Psychological Treatments Research in Tomorrow's Science: Seeing Further

Contents

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SUMMARY

Psychological treatments occupy an important place in evidence-based mental health treatments. It is an exciting time to fuel treatment research: there is a pressing demand for improvements poised alongside new opportunities afforded by closer links with sister scientific and clinical disciplines. The needs are great. Even our best treatments do not work for everyone, there are many mental health problems for which treatments have not been developed, and the implementation of treatments needs to address worldwide scalability. Meanwhile, psychological treatments are yet to benefit from numerous recent innovations in science, and arguably vice versa. We discuss opportunities for future research efforts to improve psychological treatments. Ripe areas of enquiry include (1) understanding underlying mechanisms; (2) increasing access worldwide; (3) developing cross-modal combination treatment approaches; and (4) enhancing a preventative focus and developmental approach. We need to (5) harness new technologies; (6) improve trials methodology; and (7) improve training in interdisciplinary mental health sciences. Psychological treatments should target challenges such as (8) the inherent complexities of mental health disorders and (9) suicide prevention. The challenges to which a psychological perspective can contribute will require genuine innovation (10). Improving psychological treatments presents an exciting prospect for scientists and clinicians interested in the ‘science of mental life’.

INTRODUCTION

Psychology and Psychological Treatments

Psychology from its inception was defined as 'the science of mental life'[1]. Psychological treatments have evolved to occupy a key place in evidence-based treatments for mental health. Pivotal techniques used in today's 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. In recent decades the treatment field has drifted away from its scientific roots, while mechanistic studies have drifted further away from treatment issues. Now is the time for greater synergy to invigorate psychological treatment research[2]. Psychological treatments offer great promise for continued innovation – arguably now more than ever before – not least due to the development of scientific methods and perspectives from the numerous allied fields that can be drawn upon.

While researchers and industry struggle to produce new drugs for mental disorders [footnote #1,] psychological treatments may have the potential to deliver acceptable, effective, and safe treatment options more quickly[3]. Building bridges between psychological treatment and other modalities such as via combination approaches could also benefit many. But it will not be easy. New trials of psychological treatments are greeted not only with enthusiasm, but also controversy. Questions are constantly being raised 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 intervention be disseminated nationally and internationally? Current assumptions are also being queried. 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?

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

[footnote #1]The terms mental disorder, mental health disorder, psychological disorder, psychiatric disorder, mental health problem and so forth are used interchangeably throughout this document. We recognise wider psychological treatments terminology such as mental health difficulties, behavioural difficulties and so forth.

As we argue below, the burden of mental disorders is enormous, and yet current pharmacological and psychological treatments offer only limited effects for reducing disease burden. Since the majority of patients prefer psychological treatments over pharmacological treatments[4], increased research efforts are required to evolve psychological treatments to the level of significant impact upon mental disease burden worldwide. But in order to realize the development of psychological treatments, a research agenda is needed that can guide this field for the coming years[2].

> "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…reconsider the proportion of investments in mental health relative to other diseases." [2]

Methodology and approach employed in preparing this commission

This commission arose from an initial consultation meeting at The Lancet's London Wall office in December, 2015, in which researchers from a variety of backgrounds with interests and/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"[5]. 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 USA, and 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. It was not our goal to provide an exhaustive literature review, nor 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 there continue to be many more important topic areas and perpsectives, and that this is a start for necessary and continued discussion.

The commission is comprised of ten subsections, each of which contains a theme that we consider critical to the development and improvement of research on psychological treatments. The content of these ten sections is as follows: mechanisms of psychological treatments, deployment of psychological treatments, cross-modal treatment approaches, prevention and early intervention, the role of technology in psychological treatments, evaluating psychological treatments, interdisciplinary training, complexity of mental health problems, suicidal behaviour, and finally, future directions in the development and innovation of psychological treatments."

Mental health disorders are widespread and costly

Every year almost one in five people worldwide suffer from a mental disorder[6], and more than 750,000 people die by suicide[7]. In 2010, mental and substance use disorders accounted for 183.9 million disability-adjusted life years (DALYs,[8]), with most disease burden caused by depressive disorders, anxiety disorders and substance-use disorders. These numbers are likely to be underestimates given that it is assumed in these calculations that mental disorders are not associated with excess mortality, except suicide. There is increasing evidence, however, that people with a mental disorder have a considerably higher risk of dying earlier than those without mental disorders[9]. Between 1990 and 2010 the disease burden of mental and substance use disorders increased by more than 35%, mostly driven by population growth and ageing[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[10-12]. 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 US$ 6.0 trillion by 2030[13]. It is for this reason that conceptualizations 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 to self-manage[14].

Current treatments make as yet a limited contribution to the reduction of the disease burden

Several evidence-based biological and psychological treatments are available for a range of mental health disorders. There is, however, room for considerable improvement. Current treatments are estimated to be able to reduce the disease burden by only approximately 40% and

that is only under optimal conditions, when all patients with a mental illness receive an evidence-based treatment[15]. Coverage (i.e., the proportion of people who receive a consultation for a mental disorder) is however typically much lower than 100%, is hardly above 50% for any disorder in any country, and for some disorders (e.g., alcohol-related disorders) is below 10%. We note that, according to the Adult Psychiatric Morbidity Survey conducted in 2014, there has been a welcome increase in people with common mental health disorders receiving treatment, although it is notable that this increase can largely be attributed to the use of psychotropic medication[16]. It is also well-known that the majority of patients treated for mental health disorders do not receive evidence-based treatments but rather receive a wide array of treatments including interventions with no evidence-base[17].

Patient preference for psychological treatment options alongside restricted availability

Many patients with mental disorders in high-income countries receive drug treatments, and these numbers are increasing. For example, in the United States the use of antidepressants has almost doubled between 1996 and 2005[18], from a rate of 5.84% to 10.12% (or from 13 to 27 million individuals). From 1999 to 2010, on average 8.6% of adult depression visits included the prescription of a Second-Generation Antipsychotic[19] – this rate doubled during this period from 4.6% to 12.5%. An increasing proportion of patients receive psychotropic medication without psychotherapy[20]. Meanwhile sizeable population surveys in the United States show that psychotherapy has assumed a less prominent role in mental health care[20]. For example, from 1996 to 2006, among antidepressant users the percentage of people who underwent psychotherapy declined from 31.50% to 19.87%[18]. In low-income and middle-income countries, psychological treatments are hardly available with notable exceptions[21] (see also *Section 2, Worldwid*e).

At the same time, however, there are indications that the majority of patients prefer psychotherapy over medication: a meta-analysis of patients with a range of mental disorders (including depression, anxiety, insomnia, bipolar disorder, schizophrenia, substance-related disorder, eating disorder, and personality disorder) estimated that approximately 75% of patients prefer psychotherapy as their treatment[4]. Such a preference underscores the importance of progressing psychological treatments research. Meanwhile, clearly some patients prefer pharmacological treatment, and some may in fact have no preference. We do not seek to reinforce what we believe to be a misplaced dichotomy between biological and psychological approaches (see *Section 3, on Combination Treatments*). Rather, we seek a research agenda that

is open to multiple perspectives, does not neglect one at the expense of another, considers links, is informed by patient preferences, and ultimately leads to the greatest clinical impact.

Although as mentioned above the majority of patients prefer psychotherapies above medications, the availability of such treatments is a major problem in many if not most countries[5], because of financial constraints, or because there are not enough trained psychotherapists to deliver the evidence-based treatments. This means that psychotherapies are often mostly delivered in high-income countries, to those who can afford it and know the ways to find therapists. Several alternatives are being developed to increase access to psychological services, such as the Increasing Access to Psychological Treatment (IAPT) program in the UK, where 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. Internet-interventions (see *Section 5*) can be an important help in making psychotherapies better available to those who need it because they can be offered relatively inexpensively, cheaply and with a low threshold for access. Another important development to make therapies better accessible is to use lay-health counsellors. This has been done in other fields of health care as well, and in several Low and Middle Income countries experiments have shown that these counsellors can deliver therapies in an effective way, at low cost (see *Section 2, Worldwide*).

Seeing further: Psychological Treatment Research in Tomorrow's Science

> "Improved psychological treatments to help reduce the burden of mental disease worldwide."

What needs to be achieved? In a nutshell - improved psychological treatments to help reduce the burden of mental disease worldwide. Psychological treatments are clearly just one of many necessary routes to improve global mental health yet have an important part to play. The psychological treatment research landscape is ripe for invigoration – it offers truly exciting and opportune areas for mental health sciences. Indeed, the enormous need for improved treatments provides a rich vein for scientific enquiry across disciplines. Recruiting insights from multiple areas of *science* may allow us to 'stand on the shoulders' of existing evidence-based

psychological treatments and 'see further' [footnote #2] in order to improve psychological interventions. It might also be the case that recruiting insights from *psychological treatments* will allow us to stand on the shoulders of existing scientific evidence and "see further" to improve scientific theory. Greater collaborative endeavours between clinical and basic researchers of all stripes will help in this regard[2].

Here we discuss opportunities to focus future research efforts to improve mental health. Ripe areas of enquiry include (1) understanding the mechanisms underlying psychological treatments; (2) increasing their worldwide access; (3) developing cross-modal treatment approaches; and (4) enhancing a preventative focus and developmental approach. To do this we need to harness tools provided by (5) new technologies; (6) improved trials methodology; and (7) improved training in interdisciplinary mental health sciences. The targets of psychological treatments should embrace challenging areas, such as (8) the inherent complexities of mental health disorders and of (9) suicide prevention. The array of challenges ahead to which a psychological perspective can contribute will require fresh innovation (10).

However, the idea of "seeing further" requires ideas to be taken, tested, rejected, or developed and so forth in line with scientific method and the mental health challenges of the time. That is, we need ideas and evidence to be rigorously examined, explored, and then kept, refined or discarded as appropriate in line with evolving research findings (rather than for example therapeutic habit and allegiance to a way of clinical training, or science focused inwardly on science rather than its genuine application). This means in essence that we need change – change that is not only driven by scientific knowledge but by pressing mental health issues as they arise.

We therefore make an analogy with a British contemporary art initiative – which engages with London's Trafalgar Square's empty plinth. There are statues on three of four of the plinths in the corners of Trafalgar Square. The fourth plinth stood empty for over a century. Now, the so called "Fourth Plinth Programme"[22] invites world class artists to make 'astonishing' new works for the centre of the capital city. Commissions create a rolling programme of temporary artworks rather than settling permanently on one figure or idea. These

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[footnote #2] "*If I have seen further it is by standing on ye shoulders of Giants*"; Letter from Isaac Newton to Robert Hook dated 5th February 1676, as transcribed in *The Correspondence of Isaac Newton*. (1959). H. W. Turnbull, Ed. (Vol. 1.) Cambridge: Cambridge University Press.

resultant sculptures tend to be shown for a year, sometimes only months – sometimes there are gaps. But the momentum and scrutiny continues. Associated initiatives encourage projects and creative thinking around past and present artworks displayed on the Fourth Plinth. Meanwhile, the best use of the fourth plinth remains the subject of debate and discussion in the public, media and art world.

Bringing this metaphor back to psychological treatments research - innovation, rotation of ideas and the encouragement of robust critical debate needs to be a clear part of the way forward. As mentioned above, ideas can be taken, tested, rejected, or developed and so forth in line with scientific method and the mental health challenges of the time. That is, the objects of enquiry change, but the principles of seeking to improve our research efforts towards improved mental health persist. Rather than being prescriptive regarding the future of psychological treatments research, this article sets out various suggestions and principles to guide the research that should apply across different mental disorders / transdiagnostic processes, approaches, countries and, indeed, to the new and future generations of mental health researchers. These principles should change with scrutiny over time, as new principles are developed, scrutinised, and refined to reach the need and scale of mental health problems worldwide. How best to strengthen psychological treatments should be subject of research, debate and discussion involving both the psychological treatments and mental health science fields, and many of those beyond.

Figure. The Forth Plinth, Trafalgar Square London (photo by E. Holmes, 2016)

When considering the traditional delivery method of psychological treatments, it is fascinating that two humans talking with each other for a matter of hours during therapy sessions can bring about changes that remediate years of suffering mental distress. While clearly the presence of another human can be helpful, that alone is unlikely to provide the key to psychological treatment success. Evidence-based psychological treatments involve far more than only skills which boost therapeutic alliance. We now know therapeutic effects can be achieved without a therapist being physically present (e.g., via Internet therapy) and that some psychological techniques can be effective when delivered by lay workers with modest training. Moreover, neuroscience continues to reveal how efficiently the mind can work under certain parameters (e.g., in modulating memory) by a range of techniques which may or may not require another human to be present. The emotional, behavioural and social changes rendered through therapy open fascinating mechanistic questions for science e.g., why do effective psychological treatments work? The identification of specific targets for mechanistic questions might be facilitated by not only by quantitative scientific methods but by qualitative methods used in humanities and social sciences, such as detailed narratives of individuals' experiences as they undergo psychological treatments. Once potential targets are identified in this way, they could be subjected to experimental investigation to establish causality for therapeutic change.

We turn now to focus and elaborate on ten key themes that we see as instrumental to consider in developing an agenda to progress the science of mental health treatment research. These themes are not exhaustive and many more are to be welcomed for future scrutiny.

1. **Why** do existing treatments work? *Making the case for mechanisms of psychological treatments*

> "Although there are many EBTs *(evidence based therapies)* available, there is little understanding of the mechanisms of change (i.e., precisely how they work; Kazdin, 2007)[23]. Understanding mechanisms of action may be extremely important…"
>
> Kazdin, A. E. (2007). Mediators and mechanisms of change in psychotherapy research. *Annual Review of Clinical Psychology, 3*, 1-27.

Overview: Mechanisms

It is now known that certain psychological treatments are effective but we know little about the processes through which therapeutic change occurs. Knowledge of mechanisms is essential to deriving and honing treatment strategies to more directly target agents of change, trim away irrelevant strategies, and develop novel approaches that are even more expeditious and effective. Knowledge of mechanisms also permits greater precision in matching psychological treatments to the needs of each individual in order to improve outcomes.

Mechanisms research presents exciting directions for the future of psychological treatment research. However, the current state of play and wealth of neuroscientific studies in the area of psychopathology have generally taken the approach of simply describing differences between groups of individuals with and without a diagnosis – an approach which cannot unambiguously identify causal mechanisms. Thus, to move the field toward causality, ***we should seek to maximize research on mechanisms by firmly framing it within a clinical treatment context to: a) understand how existing treatments work; b) improve these treatments; and c) derive new treatments.*** *Greater collaborative endeavours between clinical and basic researchers will help in this regard.*

What is a mechanism of psychological treatment?

Mechanisms are "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 or precisely what was altered that led to symptom change"[23]. A mechanism is an explanatory construct and not simply an intervening variable that explains the statistical relation between an intervention and an outcome - i.e., a mediator. For example, the finding that changes in perceived self-efficacy and outcome expectancy statistically mediate subsequent changes in anxiety and functioning[24] does not explain *how* 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 behaviors, *see Panel 1*.

Panel 1. What is a Mechanism of Psychological Treatment?
• Processes through which treatment leads to symptom change
• An explanatory construct – not simply an intervening variables that explains the statistical relationship between an intervention and outcome (i.e., mediator)
• Processes include (but are not limited to) neural systems, other physiological systems, cognitions, and behaviors

The processes through which psychological treatments produce change often overlap with, or are complementary to, mechanisms that are responsible for the onset and/or particularly the *maintenance* of psychopathology (hereafter referred to as mechanisms of psychopathology). The NIMH Research Domain Criteria (RDoC) Initiative has made strides in directing the search for mechanisms of psychopathology away from the constraints of categorical diagnostic criteria and towards dimensions of observable behavior and neurobiological measures (NIMH Strategic Plan, http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml). 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)"[25]. In essence, the RDoC framework aims to identify biopsychological explanations or "process constructs" for clinical phenomena; these same "process constructs" could explain change in clinical phenomena throughout treatment. The provisional list of RDoC explanatory constructs includes Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Systems for Social Processes, and Arousal/Modulatory Systems, with each construct comprised of more specific subconstructs[25]. The constructs are assessed with measures that represent at least seven

levels (called 'units of analysis'), including genes, molecules, cells, circuits, physiology, behavior, and self-reports. Identifying a mechanism using one unit of analysis does not exclude mechanisms identified using other units of analysis. The RDoC matrix also includes paradigms for assessing units of analysis (as shown in Table 1 below).

Table 1: NIMH Research Domain Criteria Matrix.

	RESEARCH DOMAIN CRITERIA MATRIX							
	UNITS OF ANALYSIS							
DOMAINS/Constructs	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Reports	Paradigm
NEGATIVE VALENCE SYSTEMS								
Acute threat ("Fear")								
Potential Threat ("Anxiety")								
Sustained Threat								
Loss								
Frustrative Nonreward								
POSITIVE VALENCE SYSTEMS								
Approach Motivation								
Initial Responsiveness to Reward Attainment								
Sustained/Longer-Term Responsiveness to Reward Attainment								
Reward Learning								
Habit								
COGNITIVE SYSTEMS								
Attention								
Perception								
Declarative Memory								
Language								
Cognitive Control								
Working Memory								
SOCIAL PROCESSES								
Affiliation and Attachment								
Social Communication								
Perception and Understanding of Self								
Perception and Understanding of Others								
AROUSAL AND REGULATORY SYSTEMS								
Arousal								
Circadian Rhythms								
Sleep-Wakefulness								

Mechanisms of psychopathology vary from being predominantly distal (e.g., effects of early life adversity which may have occurred many years previously upon inflammatory markers for depression[26]) to predominantly proximal (e.g., ongoing biases in autobiographical memory for depression[27]) (see[28] for a recent discussion of these ideas). They also vary from being predominantly fixed (e.g., genes, albeit with variations in expression) to predominantly malleable (e.g., negative interpretation bias for ambiguous stimuli). Psychological treatments generally target predominantly proximal and malleable mechanisms of psychopathology, as is the intended effect of attention bias modification training for anxious individuals who exhibit

selective bias of attention towards threat-relevant stimuli[29]. Alternatively, psychological treatments may target factors that differ from but compensate for mechanisms of psychopathology, as is the intended effect of compensatory cognitive training for psychosis[30]. Even though less commonly targeted, distal mechanisms may be particularly important targets of prevention efforts. Notably, not all treatment mechanisms are directly tied to mechanisms responsible for the onset or maintenance of psychopathology; in some cases, treatments work through independent processes, as is the case for applied behavioral analysis techniques for treating autism[31].

What is the state of the field?

