief psychological intervention to reduce subsequent suicidal ideation and behaviour in patients admitted to hospital for self-harm. *Br J Psychiatry* 2016; **208:** 470–76.

312 O'Connor RC, Ferguson E, Scott F, et al. A brief psychological intervention to reduce repetition of self-harm in patients admitted to hospital following a suicide attempt: a randomised controlled trial. *Lancet Psychiatry* 2017; **4:** 451–60.

313 Hegerl U, Althaus D, Schmidtke A, Niklewski G. The alliance against depression: 2-year evaluation of a community-based intervention to reduce suicidality. *Psychol Med* 2006; **36:** 1225–33.

314 Chesin M, Stanley B. Risk assessment and psychosocial interventions for suicidal patients. *Bipolar Disord* 2013; **15:** 584–93.

315 de Beurs D, Kirtley O, Kerkhof A, Portzky G, O'Connor RC. The role of mobile phone technology in understanding and preventing suicidal behavior. *Crisis* 2015; **36:** 79–82.

316 Mishara B, Kerkhof A. Suicide prevention and new technologies. Evidence based practice. London: Palgrave Macmillan, 2013.

317 Cleary A. Suicidal action, emotional expression, and the performance of masculinities. *Soc Sci Med* 2012; **74:** 498–505.

318 Colucci E, Lester D, Hjelmeland H, Park BCB. Suicide and culture: understanding the context. Göttingen: Hogrefe Publishing, 2013.

319 Scourfield J. Suicidal masculinities. Sociological Research Online, 2005. http://www.socresonline.org.uk/10/2/scourfield.html (accessed Jan 17, 2018).

320 Lezine D. Lived experience and suicide prevention. In: O'Connor RC, Pirkis J, eds. International handbook of suicide prevention, 2nd edn. Chichester: Wiley, 2016: 681–95.

321 Becker CB, Zayfert C, Anderson E. A survey of psychologists' attitudes towards and utilization of exposure therapy for PTSD. *Behav Res Ther* 2004; **42:** 277–92.

322 Dijstelbloem H, Huisman F, Miedema F, Mijnhardt W. Why science does not work as it should and what to do about it., Science in Transition, 2013. http://www.scienceintransition.nl/wp-content/uploads/2013/10/Science-in-Transition-Position-Paper-final.pdf (accessed March 15, 2017).

323 Ioannidis JP. How to make more published research true. *PLoS Med* 2014; **11:** e1001747.

324 Johnsen TJ, Friborg O. The effects of cognitive behavioral therapy as an anti-depressive treatment is falling: a meta-analysis. *Psychol Bull* 2015; **141:** 747–68.

325 Bower P, Gilbody S. Stepped care in psychological therapies: access, effectiveness and efficiency. Narrative literature review. *Br J Psychiatry* 2005; **186:** 11–17.

326 Wang PS, Aguilar-Gaxiola S, Alonso J, et al. Use of mental health services for anxiety, mood, and substance disorders in 17 countries in the WHO world mental health surveys. *Lancet* 2007; **370:** 841–50.

327 Bockting CL, Hollon SD, Jarrett RB, Kuyken W, Dobson K. A lifetime approach to major depressive disorder: the contributions of psychological interventions in preventing relapse and recurrence. *Clin Psychol Rev* 2015; **41:** 16–26.

328 Loerinc AG, Meuret AE, Twohig MP, Rosenfield D, Bluett EJ, Craske MG. Response rates for CBT for anxiety disorders: need for standardized criteria. *Clin Psychol Rev* 2015; **42:** 72–82.

329 Rosen GM, Davison GC. Psychology should list empirically supported principles of change (ESPs) and not credential trademarked therapies or other treatment packages. *Behav Modif* 2003; **27:** 300–12.

330 Meade MS, Emch M. Medical geography, 3rd edn. New York, NY: The Guildford Press, 2012.

331 Naylor C, Parsonage M, McDaid D, Knapp M, Fossey M, Galea A. Long-term conditions and mental health. The cost of co-morbidities. London: The King's Fund and Centre for Mental Health, 2012.

332 Grant J, Cottrell R, Cluzeau F, Fawcett G. Evaluating "payback" on biomedical research from papers cited in clinical guidelines: applied bibliometric study. *BMJ* 2000; **320:** 1107–11.

333 Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry* 2010; **167:** 748–51.

334 Nature Editorials. Therapy deficit. *Nature* 2012; **489:** 473–74.

335 MQ Landscape Analysis. UK Mental Health Research Funding. Clerkenwell: MQ Transforming mental health, 2015.

336 Davidson L, O'Connell MJ, Tondora J, Lawless M, Evans AC. Recovery in serious mental illness: a new wine or just a new bottle? *Prof Psychol Res Pr* 2005; **36:** 480–87.

337 Rachman S. Betrayal: a psychological analysis. *Behav Res Ther* 2010; **48:** 304–11.

338 Wykes T, Haro JM, Belli SR, et al. Mental health research priorities for Europe. *Lancet Psychiatry* 2015; **2:** 1036–42.