A number of pivotal evidence-based psychological treatments have evolved by specifically targeting identified mechanisms of psychopathology. One example is the treatment of panic disorder. Through a series of experimental investigations and prior animal modelling, interoceptive conditioning (i.e., acquired fear of visceral or other internally generated stimuli due to pairing with an aversive outcome, as in the case of pairing elevated heart rate with the possibility of heart attack) and catastrophic misappraisal (i.e., misinterpretations of interoceptive stimuli as harmful or threatening) were recognized as mechanisms underlying the fear of bodily sensations that characterizes panic disorder[32-34]. Psychological treatments were developed to target those mechanisms precisely in the form of interoceptive exposure[35] (i.e., repeated exposure to interoceptive stimuli in the absence of aversive outcomes) and cognitive restructuring[36] (i.e., 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 nontargeted supportive psychotherapy (Hedges g = .35, CI 95% .04-.65)[37]. Similarly, the conceptualization of instrumental reinforcement of compulsions led to a treatment known as exposure and response prevention for obsessive compulsive disorder[38]. In this conceptualization, the distress-reducing effects of compulsive washing in response to obsessive thoughts of being contaminated reinforces and therefore increases compulsive washing with each subsequent obsessive thought; the treatment combines exposure to reminders of the obsessive thoughts (such as a dirty piece of clothing) or the thought itself (such as the thought of being covered in germs) with prevention of washing. This treatment approach is very effective for obsessive compulsive disorder, and more so than nontargeted psychological control conditions such as relaxation training (Hedges g = 1.29, CI 95%

0.76–1.81)[39]. Another example is behavioural activation therapy which targets deficits in positive reinforcement as a contributing factor for depression[40]. This approach aims to increase access to positively rewarding stimuli, and more recently, achieve actions that are value-driven and overcome task-related avoidance[41]. Behavioural activation for depression is highly effective relative to comparison control interventions, including waitlist and nontargeted psychological control conditions (Hedges g = 0.87, CI 95% 0.60 ~ 1.15)[42] . Overall, this mechanistic approach informed the development of psychological treatments that are more precise, efficient, and effective than treatments that do not target specific mechanisms. That said, the strongest effect sizes derive from comparisons with no-treatment or wait-list control conditions, with the latter potentially inflating effect sizes[43], and some of the meta-analytic findings presented above included wait-list control conditions (e.g.,[42]). That comparisons to usual-care typically yield lower effect sizes than comparisons to no-treatment or wait-list controls[44] may speak to the importance of common factors (such as goal consensus, therapeutic alliance, empathy, expectations and therapist effects) that are relevant to all psychotherapies[45]. Notably, common factors do not obviate the importance of mechanistic research but rather imply the value of taking common factors into account when evaluating mechanisms of specifically targeted therapeutic approaches.

However, despite purported treatment mechanisms, including the ones described for panic disorder, obsessive compulsive disorder, and depression, we have little evidence for the precise mechanisms through which psychological treatments actually work. Although recent developments in neuroscience have ignited more interest, as described below, the majority of studies to date have not evaluated *mechanisms of treatment*. Even the study of mediation is limited and often plagued by lack of sufficiently rigorous methodology needed to claim that a particular variable statistically predicts subsequent change in outcomes[23]. For example, while there is good evidence for the efficacy of interoceptive exposure and cognitive restructuring for panic disorder, and while extinction of fear of interoceptive cues and reduction in catastrophic appraisals occur as a result of treatment, we have little direct evidence that the treatments work through extinction of conditional fear of interoceptive cues or reduction of catastrophic appraisals – a claim that would require that changes in the purported mechanisms explain subsequent changes in symptoms (as described in a later section). Similarly, while behavioural activation for depression may lead to changes in reward processing, there is no evidence 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 a mechanistically informed approach. Instead, the focus has shifted towards 'modifying or adapting' existing manualized psychological treatments, sometimes superficially, for different populations and settings. This approach of modification most commonly applies to cognitive and behavioral therapies. Although valuable for the advancement of treatment implementation in different settings, this has resulted in a regrettable divorce from the foundations of mechanistically informed psychological treatments that in turn has thwarted investigation of their mechanisms of action.

Why it is important to understand mechanisms of psychological treatments?

Without knowledge of mechanisms, pathways to intervention development and refinement remain limited. With knowledge of how change occurs, therapeutic strategies that more directly, precisely and effectively produce such change can be developed[46]. Also, those therapeutic strategies that do not have an impact upon the critical processes can be removed, making treatments more efficient as well as more effective[46]. Moreover, by disconfirming a purported mechanism, research attention can be redirected toward investigating alternative mechanisms and to the development of novel treatments that most effectively and efficiently target them, *see Panel 2*.

Panel 2. Reasons for Understanding Mechanisms of Psychological Treatments
• Hone treatments to more directly and efficiently target processes responsible for change
• Uncover essential moderators of treatments outcome and improve precision in treatment matching
• Develop training programs for prevention of and recovery from psychopathology
• Limit wasteful and inefficient treatments
• Provide evidence for specificity above and beyond nonspecific factors responsible for the "dodo bird" effect

Psychological treatment mechanisms may uncover essential moderators of treatment outcome, and thereby lead to greater precision in matching treatments to individual needs[44]. A few recent examples are provided below. Conclusive findings will depend upon replication with significantly larger sample sizes than those in the extant literature; these examples

simply provide illustrations of ways in which the field could consider moving forward. For example, initial interest in attention bias modification training for anxious individuals waned as a result of mixed findings and limited effect sizes[47]. More recent research has provided some indication that the effects of attention bias modification training are superior for individuals with stronger levels of attentional bias at baseline[29] and for those with low expressing forms of the serotonin transporter gene (5-HTTLPR)[48]. As another example, it has been suggested that extinction-based exposure therapy to trauma cues for posttraumatic stress disorder may function in part by enhancing prefrontal cortex (PFC) inhibitory regulation over amygdala responding[49]. Neuroscientists have identified subtypes of individuals with posttraumatic stress disorder, with the majority showing amygdala hyperactivation and PFC hypoactivation to trauma reminders and a minority (~30%) showing the reverse pattern of amygdala hypoactivation and PFC hyperactivation[50]. If it can indeed be established that exposure therapy works at least partially through enhancing PFC regulation of the amygdala, then exposure therapy may be more effective for the former set of individuals with posttraumatic stress disorder compared to the latter.

Not only is identification of such "mechanistic" moderators valuable for precision in treatment matching, but uncovering such moderators in turn improves the elucidation of psychological treatment mechanisms[46]. To follow the prior example, by collapsing across the entire sample with posttraumatic stress disorder (those showing amygdala hyperactivation as well as those showing amygdala hypoactivation) the extent to which change in amygdala activation serve as a treatment mechanism is likely to be nullified. By recognizing individual baseline differences, differential mediational pathways could be uncovered for different individuals (such as the possibility of amygdala deactivation for those who initially present with hyperactivation and vice versa for those who initially present with amygdala hypoactivation). Again, these are simply illustrative examples, but a mechanistic approach to moderation avoids the trial-and-error default position of assuming that a given psychological intervention strategy works through the same mechanisms for everyone. Another speculation is that behavioral activation for depression[41] (which involves scheduling activities that are rewarding) leads to symptom improvement through enhancing approach motivation or initial responsiveness to reward within 'Positive Valence Systems' for some individuals, while for other individuals it may 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 every day habits that pertain to prevention of and recovery from mental health. Examples of such attempts include training in mindfulness techniques to reduce affective memory bias and reduce development of, or relapse into, depressive ruminative states[51]. Other examples include 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[52]. In one study, short-term focused CBT was associated with significantly lower scores on depression three to five years later relative to usual care alone[52]. Similarly, cognitive therapy decreased recurrence of depression relative to treatment as usual over a ten-year interval in remitted patients with histories of recurrent depression[53]. Together, these data suggest that CBT/CT provided skills that were embedded into everyday lives and led to sustained improvements in the long term.

Failure to address mechanisms of psychological treatments bears certain costs. For example, the development of novel and more effective treatments could be stymied by c**ontinued focus of attention upon modifying procedural elements to existing treatments without fully understanding the processes that lead to change.** We encourage the development of a larger evidence-base for critical processes for therapeutic change, and specifically which psychological treatments (existing and newly developed) "hit" which process/es. This evidence-base can and should include both common factors as well as specific factors of psychotherapies[25]. That is, it will be informative to know which psychological treatments exert their effects primarily through common, nonspecific factors versus more targeted, specific factors, and whether the common and specific factors are of greater relevance for one mental health problem or individual over another. Moreover, such an evidence-base offers the potential to move the field forward beyond the longstanding debate between (a) all psychological treatments are equally effective (i.e., "dodo-bird hypothesis")[54] and (b) differential treatment effects[55]. That is, we have the opportunity to evaluate whether matching mechanistically focused treatments to individual profiles of underlying dysregulation leads to superior outcomes relative to nonspecific factors that are common across psychological treatments. Of course, applying mechanistically focused personalization and understanding the role of common factors are not the only pathways by which we can improve psychotherapy outcomes; other factors that warrant consideration include the personal resources and social

context of those in need, as well as the service delivery systems in which treatments are delivered.

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
o Human studies to demonstrate that manipulation of purported construct leads to symptom change (experimental psychopathology)
o Animal studies to allow more precision and elucidation of targets that cannot be studied in humans
o Reverse-translation models utilizing clinical research to inform models to be tested in animals
• Iterative reciprocal information flow between experimental psychopathology studies in humans and animals

As reviewed by Kazdin[23], mechanisms involve a deep level of explanatory specificity and hence are theory-driven. They are elaborated through plausible and coherent reasoning based on integration with broader scientific knowledge, and at the same time possess specificity in the explanation provided for how change in the mechanism in turn accounts for change in outcomes[23]. Once theoretical mechanisms are elaborated, they are subjected to experimental investigations that validate their causal influences upon selected outcomes. This endeavour is represented in the field of "experimental psychopathology" (see Panel 3).

Demonstration that experimental manipulation of a purported mechanism leads to symptom change is a powerful method for validation. Experimental studies of this kind in human samples can identify key processes that maintain or change aspects of psychopathology. These studies also elucidate which of the processes underlying psychopathology can (versus cannot) be modified, and therefore are appropriate treatment targets. A recent burgeoning of interest in the mechanisms that underlie psychopathology has been fuelled largely by advances in cognitive science and neuroscience[46]. As one example, increased activation in affective brain networks and decreased activation in cognitive control and social cognitive networks as youths listen to criticism from their

mothers has been identified as a potentially critical mechanism in emotional development[56]. These findings could inform treatments aimed at increasing effective parenting to reduce the risk of mental health disorders 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. For example, pharmacological agents that facilitate the consolidation of fear extinction learning (e.g., d-cycloserine) have been shown to have beneficial effects in the context of exposure therapy[57] (although there are some mixed effects, possibly due to mechanistic moderators[58]). Another example derives from the evidence that retrieving already stored memories induces a process of reconsolidation[59]. Once retrieved, the memory has to be rewritten into long-term memory, which requires neurochemical processes (de novo protein synthesis) in the brain. This process give rise to the fascinating possibility of changing memories post factum, during the reconsolidation time window upon retrieval. Pharmacological (i.e., propranolol) agents and behavioural techniques (i.e., extinction) have been shown to interrupt the reconsolidation process in humans, albeit with some mixed results[60], limiting boundary conditions and conceptual challenges[61,62]. Most recently, engaging in a highly visually- absorbing computer game ('Tetris') after a memory-reminder cue was found to interrupt reconsolidation of intrusive visual memories induced by experimental trauma[63].

In other areas, demonstrations of disturbances in autobiographical memory as potential mechanisms of depression have led to novel therapeutic strategies such as memory specificity training or positive memory elaboration for depression[27]. More mechanistic research is needed in general and particularly in youth samples, where there is great need for innovative psychological treatments that precisely target narrowly specified mechanisms consistent with developmental models of aetiology (*see also Section 4, When in life).*

Purported mechanisms can be tested in animals with a much more precise level of measurement and causality than is possible in human beings. Furthermore, animal studies are invaluable for identifying basic processes and mechanisms that are not possible to address in humans due to practical or ethical constraints. Indeed, the clinical applications of d-cycloserine for exposure therapy and the disruption of reconsolidation for fear memories first derived from careful experimentation in animals[59,64]. Animal studies have also elucidated the

potential value of disruption of reconsolidation in the treatment of substance abuse/dependence[65]. Ongoing animal work is currently examining pharmacological agents that regulate the stress response via inhibition of the renin-angiotensin system (i.e., losartan) as another method for enhancing consolidation of extinction[66]. Advances in understanding the neurobiology of rodent self-grooming may identify potential treatment mechanisms for repetitive behaviours such as compulsions[67].

In reverse-translation approaches, clinical research informs models to be tested in animals. For example, paradigms for assessing depressive cognitive styles such as pessimism that have been validated in human samples have now been reverse-translated to paradigms that measure judgment bias in rodents[68]. Similarly, drawing from human work on reward systems, paradigms have been developed to assess decision making between cues that predict reward versus cues that predict punishers in rodents; decision making was shown to be influenced by negative state induction (via unpredictable housing treatment)[69].

Iterative reciprocal information flow is needed between experimental studies in humans and animals. While there are some examples of such reciprocity, as in the cases of d-cycloserine and memory reconsolidation, 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 samples. The reverse and forward translation of advances in basic science and clinical science is essential.

Panel 4. Recommendations for Evaluation of Mechanisms of Psychological Treatments
• Evaluate within the context of properly powered clinical trials
• Develop measures (i.e., of mediators) that are reliable, valid and sensitive to change and represent multiple modalities (genes, molecules, cells, circuits, physiology, behavior, cognition, self-report)

• Establish mediation by showing change in mediator over treatment and that change in the mediator precedes and predicts clinical outcome
o Temporal precedence (change in mediator precedes and predicts subsequent change in symptoms); value of repeated measurement
o Specificity of mediation to a single or limited number of mediators
o Specificity of mediation to a theoretically-relevant mediator versus non-relevant mediator for a given treatment, or of a theoretically relevant mediator to one treatment relative to another treatment to which it does not have theoretically relevance
o Dose response relationship between degree of change in mediator and degree of clinical improvement
o Consistency in independent replication
• Evaluate mediation for elements or specific therapeutic strategies rather than packages of treatment elements

Once a mechanism has been identified through careful experimental demonstration, for example via a series of experimental psychopathology studies, then it can be evaluated within the context of properly powered clinical trials, involving more extensive collaborations than currently exist. This requires measures of the purported mechanisms that are reliable, valid, and sensitive to change, as these measures will become the mediators that are evaluated statistically. A major contribution to this effort will be funding to establish a list of candidate mechanisms that explain therapeutic change (based on demonstrations that their experimental manipulation influences selected outcomes in animal or human studies) and a list of measures for each candidate mechanism. Here, the RDoC notion of units of analysis provides a helpful framework for choosing measures from multiple modalities.

Kazdin[23] has carefully outlined the steps necessary in order to establish that a measure is a mediator of a psychological treatment. As an initial step, a strong association must be demonstrated between the psychological treatment and the hypothesized mediator (i.e., the mediator changes over the course of treatment), and between the mediator and therapeutic outcome (i.e., change in the mediator is related to clinical outcomes). Kazdin[23]lists a number of methods that allow greater attribution of causality to the mediator (underlying mechanism). One method is temporal precedence, since mediation cannot be presumed unless changes in the purported mediators (underlying mechanisms) occur prior to

and then predict changes in outcomes. Temporal precedence necessitates repeated measurement of mediators (underlying mechanisms) and of outcome variables throughout treatment, ideally in every treatment session.

Greater attribution of causality also derives from evidence for specificity of the linkages; the finding that multiple mediators (underlying mechanisms) explain an outcome is much less convincing than identifying a single, targeted mediator. Even more convincing is when the purported mediator (underlying mechanism) of a particular psychological treatment predicts outcomes relative to an alternative mediator of a different mechanism that is not theoretically tied to the treatment. Moreover, stronger mediation by a purported mediator for a treatment to which it is theoretically tied relative to a treatment to which it is not theoretically relevant is another avenue for demonstrating specificity. Evidence for a dose response relationship, in which stronger doses of the proposed mediator are associated with greater changes in symptoms, also strengthens the argument for causal linkage. The consistency with which the relations are observed, across independent replications, is another validator. Of course, the demonstration of these criteria will require large samples, much larger than those that neuroscientists and clinical scientists typically study. Hence, a mechanistic approach will necessitate collaborative, multi-site studies.

Among the challenges for research on mechanisms are sample size and the need for interdisciplinary research, although we also note that for certain mechanistic questions appropriately powered experimental studies of small samples are also informative. Research on mechanisms is more complicated than examining whether therapies work or not, because causality of the mechanisms are not established easily, and furthermore, doing so requires several types of research from different domains. Given that mechanisms have not been established in the past decades of psychotherapy research, in order to make progress the way forwards will require a strong investment from funders and collaboration among researchers, focusing on common goals.

Finally, the field would be advanced by a listing of the various therapeutic elements that comprise psychological therapies, as has already been initiated[70]. As it currently stands, psychological treatments are mostly packages of different elements, such as cognitive restructuring, self-monitoring, problem solving, relaxation training, assertiveness training, and so on. The more elements that are combined in a psychological treatment, the harder it is to establish mechanistic specificity. **Greater precision is likely from evaluating the**

mechanisms of particular procedural elements rather than combinations of elements[71] (*see Panel 4*). The fact that the task ahead is difficult is underscored by the absence of large scale, major progress since Kazdin's original call for better methods for establishing mediation and mechanistic approaches. However, as noted, greater collaboration across clinical researchers and basic scientists combined with new methods and technologies position us to make more headway than ever before.

2. **Where** can psychological treatments be deployed? *Research to improve mental health worldwide*

Overview: Where - mental health worldwide

Low or no access to efficacious psychological treatments is not only a major problem for the majority of people in low- and middle income (LAMIC) countries, but is also problematic for a significant portion of people in high-income countries. In the future brief, flexible, modular and efficacious treatments derived from mechanistic research could enable us to more efficiently adapt such treatments to different cultural contexts. Furthermore, they could help us train lay persons with no previous experience of providing services within mental health to help implement such interventions within a frame of low-intensity treatment using modern techniques on a broad basis both in LAMI and high-income countries. Further research is needed on 1) how to derive such treatments and adapt them to the local needs, priorities, traditions, and cultural norms for different environment, 2) education and training for lay persons to acquire proficiency to deliver such treatments as lay counsellors in a sustainable way, and 3) models of delivery of mental health with long-term sustainability.

What is the impact of mental health disorders internationally?

As discussed, mental disorders constitute a significant part of the overall burden of disease worldwide[8,72,73]. Together with substance use disorders, mental disorders account for 183.9 million disability-adjusted life years (DALYs) or 7.4% of all DALYs worldwide[8]. The costs of untreated mental health problems are huge[5,8], not only in terms of monetary cost for society, but also in terms of decreased quality of life of individuals and lost opportunities. Mental health problems also interact with other serious conditions such as cardiovascular diseases, ischemic stroke, and HIV, increasing the risk of premature death[74-77].

Psychological treatments from an international perspective

There are a significant number of efficacious psychological treatments for a wide range of mental disorders, which 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, the majority of those in need around the globe do not have access to

such treatments. According to the WHO, at a global level, 90% of individuals with mental health problems do not receive treatment[78]. The majority of the world lives in developing countries, and yet most of health care resources are situated in developed countries. Despite this fact, **low or no access to efficacious psychological treatments is not only a major problem for the vast majority of people in low- and middle-income countries (LAMICs)[79], but is also problematic for a significant portion of people in high-income countries**[80]. As argued by Kazdin and Blase[5], we will have only limited success in decreasing the prevalence and incidence of mental illness without a major shift and expansion in clinical practice and intervention research.

Panel 5. What Increases Access to Psychological Treatments Worldwide?
• Existence of low cost, simple, specific and effective treatments: such treatments can more easily be implemented regardless of context • Task shifting: educating people without prior experience of work within 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, CD/DVD, Internet or other media combined with brief, usually remote, support (e-mail or phone) during a few weeks
• Cultural adaptation: rooting the treatment in sociocultural context (traditions, expectations, norms, symbols, etc.) to make sure that it is perceived as intended

Lack of skilled human resources (i.e., therapists) and low acceptability of psychological treatments across cultures have been suggested as the two major barriers for increasing access to evidence-based psychological treatments in LAMICs[81]. WHO estimated a shortage of 1.18 million mental health workers for 144 LAMICs[82]. Other significant 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[83], *see Panel 5*.

Research to improve worldwide access to psychological treatments

Global access to psychological treatments could become a reality given adequate global and local political decisions and a research agenda including (and not limited to) the following conditions, *see also Panel 6*.

We need to derive psychological treatments that are brief, flexible, modular and efficacious, streamlined to remove any and all complexities unnecessary for treatment gains. These are the characteristics that would be advantageous for the successful scale-up of psychological treatments. Such treatments will be aided by research into mechanisms of action in psychological treatments (*see Section 1 above, on Mechanisms*), and a consideration of the core psychopathology of, and across, mental disorders. Large and complicated psychological treatment packages can only be delivered by highly trained professionals to a minority of people who can afford the high costs associated with such treatments. On the other hand, simplified, clearly defined treatments may be more readily adapted to local needs and delivered by lay mental health workers on a larger scale, and delivered as low-intensity treatments e.g., via the Internet. Mechanistically-informed treatments could also afford flexibility, for example in shaping the treatment in line with local cultural norms and conditions.

Instead of adapting "top down" a treatment package developed in another cultural context, mechanistically-driven psychological treatment innovation offers a profitable research direction. **For example, if one of the major maintaining factors in depression concerns lack of positive reinforcement in daily life (*c.f. Section 1, Mechanisms, Positive Valence Systems*), then treatment strategies to increase positive reinforcement can be formed in many different ways depending on what is the most relevant, acceptable, and affordable in the specific context or culture in which the problem exists** e.g. via various cognitive, behavioural or psychosocial techniques. Such treatments could each have flexible forms, but be functionally identical.

Psychological treatment development for example in LAMICs has typically focussed on the important issues of availability and access, and researchers have taken a pragmatic approach to treatment development itself. Yet future research might also seek to harness scientifically driven developments. Moreover, the utility of building psychological treatments on the basis of sound psychological theories and empirical knowledge gained from research on the processes of action in treatment may afford particular strengths: by *opening*

opportunities for cultural adaptation and psychological treatment across international contexts. As another example, research that has tested theories about the mechanisms of action in exposure therapy for anxiety disorders[84-88] has provided invaluable knowledge, leading to the enhanced flexibility of exposure therapy, which in turn could be tailored for global adaptation. It is the hope that research on basic mechanisms will indicate potential for brief, flexible, and highly efficacious psychological treatments[89-92]. Future research needs to move such work into intervention formats that are acceptable and efficacious cross-culturally, and are deliverable on a wider scale.

We need to rethink the traditional models of one-to-one delivery of psychological treatments by skilled psychotherapists who have had many years of training, and consider more efficient ways of treatment delivery[5,93]. Given the limited human resources in terms of highly trained and skilled professionals internationally, a shift towards collaborative models of care delivery has been proposed in which novel strategies such as task shifting (e.g., educating people with no prior experience of work within mental health services to become lay counsellors) has been successfully used to deliver streamlined treatment of psychological disorders with promising results[81,94-96]. Nevertheless, empirical questions remain: how best can we train people to become lay counsellors in a *sustainable* way, and what barriers might there be for such sustainability? The delivery of therapy in group rather than one-to-one has clear benefits for delivery efficiency.

Other research questions include how many training, supervision, and booster sessions will be needed to ensure high quality delivery of treatments? As summarised by Dawson and colleagues[97], the majority of studies in which potential treatment group leaders have received brief training (1-4 weeks) have shown effective outcomes, but more research is needed in this context. While task shifting and training the trainer have been pioneering in a global mental health context, these are not strategies used in developing countries alone. For example, the IAPT (Improving Access to Psychological Treatments) initiatives in the UK[98,99] resembles an advanced form of task shifting (rapidly educating a new category of mental health professionals called 'Psychological wellbeing practitioners'), with its strengths and limitations that help us improve future large-scale endeavours. How can technologies be employed to train on a large scale and to maintain fidelity of treatment delivery? For example, models of training inexperienced clinicians with the aid of computerized guides

have been employed in primary care clinics in the United States, albeit on a much smaller scale than IAPT[100]. Research using the outcome and long-term follow-up data arising from such endeavours will yield many lessons as to how to increase access to psychological treatments worldwide.

Technology is another important pathway by which to open the availability of psychological treatments[93] (*see also Section 5, Technology*). The use of the Internet or mobile phones to provide psychological treatments combined with minimal individual support through e-mail or telephone has shown highly promising results in many studies in the developed countries[101-106]. However, given that a recent systematic review of online psychological interventions for mental health in LAMICs found only three such studies[107]; greater research efforts are required. This will be particularly important given that mobile phones are rapidly becoming increasingly available worldwide, as is the availability of the Internet - offering tremendous potential for education, assessment and treatment. In 2015, a median of 54% of the population across 21 emerging and developing countries reported either using the internet at least occasionally or owning a smartphone[108].

Low-intensity treatments delivered by computerized or mobile-based guided self-help technologies present an ideal first-line or 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 (e.g., for bulimia nervosa and binge eating disorder[109]). Countries such as Sweden and Australia have led the way in research on Internet-based treatment and the implementation of low-intensity treatments within psychiatric care[110-117], providing models that can be used or developed for improving access to care worldwide.

Another major benefit of the internet is scalability of screening and assessment, which can readily be expanded to encompass the implementation of booster sessions by means of reminders, use of instructional movies and texts, as well as enhanced possibilities for long-term follow-up. Moreover, recent developments with regard to assessment in terms of continuous ambulatory assessment of symptoms may bring us much closer to the desired goal of assessments with high treatment utility, as they may help reveal the mechanisms of psychopathology and treatment on an individualized level (*see also Section 8, Personalised models*). Future research and implementation efforts should involve not only treatment, but

also *prevention* in an international context (*see also Section 4, Prevention*). As with treatment, prevention programs should target the core mechanisms that underlie the development of mental disorders, combined with culturally-specific risk and buffering factors (e.g., higher availability of social support and engagement of family in some contexts/cultures).

Contextual factors play an essential role in any efforts to increase access to psychological treatments and are in themselves 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[118]. Initiatives to improve mental health in LAMICs need to be rooted in the local society to assure sustainability, and in order to illuminate ways to maximise and achieve this. Engaging the local government, considering local legislations and traditions, involving patient organisations, creating conditions for continued education, and mutual exchange are important candidates. One area that currently demands research is efforts to help people who are refugees from war and persecution[119]. Not only are treatment developments imperative, but particular contextual factors require investigation (e.g., 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 relationship between religious/cultural beliefs and attitudes towards mental health is a crucial factor. The potential of highly available media such as radio and TV might have been underestimated with regard to attitudinal as well as behavioural change. As an example, there is clearly stigma related to talking openly about family planning among people living in poor communities in some LAMIC. The successful use of a well-designed TV-series to improve family planning and to reduce fertility rates in Mexico[120] might constitute a good example of the effective application of such strategies to reduce stigma. The capacity of such strategies to combat the stigma related to mental health and seeking treatment for mental health problems warrants investigation. Another example is the "Headspace" initiative in Australia (https://www.headspace.org.au) which provides a model that could be adapted to different cultural contexts and norms with the goals of decreasing the stigma of mental illness and facilitating access to treatment.

The economic aspects of international mental health efforts should also be subject to more rigorous research efforts. Current evidence from the UK[121] suggests that the payoff for psychological treatment approaches such as early intervention for psychosis, conduct disorder and suicide prevention has a ratio higher than 10 (i.e., for every £1 invested in such intervention, there will be more than £10 benefit). As estimated by the World Economic Forum, the cumulative global impact of mental disorders in terms of lost economic output will be US$16 trillion over the next 20 years[122]. Almost any estimate of the costs and benefits of investment on mental health research points in the same direction[123]. Although costs may increase in the short run, the benefits are much larger in the longer term. 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.

Research collaboration and exchange between cultures

Focusing on international mental health in order to bring about improvements in psychological treatments would best be enabled by a mutual exchange of knowledge, experience and expertise between disciplines and across geography (*see also Section 7, Training*). Opportunities for students and professionals (both scientific and clinical) from different parts of the world to visit one other to learn about conditions for, and challenges in, improving access to psychological treatments in contexts other than their own may prove to be a key factor for creating the enthusiasm and lasting collaborations needed to develop sustainable interventions. Such an exchange might also facilitate cross-cultural comparisons that might contribute to further fundamental understanding and more efficient prevention and treatment of mental illness.

Panel 6. Example Directions for Future Research to Improve Access to Psychological Treatments Worldwide

- Build brief, flexible, modular and efficacious treatments which are streamlined based on knowledge from research on mechanisms of action in psychological treatments

• Use the knowledge regarding mechanisms of action of psychological treatments to derive treatments aligned with the local needs, priorities, traditions, and cultural factors specific to the environment in which the treatment will be delivered
• Investigate how much education and training is needed for persons without or with limited previous experience of work within mental health to acquire proficiency to deliver basic psychological treatments as lay counsellors in a sustainable way
• Investigate how new models of delivery of psychological treatments can be scaled up in a *sustainable* way since the long-term sustainability of most models is unclear
• Investigate the use of media such as TV, Radio, and Internet to combat the stigma related to mental illness

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

Overview: With what

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, 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 treatments within the same research framework. The potential for negative effects of treatment combinations should also be a priority for investigation in future research programs.

Creating synergy and avoiding harm with combination treatments

An individual with a mental health disorder (*or comorbidities thereof, see Section 8*) is likely to receive a combination of different treatment approaches as part of his or her care, often including psychological therapies, as well as different types of medication and social interventions, *see Panel 7*. However, current clinical guidelines remain largely silent about combination treatments. Meanwhile, the vast majority of research also focuses on a single treatment at a time, often with the presence of another treatment as an exclusion criterion to participation in randomised controlled trials (although see also meta-analyses of existing combination treatment studies)[124-125]. Clearly, given the sheer number of possible treatment combinations there is much yet unknown, and no guiding framework exists. As such, the generalisation of research based on single (rather than combined) treatments to the typical clinical reality of combination in practise lacks validity. However, this state of the literature nonetheless opens exciting basic and clinical science questions about what does happen when psychological treatment is combined with other therapeutic approaches.

Empirical studies suggest that there may be small benefits, for example, when a psychological treatment (such as cognitive behavioural therapy, CBT) and a pharmacological treatment (such as a selective serotonin reuptake inhibitor, SSRI) are combined in the acute treatment of emotional disorders including depression[126]. However, the longevity of effects

after treatment discontinuation may actually be reduced in some cases. For example, in the treatment of anxiety disorders, posttreatment 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[127,128]. Such findings emphasise the importance of capturing clinical effects after treatment end as well as during acute response, and also of focusing on potential mechanisms which could underlie these differential outcomes (see synergistic vs harmful combination effects Panel 7).

For the most part, combination treatments in the clinic are driven pragmatically; for example, a client may receive two effective treatments, often with each from a different practitioner (e.g., a clinical psychologist and a psychiatrist). Such an approach contrasts with the attempt to combine treatments based on 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 offered alone. Such approaches may be used to potentiate the mechanisms that are theorised to support a therapeutic effect or to overcome the limitations or barriers to a particular mechanism applied on its own (*see Section 1, Mechanisms*). Interventions that are delivered together with psychological treatments may cover multiple modalities and may include the addition of pharmacological agents, neuromodulation, social, nutritional, or other forms of psychological intervention such as computerised training (e.g., cognitive bias modification, CBM).

Panel 7. What is a Combination Treatment?

- Combination treatment: the application of two or more types of intervention in patient groups, which have been specifically assessed for efficacy in combination. In the current context, we refer to the combination of psychological treatments with other types of interventions, across modalities, including the addition of pharmacological agents, neuromodulation, social, nutritional, or other forms of psychological intervention such as computerised training
- Synergistic versus harmful combination treatments: some treatments may work well together and have greater efficacy than either applied on its own. For example, the use of a pharmacological agent to improve learning has been hypothesised to

enhance the retention of cognitive behavioural therapy's benefits[58], although see[129]. By contrast, some treatments may impair efficacy in combination. For example, patients who receive benzodiazepines during psychological treatment may show reduced longer term benefits of CBT after drug discontinuation[128]
• Patient perspective: the views, acceptance and opinions of the individual receiving the treatment can influence its effects. Patient preference needs to be considered in formal research programs that attempt to bridge the psychological-pharmacological divide • Pre-clinical: 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: The success of translational research depends in large part on the validity of the experimental model used to mimic the disorder in the laboratory • Back translation is used to describe the use of evidence from clinical research and experience to drive, test and refine the development and validation of animal and human preclinical models • Experimental medicine / experimental psychopathology: the use of a model, typically in humans, to explore key mechanisms and processes that are hypothesised to be important for treatment action in psychiatry. These models can be used to screen novel treatments and to refine their application prior to full clinical testing

Utilising contemporary cognitive neuroscience research to boost psychological interventions

Research focused on boosting the effects and retention of psychological treatments have utilised recent developments in neuroscience and experimental psychology[88]. Understanding the molecular basis of memory processes provides key targets that may be manipulated to facilitate extinction, reconsolidation of memories and learning which are key components of many psychological treatments, and operate across a number of disorders[59,130]. As such, drug treatments which are able to facilitate extinction of fear associations, reduce reconsolidation of troublesome aversive memories or enhance retention of more positive

memories or experiences during therapy may have a useful role in combination with psychological treatments.

Augmentation of existing psychological treatments. There has been growing interest in the use of drugs targeting the glutamatergic system (such as d-cycloserine) to facilitate underlying processes of extinction and retention during exposure therapy in anxiety disorders such as agoraphobia, social anxiety and post-traumatic stress disorder[58]. However, identifying the factors which may moderate this benefit is challenging, and a recent Cochrane review found no evidence that d-cycloserine vs placebo conferred any advantage overall when combined with CBT in the treatment of anxiety disorders[129]. Direct brain stimulation techniques such as Transcranial Magnetic Stimulation (TMS) applied over the medial prefrontal cortex (implicated in extinction and inhibition) has been reported to modulate conditioned fear learning and extinction in healthy volunteer models[131]. It is hoped that the use of add-on treatments with effects on underlying mechanisms of learning and memory might speed up treatment effects, reduce the number of treatment sessions needed, or even help the longevity of effects. However, the field is also young and has challenges; it requires understanding the best methods to facilitate learning in an area where much is still unknown. For example, the optimal parameters for supporting learning pharmacologically or through neuromodulatory devices are elusive and require dedicated strategic focus to support preclinical work in humans and animal models[58] *see also Section 1, Mechanisms*.

A focus on mechanistically derived combinations also requires understanding and predicting the effects of a psychological treatment alone and in combination. For example, enhancing learning by pharmacological means (i.e., DCS) in an exposure treatment which has failed or where extinction has not occurred would be expected to have counterproductive effects; i.e., to strengthen *poor* outcomes. These complexities underscore the necessity and potential impact of elucidating the mechanisms of treatments in isolation and in combination (*see Section 1, Mechanisms*).

The need for better pre-clinical models. These observations highlight the critical role for preclinical and experimental medicine models in understanding both the key processes and mechanisms that are important for treatment combinations and assessing early signals of efficacy for future clinical testing. While animal models were key to psychological treatment development in the 1950s and 1960s, translation has been less common in recent decades.

Animal models are commonly used in the pharmaceutical industry to screen novel agents, but rarely use a combination approach - i.e., by testing the effect of a drug together with a psychological intervention. This may lead to the early rejection of a drug which may have weak effects on its own but which may be useful clinically in an adjunctive role with psychological treatments.

To support this endeavour, we therefore need strategic focus and funding avenues for mechanistically-informed treatment combination approaches in animal and in human models. We need to enhance the back translation of findings from the clinic to these models and stimulate interest in using combination models to assess novel treatments including drug development within pharmaceutical industry. Research in this area needs to incorporate measures which can assess and predict when and for whom combination treatment will be helpful. Regulatory support for this approach (from the FDA and EMA), linked to approval and licensing of agents, 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.

Unifying approaches and measures across treatment research

Treatment combination across modalities can be limited by the barriers between researchers, clinicians and funders operating within these treatment approaches. The framework, language, and level of analysis are often different, making it difficult to see natural synergy. However, exploring treatments using a common framework may help to reduce these barriers and lead to novel hypotheses unpredicted by either approach alone. For example, recent studies have used measures across fields to understand treatment effects, such as using neuroimaging to understand and predict therapeutic response to psychological treatments[132] and employing psychological outcome measures to explore the effects of drug treatment[133].

As an example, the focus on antidepressant drug action has traditionally been considered at a molecular, cellular or chemical level, but there is increasing evidence that antidepressants affect core psychological processes that are important in depression before therapeutic effects are observed, and which may help explain their later clinical actions in depression (*see*[133,] *Figure 1*). Antidepressants increase the relative processing of positive vs

negative information early in treatment which may be important in the recovery process from depression as the patient experiences more positive feedback and reinforcement, countering the negative biases that are theorised to play a key role in maintenance of the disorder[134,135].

However, a key barrier to the successful translation of these effects into clinical benefit is the need for interactions with the environment. If a patient is socially isolated or in a particularly toxic environment, then increased positive bias and processing would be expected to have only limited effects. In line with this, Shiroma et al.136reported that increased positive bias induced with antidepressant drug treatment interacted with interpersonal support in the patients' environment to predict therapeutic response (*see Figure 2*). This kind of inter-disciplinary approach therefore has the potential to generate new hypotheses concerning combination treatment which would not have been predicted from either approach alone. Using this example, it is predicted that combining antidepressant drug treatment in its early phases with a psychological intervention[134] which has the potential to increase interaction with the environment (such as behavioural activation), may remove a barrier to successful antidepressant drug treatment (*see Figure 1*).

To facilitate interdisciplinary combination approaches, therefore, 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 for improved combination treatments of the future. This requires organisations, funding bodies and researchers to work together, but the results will no doubt be exciting. An example of this followed the joint symposium recently presented at two very different meetings (the British Association for Psychopharmacology (BAP) and the British Association for Behavioural and Cognitive Psychotherapies (BABCP). This 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 strategy[137]. We need to build on this exciting initiative, call researchers across fields and set strategic funding to strengthen this early promise.

<u>Testing the efficacy of combination treatments</u>

Developing and assessing the efficacy of combination treatment also raises complexities for trial design and methodology (*see also Section 6, Trials*). Treatment trials

that compare active vs 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 upon study design. In particular, the effects of two treatments will often be assessed in isolation, in addition to their combination leading to a factorial design with 4 groups (treatment 1 + placebo vs treatment 2 + placebo vs treatment 1 + treatment 2; placebo + placebo). Mechanism studies in particular also need to consider possible state dependency of learning; *i.e.*, that memory will be enhanced if tested in the same vs different state, including internal states produced by a drug[138]. This field of combination treatments will therefore benefit from a number of approaches and from testing effects 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[139] and psychological[140] treatments used in anxiety disorders on the same underlying cognitive processes. This approach has been used to explore the effects of combined treatment. For example, the effects of pairing computerised cognitive bias modification training with brain stimulation of the Dorso-Lateral Prefrontal cortex (DLPFC) was assessed using reactivity to a stressor as a proxy marker of efficacy in a healthy volunteer model[141]. The effects of cognitive bias modification and SSRI treatment alone and in combination have also been explored using the same outcome measure along with effects on negative memory bias, showing surprisingly that the combined effects could be worse than either applied in isolation in healthy volunteers[142]. Early changes in these measures are associated with later therapeutic benefit in patient groups[136] and can therefore be used to guide initial proof of principle studies for treatment combination and to reject those which have little therapeutic promise. Combinations which appear successful using these surrogate markers can then be put forward for the next stage of clinical assessment, typically in a randomised controlled trial, with sufficient statistical power, and appropriate control conditions. This approach may be supported by big data approaches in which the data are collected under more naturalistic conditions (such as large scale analysis of medical records or prescribing patterns *see Figure 2*). Particular treatment combinations and timing of treatment combinations may be isolated by pattern analysis from large data sets. To facilitate

this, it is important to standardise assessments and the treatment elements applied so data can be combined and explored together. For further discussion of combination treatments, *see also Section 8 (and Panel 18)* on personalised medicine approaches. **Therefore, 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**.

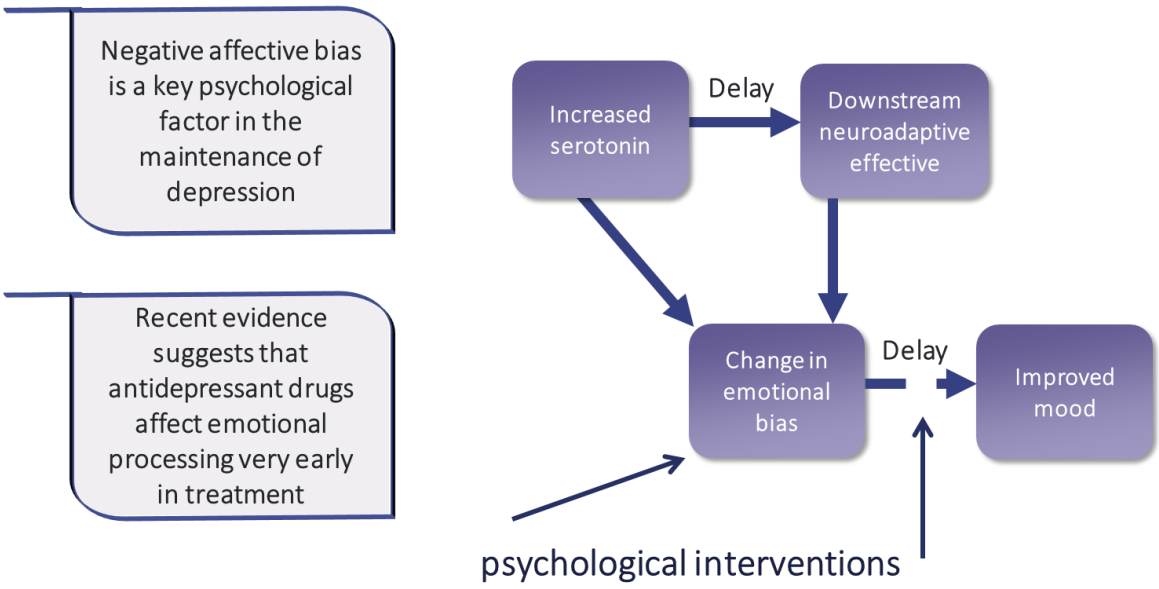
Breaking down barriers: Psychological and biological treatments can tap into the same core processes

Patient preference is also important to consider when evaluating the effects of combination treatment. Individuals often express a preference for either psychological or pharmacological treatment, and so the combination may be a difficult choice for some. This division underscores the view mirrored across society, clinical practice, and science that these are different processes and approaches; i.e., that there is a dichotomy between a psychological or biological view of mental health disorders. This view is challenged by evidence that psychological and biological treatments tap into the same core processes and represent different methods rather than different concepts[133]. Challenging these assumptions and creating more synergy at multiple levels (including the public, clinicians and scientists) will therefore be a critical step towards more optimal development of treatments. As part of this, the ethical implications of combination treatments and their development should be incorporated along with these areas for research strategy. Finally, we also need to consider the attribution of treatment effects from the patient's perspective. For example, if any benefits from combined treatments are attributed to the medication, then the long term advantage of CBT can be lessened[143]. Studies to characterise attribution bias in combined treatment approaches and consideration of the strategies which may be effective in reducing these effects is a key priority for future work, *see Panel 8*.

Panel 8. Example directions for Future Research in Combination Treatment Approaches
• 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
• Stimulating pharmaceutical companies to develop and assess novel therapeutics in a combination role with psychological interventions. Fostering 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 disorders
• Consideration of the potential harmful effects of combination treatment for treatments which work well in isolation including a focus on attribution bias and long term outcome.
• Research on the views and acceptability of combined treatments in psychological disorders and the importance of patient preference and views about treatment for their clinical actions.

Figure 1: *Antidepressant drugs are hypothesised to work via early changes in negative affective bias, i.e., by reducing the influence of this key maintaining factor in depression*[133]. *This raises the possibility that psychological treatments could be used in combination to a.) boost effects of antidepressants on negative affective bias and b.) facilitate the translation of effects on bias into clinical action, via increased interaction and exposure to social and emotional cues.*



Harmer CJ et al. Br J Psychiatry 2009;195:102-8

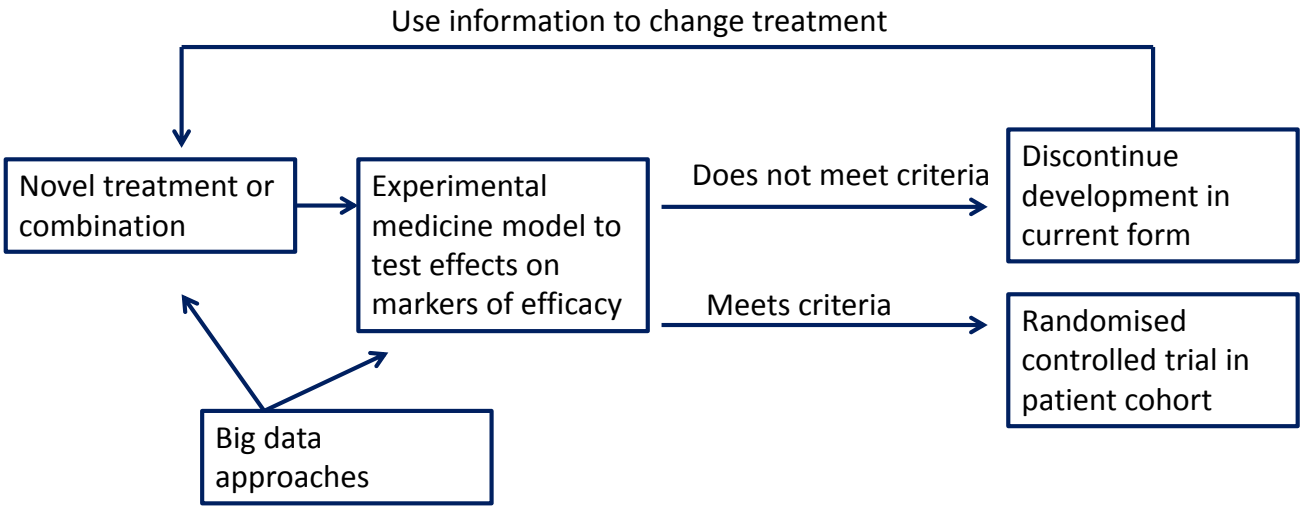
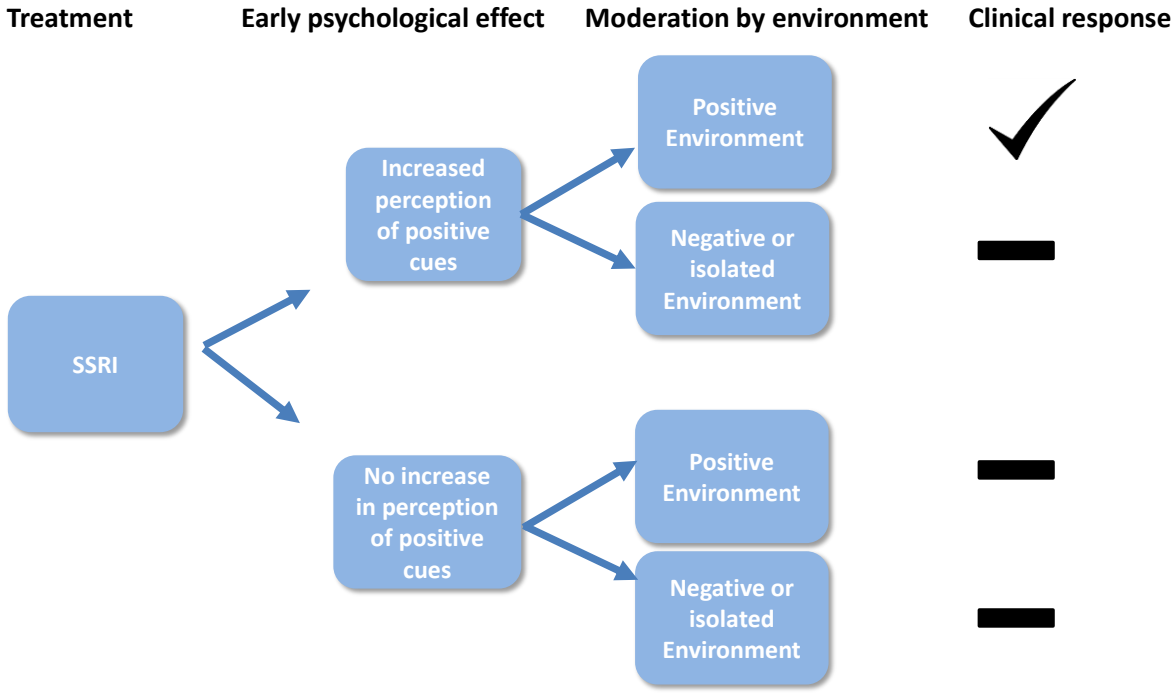


Figure 2: Using experimental medicine models for earlier assessment of efficacy of novel treatments and combinations. The use of surrogate markers within experimental medicine models can be used to screen new treatment combinations in small groups of patients or volunteers. This information is used to refine decision making about subsequent RCT application and design. If insufficient evidence of efficacy is seen in the model, this information can be used to change treatment focus, dose/duration or target. If pre-set criteria are met, the efficacy can be assed using RCT designs. Big data approaches may be useful to highlight particularly promising treatments or combinations and provide additional evidence of efficacy from naturalistic data capture methods

Figure 3: Increased perception of positive cues has been associated with later 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, environment had little impact [13]



4. **When in life?** Psychological science, prevention and early intervention: *getting it right from the start*

Overview: Prevention - and a developmental perspective

Opportunities for prevention and early intervention for mental health problems exist across the lifespan. However, the early years of life represent perhaps the greatest opportunity to set a path to good mental health. This requires both population-based change and the accurate identification of those at risk – in both approaches there is need for effective and safe interventions. Currently many widely used approaches have limited or no scientific underpinning. The rigorous and sustained application of psychological science approaches to this area of practice is critical and offers enormous promise. The focus of this section is primarily on children and young people.

Prevention and early intervention

Opportunities for prevention and early intervention for mental health problems exist across the lifespan. 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 human, societal and economic sense[144-146]. Psychological science can inform and underpin the development of these early preventative interventions, even where the risk factors are social in origin.

The early years of life

The early years of life, right from conception, through to childhood and adolescence represent a wonderful opportunity to set a path to good mental health. Most psychopathology has its origin or onset before the age of 18 years[147]. There is enormous potential to either prevent mental health problems from the start, or to intervene early to reduce the current and future impact of any mental health problems that do occur. 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 may be greater than at any other point in life. At the current time there is a potentially greater role in early life for

psychological approaches compared to pharmacological and other physical interventions, although many interventions, such as nutritional approaches, remain under-researched. For psychological interventions to make significant inroads into the effective prevention of mental illness some key requirements for interventions and new scientific and clinical challenges have to be met[2]. The following sections outline some of these requirements and some of the key challenges and questions that remain to be tackled.

Requirements and challenges for prevention and early intervention

Panel 9. Psychological Treatments: What are Preventive and Early Interventions?

Prevention: often defined as those interventions which are conducted before people meet formal criteria for a disorder[148]. 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 (e.g., school programs or mass media campaigns); selective prevention which is aimed at high-risk groups, who have not yet developed a mental disorder (an example would be the Nurse Family Partnership programme developed in the US which initially aimed to prevent later psychosocial adverse outcomes for women and their children in socio-economically deprived areas[149]; and indicated prevention which is aimed at individuals who have some symptoms of a mental disorder but do not meet diagnostic criteria (an example would be the intervention developed by Rapee and colleagues for parents of pre-school children who are at risk of anxiety disorders, which has potential long-term effects from a brief intervention[150].

Preventive approaches in childhood and adolescence (see *Panel 9*) will often require the effective identification of risk factors or at-risk groups (unless an intervention is going to be delivered to the whole population). Existing preventive strategies to reduce mental health problems are often very clear in the identification of risk factors for future disease or disorder[144]. A range of key early-life risk factors have been established; including exposure to severe adversities such as child maltreatment, disturbed parenting, parental substance misuse, exposure to domestic and other violence, and loss events, such as serious illness in, or death of, a parent[151]. Identification of such risk factors is important in selected and indicated

prevention approaches, and identifying those young people who may potentially benefit from intervention most is a key first step. However, knowledge to date is by no means complete, and further research is needed on these and additional risk factors, as well as interactive effect between risk factors.

Identifying and elucidating these risk factors is not sufficient. For change to occur there have to be effective and acceptable interventions. These may target modifiable risk factors, or may use other theoretical approaches to change, including tackling key psychological mechanisms. This remains a significant gap in our knowledge as many early interventions do not have sufficient evidence to be considered to be effective. Developing and testing early interventions that may be effective in reducing future risk of psychological illness is a fundamental and largely unmet challenge.

Current research limitations regarding early interventions

It is often implicitly assumed that any kind of early intervention is better than nothing. However, this is not the case, and almost any intervention which can actually do or change something has the potential for harm if used in the wrong circumstances; for example, as has been discussed in the area of eating disorders[152]. 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. It is critical to acknowledge that not all interventions are the same: even interventions with overlapping appearance or content can have different effects[153].

There is a relative paucity of evidence for psychological treatments in many areas of child and adolescent mental health practice, particularly for very young children, presenting a great opportunity for future research. This is a promising area as where sufficient high-quality evidence does exist, differences in treatment effectiveness are emerging[55,154]. A related consideration is that an intervention may not have the same treatment effect in every setting or with all individuals equally (see for example apparently contradictory findings for the Family Nurse Partnership intervention[155,156]). Disentangling these challenging problems is made more difficult when the components of a psychological intervention are not clearly specified or publically available; this is often for commercial or some other protective reason.

Whilst these may be important imperatives to consider, they hamper efforts to identify and replicate the critically effective components of any intervention.

A further significant challenge is a lack of understanding of the mechanisms by which intervention occurs in many preventive and early interventions. As set out in Section 1 (*Mechanisms*), this is crucial to development of new and more effective methods of successful treatment. However, in a preventive and developmental context, this is likely to more fluid than at other points in life. For example, different mechanisms may operate at different points in childhood, and each of these may be different from the mechanisms operating in adulthood, even for the same condition or presenting problem (see also section 8 *Complexities*). There are relatively few well-studied examples of this, although some are emerging, such as the lack of evidence for specific cognitive biases for emotional stimuli in young children at risk of anxiety disorders that have been identified in adults with anxiety[157]. In early childhood there will also be a need to go beyond the individualised mechanisms suggested in the RDoC explanatory constructs (*see Section 1, Mechanisms*). For example, other mechanisms, existing in the social world of young children may open critical pathways to help change precursors of psychopathology, such as via the early relationships, or attachments, that children form to their parents or carers (see also the social processes domain of RDOC). Parental sensitivity has been shown to be a key mechanism of change in for example the context of attachment[158,159], although the detailed processes which might then lead to the development of psychopathology largely remain to be elucidated. It is clear that a better understanding of mechanisms underlying treatment gains may also be critical to any step-change in effectiveness of prevention and early intervention.

Making interventions stick - persistence of effects

One further challenge for preventive and early intervention approaches, which is shared with many other forms of psychological intervention, is how to make interventions "stick" - that is, 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 life functioning. There are a number of interventions which have demonstrated efficacy in randomised controlled trials at the end of treatment (see some examples below), but it is an all-too-common experience that these treatment effects dissipate as people are followed up for

months or years (e.g.,[160]). There are relatively few psychological interventions that have convincing evidence of sustained benefit. We do need longer-term evidence (*see Section 6, Trials*), but also developments in psychological science to inform how to make our interventions stick. Further, work is needed to develop approaches to take psychological interventions outside of the therapy room, which may make interventions more widely available and acceptable, and make effects more likely to generalise to everyday life functioning. The use of technologies may aid in this regard (*see Section 5, Technologies*). One example, which a number of research groups are tackling, is how to prevent or treat early signs of depression using gaming and other technologies[161]. A further approach is to take interventions out into schools[162]. Both of these types of approaches have utilised primarily cognitive behavioural interventions to date, although others, such as Interpersonal Therapy (IPT) also show promise for depression in children and young people.

Positive examples for the future

Despite these challenges, there are areas in which promising evidence is accumulating for prevention and early intervention. Three examples are described briefly in panel 10 as they provide pointers to the way in which future research and clinical practice might more effectively develop in this area.

Panel 10. Examples of Promising Preventive and Early Intervention Approaches

Example 1: During infancy, there is accumulating evidence that brief, focussed interventions such as ViPP (Video Feedback to Promote Positive Parenting: for example, see[163,164]) can improve parental sensitivity and the child's attachment relationship with their primary caregiving parent. This draws on both attachment theory and social learning theory. There is some, although limited, evidence of effects on child behaviour as well for this intervention, which is largely lacking for other video feedback parent-focussed approaches at the present time.

Example 2: In slightly older pre-school children (aged 3-5 years), an intervention for the parents of children with increased risk of anxiety disorders (identified by having high levels of behavioural inhibition) has been shown to reduce the risk of subsequent anxiety disorders. This intervention was brief (6 sessions), and used an educational approach with

some behavioural components focussed on exposure. Effects were still seen in the longer-term (11 years later), although only convincingly in girls, and shown to be cost-effective using Australian criteria for cost-effectiveness[150,165].
Example 3: In school age children there is consistent evidence of benefit of parenting groups based on social learning theory, such as the 'Parenting Programmes' to improve child behaviour[166]. Longer-lasting benefits have been demonstrated in some studies, and economic modelling studies point to societal, financial and individual health gain[167].

These three groups of interventions are important because they highlight that preventive intervention and early intervention are possible from very early in life, and that longer-lasting benefits are possible. All three interventions are derived from scientifically rigorous, sustained approaches to intervention development, which are critically informed by theory. They also highlight some of the challenges mentioned above, including that we still have relatively limited understanding of which sub-groups are most likely to benefit from which interventions. Other preventive/early interventions do exist, with varying levels of research evidence to support them in a range of psychological/psychiatric conditions. However, the three examples above offer particular pointers to a rigorous approach to intervention development and delivery that is more likely to benefit children and young people in the long run.

Prevention of mental disorders in adults

In this section we have focused on prevention of mental health problems in children and adolescents, because most mental disorders have their origin in early life[147]. However, there is a broader area of research on the possibilities to prevent the onset of mental disorders in adulthood that we briefly want to mention here. Prevention of mental disorders is considered to be one of the main challenges for the future of mental health care, because of the high burden of disease of mental disorders for individual and societies, the relatively small effect of current treatments and because of the enormous societal costs of mental disorders once they have emerged[168].

In the past two decades a growing number of randomized controlled trials have shown that it is in some cases possible to prevent or at least delay the onset of mental disorders in

adolescents and young adults, especially depression and psychotic disorders. Psychosocial preventive interventions, typically based on psychological treatments such as cognitive behaviour therapy (CBT) or interpersonal psychotherapy (IPT), have since then been tested in at-risk populations and in people with subthreshold symptoms of depression or psychosis, who do not meet diagnostic criteria for a full-blown mental disorder. Results of these interventions (now across several dozens of randomized trials) show them to be effective in reducing the incidence of new cases of depressive disorders at follow-up by about 20 to 25%[169,170], and in preventing or delaying the onset of about 50% of psychotic disorders in those at high risk for developing a psychotic disorder ([171], see also the influential work in Australia published by McGorry and colleagues, e.g.[172]). Because of these promising results, 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, future research is demanded to expand our repertoire of approaches. These approaches need to be theory-driven and rigorously trialled (*see Section 1 Mechanisms and Section 6 Trials*) to expand the range of mental health disorders that can be addressed. This includes early preventive approaches focussed on infancy and childhood, and also interventions through adolescence, when young people begin to present with many of the common mental health problems that will affect them through adult life.

Particular attention needs to be paid to ensuring that interventions can produce effects that may have lasting benefit for children and adolescents, and significant efforts need to be made to develop or adapt interventions so that they can be used across a range of settings and can be accessible on an international scale[173] (*see Section 2, Mental Health Worldwide*). Preventive, early intervention approaches for mental health problems face particular challenges in terms of demonstrating effectiveness and being applied consistently and thoughtfully to everyday practice in healthcare, however they offer huge potential for health benefit. The existing good examples considered above provide optimism for future developments in this challenging area, *see Panel 11*. However, we still need to look carefully at the limits of effectiveness, and also at the potential for harms caused (for example, potential negative effects of screening and classifying high risk groups and unnecessary

treatment offered to young people with only temporary distress or symptoms, or harmful side effects of individual psychological treatments).

Given that evidence is now accumulating that some preventative psychological treatment approaches aimed at adulthood too do indeed help to (i) prevent, or (ii) delay the onset of disorder, or (iii) reduce the incidence of recurrence of episodes, a focus here opens exciting and important areas for inquiry across populations and disorder types. Insights should be pooled across the age spectrum from the early years to older adults. Whilst there is still a long way to go before we will have widely-available and effective methods of prevention for mental health problems, the rigorous and sustained application of psychological science approaches to these areas of practice offers enormous promise.

Panel 11. Example Directions for Future Research in Prevention and Early Interventions
• When are the optimal times to intervene to prevent mental health problems?
• Who are the key "at-risk" groups to most effectively aim to intervene early or preventatively with?
• What are the potential harmful effects of specific early intervention approaches? • How do we increase the "stickiness" of treatment effects – how do we make them last beyond the end of treatment? • How can we deliver interventions on the scale (including internationally) needed to reach at-risk children and youth? • How can insights from mechanisms of change help prevent or delay disorders, and reduce the recurrence of episodes? • How can we apply insights about prevention across the life span?

5. **Technology**: *Can we transform the availability and efficacy of psychological treatment through new technologies?*

Overview: Technology

Internet-based psychological treatments have made great strides across a broad range of mental health disorders. The rise of eHealth and mHealth approaches that use information technology (e.g., the Internet, virtual reality, serious gaming) and mobile and wireless applications (e.g., text messaging, apps) marks a new era for evolving psychological assessment and treatments. In brief, technological innovations offer considerable possibilities to innovate psychological treatments, to adjust them more to daily life and to the persons using them, and improve access to treatment. Further, such knowledge could be used to better understand how therapies work and to make them better and easier to use, so that more people can benefit from psychological treatments. However, developments should be theory-driven and properly evaluated, and interventions should be less based on traditional face-to-face therapies and be more interactive and based on available technical possibilities.

Internet-based psychological treatments

Dozens of randomized controlled trials have demonstrated the efficacy of Internet-based therapies (*see Panel 12*) for a broad range of mental health problems. A growing number of meta-analyses show that these therapies are effective in the treatment of depression[174], anxiety disorders[175], sleep problems[176], bulimia[175],alcohol problems[178], and problems such as pain and migraine[179]. Current Internet-based treatments can be seen as forms of self-help interventions that are conducted through the Internet, which means that patients learn how to apply a psychological treatment to themselves with the help of a coach or psychologist[101]. Direct comparisons between face-to-face interventions and guided Internet interventions suggest that there are no major differences in efficacy between the two treatment formats[110].

Panel 12. What Do We Mean by New Technologies?

- Internet intervention: A (guided) self-help intervention delivered through the Internet

- A self-help intervention can be defined as a psychological treatment in which the patient takes home a standardized psychological treatment protocol and works through it more or less independently. Self-help interventions can be delivered with (guided self-help) or without human support (self-guided)
- Although internet-based therapies can be defined as any therapy that is delivered with the help of technology (for example through chat sessions, skype, or email), most research has focused on Internet-based self-help interventions. Because most research has been conducted on Internet-based self-help interventions we will focus on these treatments. If we refer to Internet interventions, we mean these treatments, unless we explicitly say otherwise.
- eHealth: the transfer of health resources and health care by electronic means (http://www.who.int/trade/glossary/story021/en; accessed April 15, 2016)
- mHealth: The use of mobile and wireless technologies to support the achievement of health objectives[180].

Advantages of internet interventions. Internet interventions and the trials that have examined them have many advantages. They can save therapist time, reduce waiting lists, allow patients to work at their own pace, abolish the need to schedule appointments with a therapist, save traveling time, reduce the stigma of going to a therapist, and ease psychological help for individuals who are hard of hearing[181]. Furthermore, they may reach patients who cannot be reached with more traditional forms of treatment. Interventions can also be relatively easily adapted to specific target groups, with a wide range of attractive audio-visual information with voices giving instructions in whichever gender, age, accent, language, and perhaps game format the patient prefers. Internet interventions are also probably more cost-effective than face-to-face therapies, but more health economic research is needed to verify this.

From a research perspective these interventions also have numerous advantages. One major advantage is that internet interventions are much easier to conduct than are large randomized controlled trials (RCTs), (*see Section 6, Trials*). Specifically, recruiting patients and conducting Internet interventions is much easier and more efficient than conducting RCTs of traditional face-to-face psychotherapies. Larger randomized trials make it easier to examine effective components of interventions in dismantling studies, to examine moderators

of outcome, and to examine mediators and the working mechanisms of therapies (*see Section 1, Mechanisms*). Such research will stimulate the further development of personalized treatments of mental disorders (*see Section 8, Complexities*). This approach also facilitates research that is traditionally complicated because of the large sample sizes needed, such as prevention trials aimed at the prevention of new cases of mental disorders[182] (*see Section 4, Prevention*).

Limitations of Internet Interventions. This new emerging field of Internet interventions has considerable promise to contribute to a further reduction of the disease burden of mental disorders. But there are also some limitations and challenges that have to be taken into account when this research area is expanded. The quality of interventions that are offered through the Internet is not certain and despite portals for evidence-based Internet therapies such as Beacon (https://beacon.anu.edu.au), the possibility that low quality therapies are offered remains an important threat. Beacon is a webservice at which a panel of health experts categorise, review and rate websites and mobile applications and is part of a suite of self-help programs, developed and delivered by the National Institute for Mental Health Research at the Australian National University (although it is unfortunately not currently being updated). It is also known that drop-out rates are higher in Internet-based interventions than in face-to-face therapies[183] and it is not known whether patients who drop out get worse because of the intervention. It is sometimes assumed that internet interventions may affect the therapeutic alliance between therapists and patients, but most evidence suggests that therapies through the internet are at least equivalent to face-to-face therapy in terms of therapeutic alliance[184]. Furthermore, more research should be done on the long-term effects of Internet interventions, because relatively little research has focused on that (although the same is true for face-to-face psychological treatments). We also acknowledge that Internet interventions may also have unknown disadvantages, such as misunderstandings due to reduced communication channels in unguided interventions and schematization of contents. Finally, data security as well as privacy should be well-guarded for any intervention that is offered through the Internet, and this will only become more important when other new technologies (see below) become integrated into online interventions.

Furthermore, despite increasing access, we acknowledge that 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 LAMIC countries access to the internet and/or mobile phone is expanding exponentially (*see Section 2, Mental Health Worldwide*), although creative solutions (e.g., regarding literacy) may need to be taken into consideration.

Other technological opportunities

Most psychological treatment research has been conducted with what could be called "traditional" Internet interventions. In these interventions, patients sit behind their computer and work through self-help materials. Such self-help materials have often been very close in content to face-to-face delivered psychological therapy (e.g., CBT). Accordingly, it is as if hard-copy paper manuals are simply converted to computerised form sometimes with simple additional content such as video clips. But technological developments are occurring rapidly, and such advancements will no doubt expand the repertoire of learning methods (e.g., Serious Gaming, see below). Interventions can increasingly be offered through smartphones, smart watches, google glasses, virtual reality headsets, and all kinds of other innovative devices. Many of these devices have the advantage that they can be worn during daily life and can also collect information during daily life ("ecological momentary assessment"[185] (*see also Section 8, Complexities*). Such information may considerably improve prediction models for individual patients and thus potentially improve treatments and increase the effect sizes of existing treatments. Computerized Adaptive Testing techniques assess symptoms online with greater sensitivity and specificity from fewer items[186]. Several "virtual reality" treatments have also been developed in recent years, mainly for anxiety disorders. In virtual reality therapies patients are not confronted with the real anxiety-provoking stimuli but with their virtual counterparts using real-time computer graphics, body tracking devices and other sensory input devices[187]. There is evidence that virtual reality interventions may be effective in the treatment of anxiety disorders[188,189] although many of the trials conducted to date are small and are of suboptimal quality. A considerable number of studies have demonstrated that telephone-supported therapies are effective in the treatment of common mental disorders[190].

There is a rapid proliferation of mental health 'apps' which aim to offer a range of psychological interventions[191]. However, most currently available technology-based interventions (e.g., health apps) within eHealth and mHealth are characterized by lack of

health behaviour theory and evidence for the effectiveness[192]. Critical directions for future research will be to develop theory-driven interventions and evaluate their effectiveness - since the vast majority are yet to be tested in randomised controlled trials (although there are some exceptions)[193,194] and may need specific adaptations to the design of randomized trials because of rapid technological developments[195]. Risks are also posed by widely available and untested products. In this young field, while efforts have started, the continued development of international approaches is needed to develop regulated approaches and procedures.

The format of new technologies may allow new treatment techniques to be developed that were not part of pre-existing face-to-face psychological treatments (e.g., the traditional psychological treatment manuals converted by most Internet-based therapy to date) but offer novel information processing options (e.g., virtual reality exposure, and possibly interpretation bias training). Serious gaming, such as the Sparx program, also opens opportunities for interdisciplinary research and new methods of treatment delivery[196]. Serious games refer to those games with a purpose other than providing entertainment, in this case the delivery of a psychological treatment using game principles. Sparx is an interactive fantasy game designed to deliver cognitive behavioural therapy for the treatment of adolescents seeking help for depression.

It is also very well possible that at some point the automated support of these new technologies can in some cases replace the therapist altogether ('therapist-free therapy'[197]), and lead to better, personalised treatments (*see also Section 8, Complexities*). New technologies can also be useful in predicting the development and outcome of mental disorders. For example, mobile phones are available to monitor relationships between psychological risk and suicide ideation[198], and there is evidence that certain phrases and the use of personal pronouns for example predict depression status in blogs (*see also Section 9, Suicide*), although we acknowledge that this may raise ethical concerns[198]. Because enormous quantities of data can be collected through mobile phones and other devices and can be connected with existing databases, datamining techniques may be helpful to predict the onset and course of mental disorders. Such data could aid the development of innovative psychological interventions that are much more integrated into the new technologies which are assimilated into the daily lives of patients. However, technology and data alone will not

suffice – endeavours are more likely to succeed if they are embedded in a sound theoretical framework to drive hypothesis alongside clinical knowledge.

In brief, technological innovations offer considerable possibilities to innovate psychological treatments (*see also Panel 13*), to adjust them more to daily life and to the persons using them, and to use the knowledge to better understand how therapies work and to make them better and easier to use, so that more people can benefit from psychological treatments across the age range and worldwide.

Panel 13. Example directions for Future Research with New Technologies for Psychological Treatments
• Treatment and theory development: health behaviour theory informed technological treatment innovation across all areas of psychological treatments
• Treatment evaluation: trials to evaluate the effectiveness of new products such as apps
• Learning: Maximising and innovating learning methods during psychological treatment by fresh means of for example skills learning, habit change etc (e.g., via Serious Gaming)
• Devices: the use of new technologies, like avatars, smart watches, Google glass, and other devices into existing psychological treatments to facilitate delivery and improve outcomes
• Harnessing new technologies to advance methods by which to examine causal mechanisms, refine treatments, and derive mechanistically-driven treatment approaches
• Health monitoring: to enable big data capture to predict the onset and course of mental disorders
• Personalisation of technology based interventions
• Technologically aided preventative treatment approaches adapted across the age range

6. **Trials** *to Evaluate Psychological Therapies*

Overview: Trials

There are several key issues in the design and conduct of clinical trials for the evaluation of psychological therapies, and addressing these is essential for the development and innovation of evidence-based psychological therapies. These issues present some specific challenges, given the complexities of both the therapies being evaluated and the populations who are receiving them, as well as a number of opportunities for improvement. The challenges include improvements in standards for reporting clinical trials, specification of treatment protocols and inclusion/exclusion criteria, choice of outcome measures, measurement of adverse effects and preventing 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 developing methodologies for achieving consensus regarding research questions and outcome measures, the development of new methods for analysis of mediators and mechanisms and innovations in design of clinical trials (such as adaptive trial designs and mixed methods approaches that embed qualitative studies).

Introduction

There are several key issues in the design and conduct of clinical trials for the evaluation of psychological therapies. This is an area that is essential to the agenda for development and innovation in evidence-based psychological therapies, which present some specific challenges, given the complexities of both the therapies being evaluated and the populations who are receiving them, as well as a number of opportunities for improvement. These challenges and opportunities will be considered in the context of a current feasibility study (the COMPARE trial, ISRCTN06022197) and the potential for a subsequent definitive trial to evaluate cognitive behaviour therapy for people with psychosis in direct comparison to antipsychotic medication and a combined treatment, which is a research recommendation in the UK NICE guideline for treatment of psychosis in children and young people[199]. This trial has been chosen because it is complex and challenging to conduct for a variety of

reasons that will be described, and as such, illustrates many of the problems and potential solutions.

Other important issues for psychotherapy trials include the selection of control conditions and outcome measures, the role of public and patient involvement, the inclusion of moderation and mediation analyses to facilitate identification and refinement of mechanisms and the development of new, innovative methods that are fit for purpose to answer the important questions that have been identified, *see also Panel 14.*

Panel 14. What Terms are Used in the Context of Clinical Trials?

- Clinical trial: An experiment to determine whether a treatment works, usually determined by examining effects on outcome measures. This can include:
  - A feasibility study: this is a small clinical trial which is conducted in order to determine whether it is feasible to do a larger clinical trial, which has sufficient statistical power to definitively answer a research question about treatment effectiveness. It focuses on the question of whether such a study can be done.
  - A pilot study: this is a small version of the main clinical trial, which focuses on evaluating the trial processes, such as recruitment, randomisation, treatment protocols and follow-up assessments. These trials can be internal pilots, where the data collected contributes to the larger definitive trial assuming there are no changes required, or an external pilot, where the data are analysed and set aside.
  - A randomised controlled trial: this is a study in which participants are allocated to a particular condition (usually a treatment 'arm') on the basis of random assignment in order to produce an equal distribution of measured and, crucially, unmeasured variables. Also, it ensures future treatment allocations are hidden from recruiters. The 'controlled' nature refers to using comparators (the conditions to which an experimental treatment is compared); these often include the best available treatment, treatment as usual (what routinely happens in clinical services), a treatment designed to control for factors such

as empathic human contact or a treatment with the putative 'active' ingredient removed (known as 'dismantling' designs).

- Clinical Trials Units: these are specialist units that have expertise in centrally coordinating multisite clinical trials, in addition to trial design, data management, and trial statistics and health economics
- CONSORT: The Consolidated Standards of Reporting Trials (CONSORT) Statement is an evidence-based guideline[200], based on a systematic review of evidence regarding aspects of trial design and conduct that could contribute to bias. Using consensus methods, the developers produced a checklist of 25 items and a flow diagram, which aims to minimize bias and improve reporting of clinical trials
- Sources of bias: There are many potential sources of bias that can influence the validity of a clinical trial. These include allocation concealment (whether future randomization could be guessed), adequate blinding of participants, personnel, and outcome assessors (although the first two of these are nearly impossible to achieve in a trial of face-to- face talking therapies, (*though see also section 6 Internet therapies*), amount of missing data and selective reporting of outcomes
- Blinding: This refers to whether participants or staff are aware of the treatment allocation (e.g. do they know whether they are receiving CBT or treatment as usual). Note single blinding versus double blinding is a key difference between psychological versus pharmacological trials.
- Protocolised treatment: A protocolised treatment is an attempt to standardize the delivery of a psychological therapy. It is often characterized by required processes, procedures and milestones as well as those that are prohibited. Some treatment protocols are very specific, prescribing the content of each session in a strict, at times modularised manner, whereas others are more flexible in order to account for the idiosyncratic, often complex, nature of presenting difficulties. The more rigid a trial protocol is, the easier it is to assess treatment fidelity and allow replication of the study.

The need to improve clinical trial methodology

There is a need to improve the scientific rigor and transparency of clinical trials of psychological therapies, given that these are the cornerstone of evidence-based approaches to decisions about access to healthcare. In the field of mental health, such trials often have significant methodological shortcomings that result in low quality evidence. For example, in relation to CBT for people with psychosis, many of the earlier clinical trials were subject to a variety of problems: for example, many were not registered, which is a problem in the whole field of psychotherapy research[201]. This means that we cannot be certain that their primary outcomes were those originally intended, and raises the possibility of selective reporting of outcomes (i.e., focusing on those that were statistically significant), or even that negative trials remain unpublished; many did not attempt to maintain blinding in the raters, which increases the likelihood of bias; 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 expert trial methodologists and statisticians and innovators in psychological therapy development. For example, accredited 'Clinical Trials Units', with their extensive experience of trial design and conduct, could coordinate with academic methodologists who are at the cutting edge of developments in trial statistics and methodologies[202]. In the past decade, for psychological treatment trials, in line with trials in other domains, there has been substantial improvement in the adoption of clinical trial registration and pre-specification of primary outcome including CONSORT criteria. Indeed, such issues are increasingly required by the leading journals and by ethical review boards. Particular adaptions for psychological trials need to be further developed, e.g., around issues such as double blinding which cannot be maintained with a therapist-delivered psychological treatment.

Relatedly, the potential negative effects of psychotherapy are increasingly being recognised and there is a need to document deterioration and adverse events during treatment. Negative effects that require recording range from worsening of existing symptoms to issues such as novel symptoms, poor therapeutic relationship and perceived coercion[203]. Such adverse events are present both in traditional psychotherapies as well as internet-based interventions[204]. A procedural model and checklist are available for clinicians and researchers, and the detection and management of such adverse events in treatment trials is

considered a sign of good rather than bad practice[205]. Further research is needed so that formalized measures of possible harms/"side effects" of treatment trials are the rule rather the exception in psychotherapy research (see[206,207]).

To ensure that psychological therapy trials are credible, it is important to meet the minimum standards expected from other fields (e.g., pharmaceutical trials). However, we also have an opportunity to develop our own standards, which ensure superior trial design, conduct and reporting, that other fields could aspire to meet. Over more than a decade, researchers who have studied psychological therapy in trials have embraced trial registration, pre-specification of statistical analysis plans and trial protocols, independence of statistical analyses from the psychological innovators and adherence to CONSORT's reporting recommendations[200]. Yet, not all criteria can be met given that, for instance, double blinding in these types of studies is not usually possible. Some of these factors inherently bias the judgement of quality of evidence against psychological therapies in comparison to drug trials. For example, drug trials are usually judged to be superior to psychological therapies on the issue of blinding, since in a double blind trial it is alleged that the clinician, the independent assessor and the participant are unaware of whether they are receiving active drug or placebo, whereas in a psychotherapy trial, both clinician and participant are aware of what treatment is being delivered and received.

It is interesting to note that the issue of double blinding can be problematic not only for psychological but also pharmacological treatments – despite best intentions, aspects of the treatments can break the blind. If we consider for example antipsychotic medication, it is clear that an allegedly double blind trial would be almost impossible to achieve, since there is compelling evidence regarding the rapidly observable adverse effects of both first and second generation antipsychotics (e.g., rapid and dramatic weight gain and parkinsonian side effects), which may result in clinicians and raters being unblinded. Another possibility is that subjective cognitive effects[208] may be likely to unblind participants.

A set of reporting standards that are specifically tailored to psychological therapy trials are being developed as an extension of the original CONSORT guidelines[209]. These include recommendations to improve internal and external validity, address measurement issues (psychological therapy trials often have many measures, many of which assess latent constructs), improve reporting of recruitment processes and representativeness of participant

samples and increase contextual information such as factors that helped or hindered the interventions. More broadly, further research on trials methodology (for example, on how to deal with the issue of blindness) will be an important area of future enquiry.

Reducing conflicts of interest

Some have argued that the conduct of a clinical trial by the developer of a psychological therapy is equivalent in terms of bias to industry-sponsored trials. In accord, investigator allegiance effects have been observed in psychological therapy trials[210, 211]. On the other hand, the level of independent scrutiny from peer review by methodological experts and the obstacles to obtaining funding to conduct the trial are likely to be greater for psychological therapies than for industry-sponsored pharmaceutical trials, since psychological therapy trials are usually publicly funded by research councils or national institutes. That is, although trials of psychological therapies may be conceived and conducted by the originator, they are rarely funded by the originator. Nonetheless, steps can be taken to reduce bias. These include a declaration of interests (personal financial interests such as training fees, book royalties and non-financial interests). The registration of protocols, pre-specification of statistical analysis plans, and involvement of independent methodologists in trial design and data analysis would also mitigate against such bias. Trial Steering Committees and Data Monitoring Committees with independent clinical, statistical and service user representation also increase confidence and minimise bias. These committees can provide constructive criticism and protect the safety of participants and the scientific integrity of the trial. Expertise in all relevant approaches is important for trials that compare two or more therapies; for example, the COMPARE trial team includes expertise in both CBT and antipsychotic medication.

Inclusion and exclusion criteria

The selection and justification of inclusion and exclusion criteria are vital to good trial design. They 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 entry criteria, not allowing

several or at least specific comorbid conditions (e.g., other mental health problems, physical health issues, drug or alcohol use). This is difficult to justify when the clinical reality is one of complexity, with comorbidity being the norm (see also section 8 *Complexity*). More recent trials that have evaluated CBT for psychosis have, in general, been good in terms of generalisability, allowing for inclusion of participants who meet such broad criteria (this is also true for trials of psychological therapy for depression[212]). Even trials that have focused on mechanisms of change, such as whether reducing worry processes results in reduction in paranoid thinking, have allowed significant comorbidities[213]. However, there may be a trade-off between clinical pragmatism (broad entry criteria) and the ability to scrutinise specific mechanisms within a trial. One exception to this is trials that attempt to address transdiagnostic processes by targeting a specific mechanism, such as modification of attentional biases or extended perseverative processing, or a specific problem, such as sleep difficulties or irritability, across diagnostic groups. This approach offers potential advantages in terms of recruitment, generalisability and implementation in services (see *Section 8 Complexity*, for further discussion of these issues).

Better integration of research trials within clinical settings would also allow improvements in the generalisability of results to the real world. One goal is for every individual who attends a hospital clinic, 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, in cases in which there are genuine uncertainties (e.g., what 'dose' of CBT for psychosis is required), all willing participants could be randomised to different treatment duration options (e.g., up to 16 or 32 sessions).

Choice of control condition

There is considerable debate about appropriate control conditions; for example, many argue that "treatment as usual (TAU)" is not appropriate since it may be highly variable and at times include access to the treatment being provided in the experimental arm. The use of an active control condition, which reduces confounds of nonspecific factors such as attention, warmth, human relationships etc. is often recommended; however, this may oversimplify the issue of therapeutic relationship – itself a topic of research enquiry and debate about its

importance. The provision of an alternative therapy can raise other confounds such as the 'match' between therapist and participant and the ability of a therapist to switch between, and adhere to, different treatment protocols when it is likely they have greater skill and allegiance in relation to one or the other. There are ways to deal with such issues – for example, multiple therapists providing each active treatment condition. Indeed, numerous trials have succeeded in using therapists from both background treatments (e.g., CBT and psychodynamic) who deliver both treatments. Nonetheless, there are many issues that arise in conducting trials which continue to require thought. For example, in a trial in which CBT for psychosis was compared with befriending, the befriending condition was delivered by trained cognitive therapists[214]. This could be problematic for a number of reasons, including the possibility that the trained cognitive therapists had significantly better therapeutic skills and training, or were biased because they are not allegiant to this approach. Most studies have tried to ensure that expert therapists deliver both treatment modalities (e.g.,[215,216]), such that different trial sites have different expertise/allegiance, but deliver all therapies. Furthermore, there may be differences between conditions in the effectiveness of psychological placebos. For instance, the effects of non-directive supportive therapy are comparable to CBT and interpersonal psychotherapy for depression[217], although CBT is superior in the case of psychosis[218] and anxiety disorders.

Clinical psychological trial experts such as Kazdin have formulated models to help to guide the type of trial needed to address the type of question asked – and this is a ripe area for continued methodological development. Design solutions will depend, in part, on the specific research question; for example, if the pragmatic question is whether something works better than current provision, then a two-arm trial for comparison against a specified and protocolised treatment as usual that utilises best current practice may be ideal (for example, CBT plus monthly engagement and monitoring of current difficulties compared to monthly engagement and monitoring alone[219]). If the question is whether one form of psychotherapy is better than another, then a head to head comparison may be required (for example, if CBT was to be compared to acceptance and commitment therapy, which has recently been suggested as an alternative to CBT). If the question is why a treatment works or whether a specific element is necessary, then a therapy which controls for specified factors (such as human contact) but in which the active ingredient has been removed may be indicated (for

example, CBT compared to befriending for people with psychosis[214]). Meta-analyses would suggest that waiting list controls should probably be avoided, since they can lead to inflated effects sizes for the experimental treatment, possibly by leading people to abandon efforts to solve problems or recover independently because they are waiting for therapy[43].

Outcome measures

Most trial methodologists would recommend a single primary outcome and a single time point (e.g., total symptoms at final follow-up assessment) which can sit uncomfortably with basic aspects of psychological assessment – such as the need for multiple assessments of a construct for validity and multiple time points for reliability. However, there may be times when more than one primary outcome is justified (e.g., if there is considerable disagreement between stakeholders, such as clinicians and service users), although it is important to note that multiple primary outcomes have consequences for power calculations, requiring larger sample sizes. In addition, maximising the use of data obtained at multiple time-points in order to obtain the most accurate estimate of treatment effects over the full follow-up duration can be achieved by specifying an analysis involving all available data for a particular measure, which may be preferable to anchoring judgements regarding efficacy to a single assessment point.

There is often debate about which is the most important outcome. For people with psychosis, there is debate regarding whether clinical outcomes (e.g., psychiatric symptoms) or social outcomes (e.g., recovery, social functioning and quality of life) are the most important. The answer to this question largely depends upon who is asked, such that clinicians often prefer the former and service users prefer the latter[220]. In the COMPARE trial, being a feasibility trial, all of the above are included and all participants are asked to rank the outcome measures in order of importance to them in order to inform a subsequent definitive trial. A definitive trial could require two primary outcomes: a measure of psychiatric symptoms (e.g., PANSS total), which would allow clinicians to judge findings in relation to the existing literature, and a measure of self-judged recovery or objective quality of life which would allow service users to make informed choices on the basis of their own priorities. Reliance on subjective measures alone can be a limitation - convergent objective outcomes such as behavioural, cognitive or physiological or neural response to specific

stimuli may bring methodological advantages (*see also Section 5, Technology and Section 1 Mechanisms*).

Consensus regarding outcome measures for a specific condition would also enable large "individual participant data" meta-analyses[221-223], which can hopefully inform the moderators and mediators of treatment response (i.e., what works for whom; *see also Section 8, Complexities*), and integration with and adoption of routinely collected service outcome data would also help facilitate this. There is a UK initiative that aims to establish agreement about core outcome sets for particular health conditions (COMET: http://www.comet-initiative.org/about/overview); there is work underway to establish consensus about a core outcome set for evaluations of interventions for people with psychosis[224]. It is unclear whether a detailed interviewer administered rating scale, which may provide rich data and be more engaging for participants, or a self-report measure, which may be more reliable (since there is no need for inter-rater reliability across sites and staff) and avoids rater bias, are preferable. Again, a combination of both, so long as they are clearly pre-specified as dual primary outcomes, could represent a reasonable solution that maximises the benefits of both approaches; if a trial with dual primary outcomes demonstrated consistency across them, then this would increase confidence in findings.

Another important consideration when selecting outcomes is the length of the overall battery of assessments. Psychological therapy trials are notorious for the inclusion of numerous secondary outcome measures, which may be of significant interest. However, the greater the assessment burden on participants, the more likely it is to affect retention in the trial and subsequently result in missing data in the outcomes. Limiting the selection of outcome measures is likely to minimise attrition. T this is extremely important since high levels of attrition represents a significant threat to the internal validity of the trial (although we acknowledge that limiting measurement also limits opportunities for understanding processes of change). Similarly, agreement regarding the frequency of assessment occasions and length of follow-up would help to minimise attrition and also facilitate the pooling of data and the capacity for comparisons across trials. However, there is a trade-off between collecting meaningful data that will permit identification of what works for whom across a broad range of outcomes and facilitate mediation and moderation analyses, and ensuring that participant retention is not jeopardised. The involvement of service users who would be

eligible for trial participation in trial design, as well as ensuring pilot and feasibility work has been done, are both likely to be useful strategies in achieving this balance. Another possibility for minimising burden and maximising both ecological validity and multiple measurements of outcomes is to use Experience Sampling Method (ESM) or Ecological Momentary Assessment data as outcomes. This would allow reporting of symptoms, emotions and indicators of functioning, such as time use in daily life as primary outcomes in clinical trials (see section 8 Complexity for further discussion of ESM).In addition to the measurement of wanted effects, such as improvement in symptoms or quality of life, it is also important to measure unwanted effects and report serious adverse events (SAEs) that are reported to ethics committees as part of safety monitoring. Historically, trials of psychological therapies have been poor at both monitoring hypothesised side effects and deterioration and reporting SAEs[207]. Several recent trials of CBT for psychosis have attempted to measure adverse effects via qualitative and quantitative approaches. There have been suggestions that CBT for psychosis may be associated with increasing stigma, encouraging deterioration or destabilisation or leading to SAEs such as hospitalisation. However, the trials that have measured this have demonstrated the opposite when compared to control conditions[219,225]. This is especially surprising when the inbuilt detection bias is taken into account (therapists may have weekly contact with a participant, whereas raters may only have contact at baseline, end of treatment and follow-up, which clearly reduces the likelihood of detection of SAEs).

Public and patient involvement

Public and patient involvement[226, 227] is another area that can help to improve the conduct of psychological therapy trials. People with mental health difficulties can obviously provide unique insights into to improve clinical trials, including identification of the most important and relevant research questions, possibly via consultancy groups (which was the case for the COMPARE trial), via priority setting partnerships (PSPs) that identify and prioritise the top ten unanswered questions (the James Lind Alliance facilitate the development of PSPs; see http://www.jla.nihr.ac.uk/), which has been done for the treatment uncertainties related to a diagnosis of schizophrenia[228], or by the use of Delphi methods to establish consensus on topics with experts by experience (the COMPARE trial was also

informed by Delphi studies of people with psychosis on both defining recovery[229] and identifying treatment priorities and preferences[230]).

The choice of research question via public/patient involvement is crucial to subsequent trial design. For example, a definitive trial of CBT compared with antipsychotics would need to decide whether the most important question is one of superiority (e.g., is combined therapy superior to monotherapies), one of equivalence (which would enable choice) or non-inferiority (which may indicate one treatment or another given the differences in adverse effect profiles, although this will always be dependent on individual choice, since what is an acceptable side effect will vary considerably between people). Public and patient involvement can also help with the selection of appropriate outcome measures and decisions about what should be primary versus secondary outcomes, as described above. In addition, the assessment of acceptability of psychological therapies, as well as exploration of potential adverse effects, can be helpfully informed by embedded qualitative interviews and analyses that can be user-led (again, the COMPARE trial incorporates such a study). Finally, the involvement of service users as staff and, ideally, co-applicants and investigators, should ensure meaningful participation in all phases of trial design, conduct and reporting (COMPARE has two service user co-investigators/grant holders).

Mechanisms and mediators of change

Trial design should also attempt to facilitate the identification of potential mechanisms and mediators of change (*see Section 1, Mechanisms*), as well as moderators of treatment effects - in order to inform how a treatment works, what components are necessary and sufficient and what works for whom. This approach will help to improve and refine treatments, make them more efficient and permit true informed choice for service users and carers. The identification of mechanisms could be built into all clinical trials, which would allow pooling of data, although this would also require some 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 as well as any between-group predictions.

The identification of mediators and moderators also requires considerable thought at the planning stage to ensure that the appropriate factors are measured at the appropriate time

points. The development of new statistical methods for the analysis of mediation and moderation should also help with the accurate identification of mechanisms of change and mediators of treatment outcome. Traditional approaches to mediation analysis[231] assume that confounding due to an unmeasured variable being responsible for changes in both mechanism and outcome is absent, which is problematic. More recent developments, such as attempting to measure and adjust for all important confounders[232] or attempting to effectively adjust for unmeasured confounders (hidden confounding) using instrumental variable-based methods employing analyses based on principal stratification[233] provide statistical tools that may be better suited to this purpose. Recent examples relevant to CBT for psychosis include the finding that participants with a psychosocial causal explanation of their difficulties may be more likely to engage with and benefit from CBT[234] and that participants with a good therapeutic alliance with their therapist are likely to benefit from a higher number of CBT sessions, whereas those with a poor alliance may be more likely to experience harm from a higher number of session[235]. See also *Section 8, Complexity* for a related discussion regarding personalization.

Innovation in trial design and methodology

The wider context surrounding an individual trial is important to consider. The design of clinical trials by consideration of the factors outlined above should facilitate the subsequent pooling of data (e.g., standard approaches to outcome and mechanism measurement, timing of assessments, length of follow-up, treatments that are well operationalised, inclusion and exclusion criteria that reflect real-world populations). If consensus regarding such issues can be obtained, this would permit meta-analytic approaches that could represent a sensible long-term approach to provision of definitive answers to important research questions. 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 (i.e., whether the included trials were designed to answer equivalent questions). Therefore, designing high quality trials with a view to the longer term perspective could provide an opportunity to help such meta-analyses benefit from better trials suitable for this purpose. Collaboration between research groups, investigators and methodologists with regard to

future pooling of data could be facilitated by the establishment of collective research groups recognised by group authorship, which would incentivise such involvement and co-operation. There is currently such an initiative in attempting to pool data from all CBT for psychosis trials in order to conduct an individual level data meta-analysis that will attempt to examine individual moderators of treatment response.

At times, there is a need for alternative approaches to the traditional two-arm randomised controlled trial, such as multi-arm multi-stage trials[236]. The two-arm RCT has been adopted as the gold standard from methods used to evaluate pharmacological interventions (mostly industry sponsored drug trials). However, many of the lessons learnt on the basis of such drug trials are applicable to improving the reliability and validity of research to evaluate psychological therapies, including the need to minimise bias by avoiding selective reporting, maintaining blinding, independence of randomisation, minimising attrition, appropriate selection of participants and comparators and reporting in line with CONSORT recommendations[237, 238].

The use and further development of new methodologies including adaptive designs, preference trials, and sequential, multiple assignment, randomised trials (SMART trials) should facilitate trials that are fit for purpose to answer important questions. Such methodologies will permit better generalisability to routine practice and more ethical and efficient trial conduct. For example, a SMART permitting re-randomisation for non-responders to CBT or antipsychotics to the other monotherapy or the combination, after a relatively short period of time, would confer advantages; a preference trial would maximise recruitment in a field in which both service users and clinicians may have strong treatment preferences and opinions about talking therapy and/or medication that would jeopardise recruitment, generalisability and/or adherence to allocation in a standard RCT; an adaptive design with a planned and pre-specified interim analysis may permit the early abandonment of an arm that may be inferior. Again, the linkage between experts in trial design and analysis, experts in the development of psychological therapies and experts by lived experience will be central to making such progress. Another development that could maximise both availability of trial participation for service users and utilisation of research opportunities to inform clinical practice and policy making is the "cohort multiple randomised controlled trial" design[239]. This approach allows several RCTs to be conducted

simultaneously within a larger cohort or register of patients. For each RCT, all eligible people in the cohort are identified, and then some are randomly selected to be offered the experimental trial intervention. The outcomes in the randomly selected participants are then compared with the outcomes in those who were eligible but not selected (i.e. 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 health problems and the likelihood of collecting data on long term outcomes. This approach would be ideally suited to mental health problems that are seen within specialist teams (e.g. 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. Trials within cohorts could be the ideal solution to making the most of opportunities to utilise large data sets of routinely collected outcomes while still retaining randomisation as the cornerstone of trial methodology and statistical analyses.

Finally, it is important to recognise that research to identify successful interventions is not just about RCTs (the seminal BMJ paper[240] demonstrating the lack of trial evidence for parachutes illustrates this perfectly), and clinical trials should complement other types of research questions and evidence. An example of this is the need for RCTs to include embedded qualitative studies that seek to obtain rich data that will allow triangulation with quantitative outcomes as well as inform our understanding of active treatment processes and the generation of new hypotheses to test empirically. For example, 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, conducted and analysed by researchers with lived experience of psychosis), which has the potential to inform the design of a definitive trial in relation to selection and recruitment of participants, entry and exclusion criteria, outcome measures and treatment protocols.

Conclusion

If all of the above can be achieved, this will increase our ability to identify and answer the most important questions, conduct trials with greater reliability and validity and, therefore, increase the confidence in and acceptance of their findings (*see Panel 15*). In

particular, developments in three areas could dramatically improve trial quality in the evaluation of psychological therapies. An ability to better detect responders and non-responders would allow us to identify what works for whom (see *Section 8, Complexity*); this could be achieved by ensuring better selection of measures, incorporation of experience sampling or momentary assessment in the early phases of a trial (see *Section 5, Technology*), 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. Meaningful involvement of service users and carers will allow us to identify the appropriate research questions and methods, ensure relevance of outcomes (including adverse effects) and improve retention of participants. Finally, facilitation of large scale data sets, whether by consensus regarding design considerations and measures that enable pooling of data, developments in individual participant data meta-analyses or the use of routinely collected service data, will promote confidence in the results of our clinical trials.

Panel 15. Directions and Priorities for Future Research in Clinical Trials of Psychological Treatments
• We need to establish consensus amongst stakeholders (the innovators and developers of psychological treatments, service users and methodologists) regarding outcome measures, appropriate scheduling of assessments and length of follow-ups
• We need to routinely build into the design of clinical trials the ability to analyse for mechanisms (see section 1 Mechanisms)
• We need to engage with commissioners and providers of psychological services to maximize the likelihood that such services can facilitate the collection of data and build in trials where there is uncertainty
• We need to ensure quality trial design and valid, reliable analysis of data by routine, early engagement with Clinical Trials Units, trails registration for all trials including production of pre-specified Statistical Analysis Plans, and ensure that data analysis adheres to such plans and is conducted by independent specialists in trial statistics

• We need to 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
• We need to carefully match comparators to the specific research questions that trials are seeking to answer • We need to measure unwanted effects as well as wanted effects, and arrive at a consensus about how to measure and report adverse effects • We need to increase our use of innovative trial designs that maximize value for money, value for participant input and reflect clinical practice; such designs include adaptive trials, multiple trials within cohorts, SMART trials and preference trials. Different designs will be suited to different research questions and clinical contexts • We need to encourage career paths for those focussed on advancing methods in psychological treatment trial design methodology, statistics and so forth

7. **Training**: *Can we foster a vision for interdisciplinary training across mental health sciences to improve psychological treatments?*

Overview: Training

In this section we discuss why we should endeavour to improve the links between clinical psychology, psychiatry and basic research training, and make some proposals about how this might be achieved. We review some early successes in innovation in psychological treatments when basic researchers and clinicians have worked together, and discuss the reasons that such fruitful interaction has decreased in recent years. We offer some concrete recommendations to bridge the gap between clinical practice and basic research relating to psychological interventions.

Historical shifts in interdisciplinary training

In 1949 the American Psychological Association convened the famous Boulder (Colorado) Conference on Graduate Education in Clinical Psychology, in order to agree on a standard model for clinical psychology training in the US. Heavily influenced by the ideas of David Shakow, it adopted a "scientist-practitioner" training framework that encouraged clinical psychologists to use scientific research to inform their treatment[241]. This influential proposal facilitated the development of effective new psychological interventions, which was catalysed by clinicians who performed basic research, and basic researchers who understood the principles of psychological treatments (*see Panel 16*). This confluence of expertise resulted in vital insights into the mechanisms of onset, maintenance and treatment of symptoms of mental health problems, and in some case completely revolutionised the psychological treatments available.

For example, the development of various types of exposure therapy (incorporating response prevention) for anxiety disorders, including phobias, PTSD and OCD, was initially derived from fear extinction research in rodents, which showed a reduction in Pavlovian responses to negatively conditioned stimuli when the aversive outcome was omitted[242, 243] (*see also Section 1, Mechanisms*). Importantly, the focus on response prevention, i.e., encouraging patients suffering from anxiety not to engage in their usual coping strategies

when confronted with an anxiety-provoking stimulus (for example, avoidance for phobias or rituals for OCD), came from the insight that these behaviours can maintain the conditioned association through preventing extinction[244]. This might appear counterintuitive to the patient because, acutely, the prevention of coping behaviours increases anxiety in the short-term, but leads to a reduction in anxiety in the long-term.

In depression, the influential "learned helplessness" model[245], and its later modifications in relation to hopelessness[246], originated from the finding that animals exposed to inescapable aversive stimuli subsequently failed to escape when they had the option to do so[247]. Learned helplessness theory made important contributions to our understanding of risk factors for depression, especially relating to the roles of attributional style and perceived controllability[248]. Moreover, it 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[249].

Panel 16. What Types of Backgrounds do Clinicians and Scientists in Psychological Treatment Research Have?
• Clinical psychologist: Psychological therapist, holding an advanced qualification such as a doctorate (e.g. in the UK DClinPsy, in the USA/Canada PhD or PsyD) or Masters (in most other countries), and usually also an undergraduate qualification in psychology; trained in interventions that relieve psychological distress
• Psychiatrist: Medically qualified doctor who focuses on treating mental health problems; can legally prescribe medication, but may also be trained in delivering psychological interventions
• Basic researcher: Usually a university academic holding a PhD, who conducts research in areas including (but not limited to): experimental psychology, clinical psychology, neuroscience, genetics, physiology, pharmacology, data science, social science, economics

- Clinician scientist / Scientist practitioner: Psychiatrist, clinical psychologist or other mental health practitioner who is also trained in research, often having obtained a PhD

Over the past several decades the links between basic research, clinical psychology and psychiatry have become increasingly weak. There may be multiple reasons for this. One simple fact is that due to the rapid expansion of psychology, psychological treatment researchers and practitioners rarely sit in the same building as, for example, social scientists, economists, neuroscientists or geneticists. This reduces the opportunity to both interact and share ideas, and critically stops potential insights whereby either side can see what they may be missing. 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 limited[2].

Renewing the links between basic research and psychological treatments

Clinicians providing psychological treatments need training in basic research. In most countries, there is relatively little teaching of contemporary basic research (for example, experimental psychology, neuroscience, genetics, physiology, pharmacology, data science, social science, economics) incorporated into the clinical syllabuses in the disciplines of either clinical psychology or psychiatry, or in that of allied professional training in mental health treatment. The US and Canada are notable exceptions, where many clinical psychologists complete a doctoral training programme of at least 5 years' duration, which includes substantial basic research teaching together with an extensive research-based thesis, as well as clinical training. The basic science content provided to psychiatry trainees in the US has also increased in recent decades[250], although there is recognition within the profession that further such training would be desirable[251] (see also the report of the UK Academy of Medical Sciences (2013), "Strengthening academic psychiatry in the UK"). Other than these examples, the basic research content included even in doctoral-level clinical psychology programmes (e.g., PsyD in the US/Canada, which is taken by approximately half of all qualified clinical psychologists in these countries; DClinPsy in the UK) is limited. And in other countries, where a Masters degree is the standard educational qualification required to

become a clinical psychologist (including most of the EU, Australia, New Zealand and South Africa), there is very little basic research content in the curriculum.

This raises a serious concern about the training of clinical mental health researchers of the future. In particular, there is a risk that they will not be equipped with the tools to understand, critically evaluate and utilise basic research that might be relevant to the development of new treatments or preventative strategies. A corollary to this is that there is a danger that psychological interventions may become "stuck in the past" – relying on outdated models that are not supported by contemporary research or theory. This disconnect hinders innovation, and the slow emergence of effective, truly novel psychological treatments in part attests to this. Unless clinical psychologists and psychiatrists are equipped with the skills to evaluate research on both risk factors (for example, genetic and socioeconomic influences) and proximal mechanisms (for example, cognitive and neural processing of information), it is difficult to know where to start thinking about improving preventative strategies and treatments. However, it is also important to bear in mind that learning about a technique may be forgotten if it is not put to use.

Basic researchers need training in clinical conditions and psychological treatments. From the perspective of basic researchers, despite enthusiasm for the notion that their research might contribute to improved mental health treatments, most have a very vague conception of what standard psychological interventions entail, as clinical practice is not generally taught even in undergraduate level psychology degrees. Specifically, many basic researchers have little knowledge of the evidence base supporting standard psychological treatments, and have little opportunity to interact with clinical psychologists, to see therapy in action, or to find out what the common techniques comprise. Indeed, the view that psychological treatments are primarily delivered in the context of an anti-empirical psychoanalytic 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 in our experience[2]. In order to be able to formulate relevant research questions, basic researchers who are interested in contributing to the development of psychological treatments need to understand, at least at a basic level, what the symptoms of mental health problems are (and are not), what the most commonly used and evidence-based psychological

interventions entail and how theoretical models guided their development, and which are the key questions to solve (and which are not) for the future.

Panel 17. An Example of How Neuroscience Might Inform Psychological Intervention Development: Could Understanding Reward Processing in the Brain Help in the Development of New Treatments for Anhedonia?

- Over the past decade there has been renewed interest 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 health conditions including schizophrenia and addiction, as well as being a prominent symptom in neurological disorders such as Parkinson's disease. In depression, anhedonia is associated with a more severe course of illness and poor response to standard antidepressant drug treatment[252].
- Given that anhedonia is intrinsically related to an absence of motivation and hedonic response, it has been proposed that this symptom may arise due to disruption of the brain's reward circuits[253], which have been characterised in extensive detail by neuroscience research over the past 30 years. This is not a new idea – in the 1970s Jeffrey Gray first proposed that symptoms of depression might be explained by changes in a "Behavioural Activation System" (BAS) and a "Behavioural Inhibition System" (BIS)[254], although most depression researchers focused on the BIS and its relationship with neuroticism. However, an important conceptual advance since that time has been the notion that the reward system (BAS) 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 associated with activation in different brain circuits and different neurochemical systems[255].

- This knowledge from neuroscience research has been exploited by clinical psychologists seeking to develop treatments specifically targeted at anhedonia, for example Positive Affect Treatment (PAT)[255]. This builds on Behavioural Activation therapy and Positive Event Scheduling, both effective treatments for depression[256]

that were originally motivated by ideas derived from behaviourism[40], and that are known to increase responsivity in the brain's reward system[257]. Drawing on the finding that reward processing comprises a diverse set of processes, the aim of the PAT package is to increase engagement in, attention to and anticipation of enjoyable activities[16]. Coming from a complementary angle, another novel approach based on cognitive science (here, the processes of mental imagery and interpretation bias) has been to use positive imagery training, which in trials has shown some effect in depressed individuals suffering from anhedonia[258, 259]. This focussed approach has been incoporated into the wider PAT package. While these novel interventions require further evaluation specifically in groups of anhedonic individuals, they provide examples of how scientific discoveries are being used to develop innovative psychological interventions.

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, is able to bridge this growing divide? One priority is to provide more academic training opportunities for trainees and qualified practitioners, and to attract those with a strong aptitude for research. It is notable in the UK that although competition for places on clinical psychology professional doctorate courses is intense, and these recruit highly academically able students, very few subsequently develop a clinical research career. Funding opportunities for academic training of qualified clinical psychologists are highly competitive. That said, major UK research funding bodies, such as the National Institute for Health Research (NIHR) and Medical Research Council (MRC), offer academic training pathways for clinicians. These offer clinically-qualified, non-medical healthcare professionals the chance to undertake a PhD, whilst covering a clinical-level salary, as well as tuition, travel and training costs, and research consumables [footnote #3]. This provides a valuable springboard for a clinical research career, but there is much greater scope

footnote #3: MRC: http://www.mrc.ac.uk/skills-careers/fellowships/clinical-fellowships/clinical-research-training-fellowship-crtf/ NIHR: http://www.nihr.ac.uk/funding/nihr-hee-ica-programme-CDRF.htm

for uptake by clinical psychologists, in part because they may 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, similar to the North American PhD model, which would provide sufficient time to conduct an extensive research project as well as teaching relevant scientific material alongside clinical skills. The PCSAS model recently developed in the US, which emphasizes the science of clinical psychology in training and internships, would also be an effective way of increasing research training opportunities. Another similar training model exists in Australia, in which students are enrolled in a clinical training program and PhD program concurrently – and are awarded both degrees at the conclusion (e.g., Master of Psychology (Clinical) / PhD). This 'combined' degree is offered at The University of New South Wales (UNSW Sydney).

We also need to develop training pathways for mental health researchers that foster an interdisciplinary approach, both between clinical psychology and psychiatry, and between clinical mental health disciplines and a variety of relevant basic research disciplines. One possibility 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 Clinical Academic Fellowships scheme, but we are aware of no equivalent programme for clinical psychologists, in either the UK or other European countries. Multi-skilled 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 meta-professional skills needed to conduct truly interdisciplinary translational research, and to use the knowledge derived from basic research to drive innovation in psychological treatment development.

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 evaluate neuroimaging evidence more effectively because

they understand the potential pitfalls (even though they may never use this technique), basic researchers need a route through which they can learn about what psychological treatments are and how they are theorised to work. This would provide a new generation of researchers who understand the basic principles underlying psychological interventions and could bring a fresh perspective on driving innovation. Simply sitting in the same lectures and tutorials as clinical trainees would increase the opportunity for meaningful interaction, and encourage both clinical and non-clinical students to value input from the other in developing collaborations. While neuroscience and cognitive/experimental psychology students are obvious candidates here, students with backgrounds in a whole range of disciplines, from social science and economics, to computer science and mathematics, through to molecular biology and genetics, may have an interest in psychological interventions and be able to contribute important ideas.

Training the culture to accept more crossover. At present there are structural obstacles to addressing the problems mentioned above that require bold changes in thinking to overcome. These obstacles are present both in terms of clinical accreditation and funding. There is a huge amount of research talent among mental health practitioners that is under-utilised, and perverse incentives, including a possible reduction in salary and a perception that research will not help career progression, often discourage clinicians from entering academia. Importantly, the majority of clinical psychologists and psychiatrists never have the opportunity to gain a rigorous training in basic research, and almost never train alongside each other. 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, meaning that the trainees with the most research potential may be overlooked. Finally, unlike for clinical training (at least in the UK), there is a lack of national recruitment for research training in clinical psychology. These obstacles could be addressed through targeted, longer programmes (similar to the PhD pathway in North America) that include a considerably more substantial research component to the professional doctorate (alongside standard clinical training), and recruit nationally in order to attract the trainees with the greatest research potential. More substantial research projects would also help to address the concern that learning about techniques may be forgotten if not put into practice. It

should be noted that many European clinical psychology training programmes do successfully blend clinical training with basic research – although the relatively short periods of these Masters level programmes and lack of requirement for a doctoral level thesis mean that trainees do not receive the same level of research training as in the North American PhD model. For example, an interesting model of training clinical psychologists in recent years has been pioneered by Karolinska Institutet (Sweden). In this model, clinical education is based within the Department of Clinical Neuroscience, and within a medical university. This has resulted in high level of exposure to both psychology and neuroscience, as well as encouraged awareness of the rich links to physical medicine. Almost all the instructors are involved in research, and a majority have at least 50% of their time devoted to research. Although only a Masters level qualification is required to become a clinical psychologist in Sweden, Karolinska students are poised as a new generation of scientist-practitioners - although naturally not at the same level as students who have completed a longer doctoral level programmes in North America. The development of similar programmes elsewhere would be a positive step, as would an examination of the outcomes of different international models. To our knowledge, such an investigation has not been conducted to date, but would be extremely valuable.

Models of shared research supervision. Another major limiting factor is that those who do enter research training are often only supervised by clinicians, rather than by basic researchers. This divide cuts both ways – as discussed above, there are likewise very few opportunities for basic research trainees who are keen to understand psychological treatments, and to find out what they entail, and the diverse approaches that they adopt. Such exposure to ideas, and understanding how psychological interventions are actually conducted, is an important first step for basic researchers to start to formulate valuable research questions. It would therefore be desirable, where possible, for basic researchers to play a more active role in the supervision of research projects of clinical psychology trainees, and *vice versa*. Encouraging joint doctoral supervision (whether for research or clinical students) between basic researchers and clinical psychologist PIs would be a simple and valuable step in the right direction in this regard. Returning to our Australian example above, at UNSW Sydney, combined clinical / PhD students often conduct their PhD research under the supervision of basic researchers (e.g., behavioural neuroscientists) and test questions with

clear clinical relevance (e.g., on topics such as fear extinction, drug addiction), concurrent with completing their clinical training program. 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 in the future. Finally, even amongst those clinical psychologists who do enter academia, there exist lamentably few forums for exchanging ideas with researchers from other disciplines, as the journals they read and conferences they attend are typically discipline-specific (with some notable exceptions e.g. the annual MQ: Transforming Mental Health annual science meeting; a recent meeting on neuroscientific research into psychological treatments arranged by the European College of Neuropsychopharmacology:https://www.ecnp.eu/publications/presidents_blog/April%202016.aspx; and the annual meeting of the German Association for Psychiatry, Psychotherapy and Psychosomatics: https://www.dgppn.de/). However, in some cases 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[260]. Several studies have tested the possibility that reactivated memories could be disrupted through pharmacological intervention with propranolol[261, 262], with some preliminary indications of positive effects. Other studies have tested whether the reconsolidation of established memories can be disrupted using simple psychological interventions based on cognitive science, with promising results. Engaging in a simple visuospatial task (the computer game Tetris) following memory reactivation was shown to substantially reduce subsequent intrusive memories of experimental trauma[63]. Although this line of research requires considerable further work to demonstrate robust clinical efficacy[263, 264], (*see Section 6, Trials*), it is an intriguing example of the type of cross-pollination of ideas between basic and clinical research that holds promise to lead to improved treatments in the future. Other good examples are to be found in the development of new psychological interventions for anhedonia (*see Panel 17*).

Conclusion

In the 1950s and 60s the development of new psychological interventions transformed the landscape of mental health treatment, creating effective treatments based on novel, empirically testable models. Inspired by ideas drawn from cognitive psychology and behavioural neuroscience, the interventions developed through the collaborations of previous generations of basic researchers and clinicians have become today's treatments of choice. Despite these successes, there is still great room for improvement as response to psychological interventions is highly variable; however, in recent decades the fruitful interaction between those who deliver psychological interventions and those who conduct basic research has waned. This gap 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. Above, we have outlined a number of concrete proposals with the aim of bridging this gap: these have in common the fostering of much more extensive interdisciplinary interaction and dialogue than currently exists, *see also Panel 18.* Through taking these steps, the next generation of clinicians and researchers will be better equipped than their predecessors to use new knowledge to drive the development of novel and more effective psychological treatments and preventative strategies that are needed to improve mental health outcomes.

Panel 18. 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, 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 co-supervision of the research component of professional qualifications by clinical and non-clinical PIs

• Provision of "next steps" seminars focused on academic training as a standard part of mental health clinical training programmes
• Better dissemination of research internship and doctoral funding opportunities for clinical psychologists, such as provided by the Society for a Science of Clinical Psychology (http://www.sscpweb.org/)
• Training programmes on which clinical psychology, psychiatry and basic research trainees have the opportunity to learn alongside each other
• High-level interdisciplinary meetings between basic researchers, clinical psychologists and psychiatrists, 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 understanding among psychological treatment practitioners

8. **Who** should we treat for what and with what? *Embracing the complexity of mental health conditions from personalised models to universal approaches*

Overview: Complexities

Most theoretical models and evidence based psychological treatments have typically been derived for categorically defined specific mental health disorders, such as major depressive disorder, social phobia, or posttraumatic stress disorder. However, the reality of mental health conditions is more complex, and characterised by an enormous individual variety. Heterogeneity in symptomatology is very common and a substantial proportion of individuals suffering from mental health disorders have more than one disorder (co-morbidity). Many more have sub-syndromal symptoms of other conditions, and may 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 health disorders to make further progress in reducing the burden of these disabling conditions. The complexity of mental health disorders is a challenge for research and clinical practice. Solutions to complexity of mental health disorders include both highly individualized 'personalised' approaches as well as 'universal'/'transdiagnostic' approaches that target common mechanisms. However, more studies are needed to examine whether both of these approaches improve the effectiveness of treatments for mental health disorders.

Introduction

Leading clinical guidelines recommend specific treatments for each mental health disorder, usually categorically defined by symptomatology[e.g.265,266]. However, in clinical practice the reality is different. Heterogeneity in symptomatology across mental health conditions is very common[267] and many individuals suffer from more than one mental health disorder (i.e., co-morbidity[268, 269]).

Why are mental health disorders so complex?

Unlike most areas of medicine, mental health disorders are defined predominantly by their symptoms. Lack of knowledge about aetiology contributes to this approach. Symptoms are often considered as manifestations of an underlying latent factor (e.g., sad mood and loss

of interest is caused by an underlying Major Depressive Disorder, MDD). However, these symptoms may not (only) serve as output from 'underlying' processes, but the symptoms can mutually reinforce one other as presumed by the network approach[270]. 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 MDD. Thus, it is uncertain whether these symptoms are indeed manifestations of an underlying factor[270].

Another reason that mental health conditions are more complex to study than physical health conditions is their dimensional nature. Yet, most mental health researchers make use of a categorical model that fits in most health care models to study the effects of treatments. The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5[271]) is a categorical nosology for classification, to detect for instance a depressive episode and to study the effects of a disorder specific treatment for depression such as behavioral activation (see *Section 18*, for a definition of disorder-specific interventions). In the last few years, initiatives have been taken, for instance by the NIMH Research Domain Criteria (RDoC) Initiative, to stimulate research on dimensions of observable behavior and neurobiological measures instead of categorical diagnostic criteria of mental health disorders (*see Section 1*, NIMH Strategic Plan[272]).

An additional complexity factor is individual differences at the level of psychopathology, whether it is categorical or dimensional. Studies using network analyses have yielded new insights in individual variation of psychopathology[267, 273]. These studies indicate that while for some the transition from feeling healthy to fully depressed can be abrupt (categorical) in case of a strongly connected network of symptomatology, for others, for example individuals with a weakly connected network of symptoms, external stressors (such as not being able to pay rent) may lead to an increase in symptomatology - but these symptoms gradually decrease after the stressor is gone[274]. This could also be explained by a dimensional model of psychopathology; that is, individuals with strongly connected networks might be the individuals with higher levels of neuroticism. It is unclear whether these individual differences can be explained by an underlying dimensional mechanism or categorical disorder.

Enormous individual differences have been found in emotional fluctuations – an important component of many mental health disorders - and how emotions change over time within mental health disorders[275]. Furthermore, mental health conditions are complex to study due to the interplay between individual emotions, cognitions and physiology (and other factors) and their interactions with environment. These interactions of cognitions, emotions, and biomarkers by environment change over time (*see also Section 1, Mechanisms* for the differentiation of mechanisms responsible for onset versus mechanisms that are responsible for maintenance of psychopathology), and might also change as a consequence of suffering from a mental health condition. For instance, in depression major life events are consistent risk factors for onset of the first episode (such as the death of a loved one), while less stress (for instance a daily hassle like getting a minor traffic ticket) is required to trigger a subsequent depressive episode for individuals who have experienced one or two previous depressive episodes[276, 277].

Further, a substantial proportion (at least 45%) of people suffering from mental health disorders have more than one disorder, i.e., co-morbidity (*see Panel 19*), while many more have sub-syndromal symptoms of other conditions[268]. The lifetime co-morbidity of common mental health disorders (i.e., anxiety disorders with major depressive disorder) rises up to 73%[269]. The Global Burden of Disease Study 2013 estimated that co-morbidity for acute and chronic diseases and injuries for 188 countries between 1990 and 2013, including co-morbidity of mental health conditions, has risen substantially[278]. Co-morbidity is consistently associated with a greater demand for professional help, a poorer prognosis, greater interference with everyday life, and higher suicide rates[279-284]. Better understanding of co-morbidity is crucial for knowledge on etiology and to improve psychological treatments for all mental health disorders.

Heterogeneity and co-morbidity have been considered in some fields[285-290]. Dimensional models have been proposed to explain co-morbidity, and mostly suggest shared factors for the concurrent disorders (such as neuroticism[291]), and some dimensional models add specific factors that differentiate among disorders[e.g.291-293]. For instance, the dimensional tri-level hierarchical model of anxiety and depression includes a shared higher level factor for anxiety and depression (i.e., general distress), two additional factors that are at an intermediate level in terms of specificity for anxiety and depression (i.e., anxious-misery and

fears that explain covariation in positive affect, anhedonia, sad mood and social fears and fears to explain covariation in social fears, fears of specific stimuli, fear of interoceptive sensations, and agoraphobic fears), and five additional specific unique factors for depression and anxiety disorders (depression, fears of specific stimuli, anxious arousal, social fears and interoceptive/agoraphobic fears)[294]. For example, as shown in Figure 1 the dimensional tri-level hierarchical model of co-morbidity between MDD and generalized anxiety disorders (GAD) according to this model I (as indicated by the black boxes and black lines) is explained by general distress, and at an intermediate level by anxious-misery (e.g., anhedonia and depression), and at low level by specific factors (e.g., depression and anxious arousal).

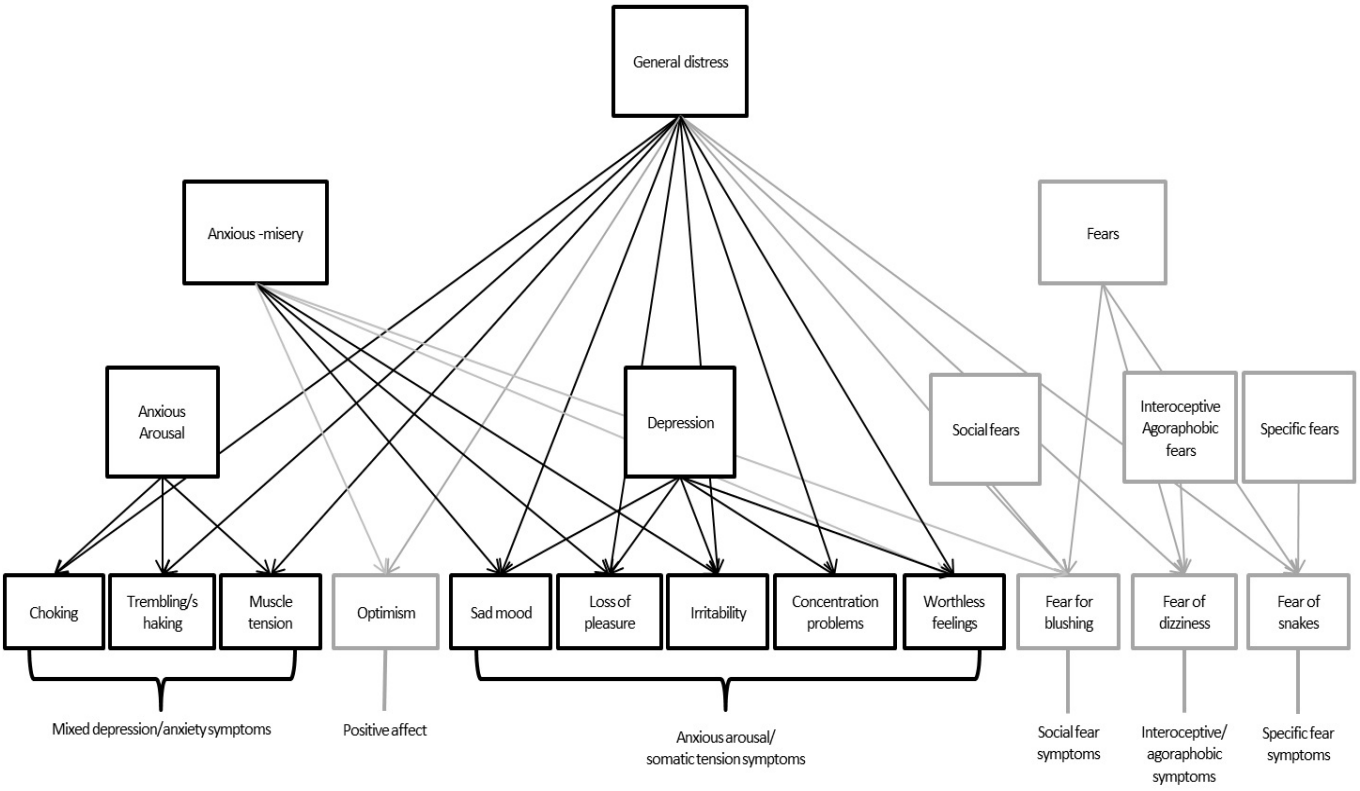


Figure 1. *Co-morbid Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) symptomatology explained by tri-level hierarchical model of depression and anxiety (based on[294]). Black boxes and lines represent factors and symptoms related to MDD-GAD co-morbidity.*

Alternatively, the network approach explains co-morbidity by spreading symptom activations. Co-morbidity is hypothesized to result from direct relations between symptoms of multiple disorders. That is, a symptom of one diagnostic category (e.g., MDD) can evoke other symptoms that in turn evoke symptoms of another diagnostic category (e.g., anxiety about several events, chronic anxiety/worry)[267, 270]. Thus, co-morbidity might be the result of shared symptoms across mental health disorders, so called bridge symptoms.

Figure 2 represents an example of a dynamic network of Major Depressive Disorder (MDD) symptoms that mutually reinforce other symptoms of MDD and co-morbid Generalized Anxiety Disorder (GAD) symptoms (adapted figure, based on[270]). Nodes represent symptoms and edges denote the presumed causal relationship between symptoms. Darker edges indicate a stronger relationship between the symptoms. For example, disturbed sleeping (symptoms of depression) could lead to fatigue and to concentration problems and irritability/agitation (so called bridge symptoms as indicated by red nodes) and other specific generalized anxiety disorder symptomatology. The bridge symptoms are criteria of MDD and GAD[267, 270, 295]. In addition, there may be individual differences in how co-morbidity develops resulting in many different paths to co-morbidity, depending on the individual and his or her environment[e.g., 267, 270, 295]. The network approach does not explain why some individuals are more prone to co-morbidity (having more symptoms) than others.

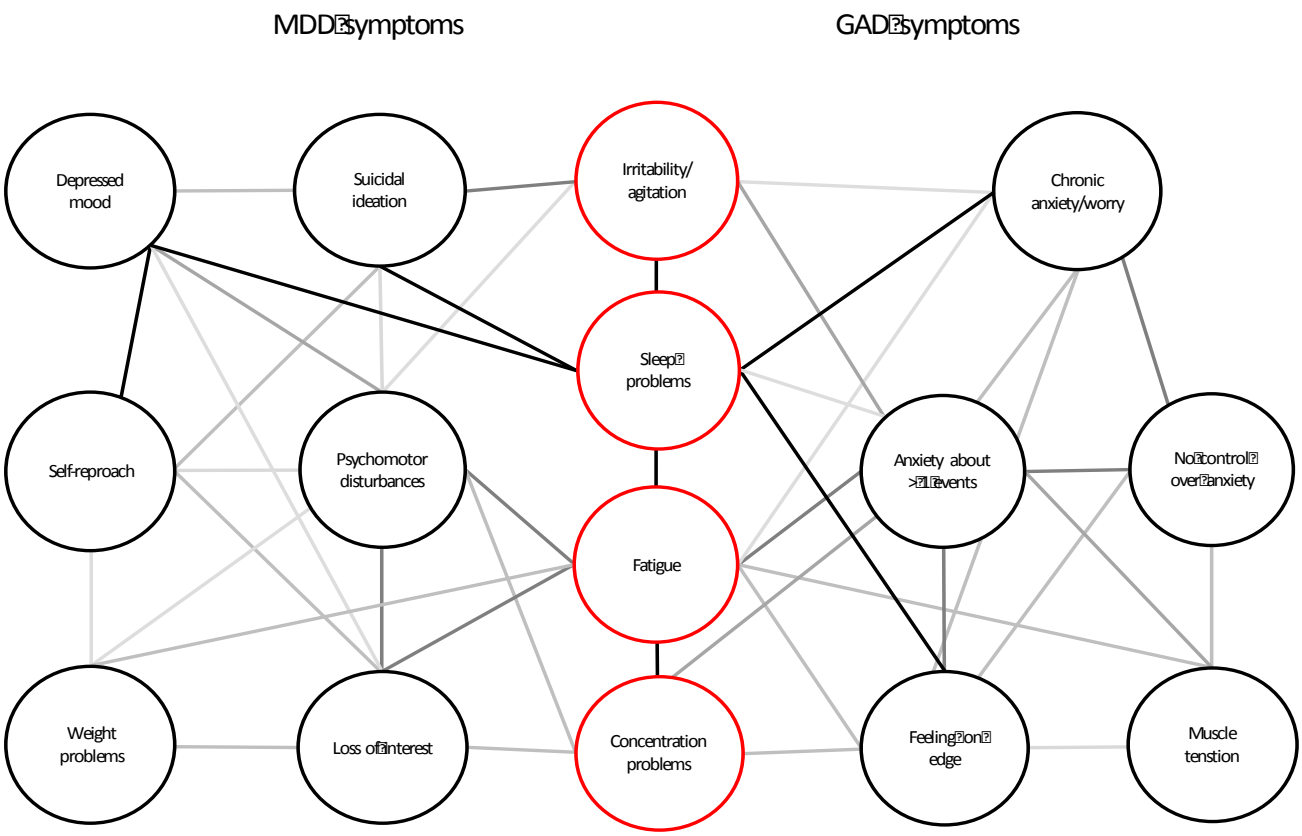


Figure 2. *Hypothetical dynamic network of Major Depressive Disorder (MDD) symptoms that mutually reinforce other symptoms of MDD and comorbid Generalized Anxiety Disorder Symptoms (GAD, adapted from[270]). Nodes represent symptoms and edges denote the causal relationship between symptoms. Darker edges indicate a stronger relationship between the symptoms. Red nodes are bridge symptoms of MDD and GAD.*

Both the network model and the dimensional (hierarchical) models (for instance dimensional underlying factors like neuroticism or general distress) might contribute to the explanation of mental health disorders, including co-morbidity. They emphasize the necessity to translate group findings to the individual struggling with mental health problems. The role of symptoms, individual differences in symptoms and emotions and potential underlying mechanisms as maintenance factors in mental health disorders are key elements to study.

Panel 19. What is Meant by Co-Morbidity, Disorder-Specific versus Transdiagnostic Treatment, and Personalised Treatment Approaches?
• Co-morbidity: two or more mental health disorders that are present during the same period of time (concurrent co-morbidity) or that are present during one's life (lifetime co-morbidity)
• Disorder-specific treatment: a treatment that has been developed and evaluated for a specific mental health disorder
• Transdiagnostic/universal treatment: the use of similar treatment approaches across a range of symptoms/mental health disorders that target the presumed underlying shared maintaining mechanisms[296]
• Personalised treatment: optimize the most efficient and favorable response to treatment based on individual's unique characteristics and/or presumed underlying mechanisms

Personalised models of mental health conditions

Although some disorder specific treatments yield positive effects on co-morbid disorders as well (for instance cognitive behavioral therapy for specific anxiety disorders also reduce depressive symptomatology[297]), there is certainly room for improvement in terms of treatment outcomes for people with mental health disorders, including individuals with co-morbid mental health conditions.

Research should embrace the complexity of mental health disorders to make further progress in psychological treatments research. One way forward is to study both inter- and intra-individual differences. Experience Sampling Methods (ESM or Ecological Momentary Assessment) can be used to develop personalized models of psychopathology[298]. ESM refers to a collection of research methods by which a client repeatedly reports on symptoms, affect, behavior, and cognitions close in time to experience and in the clients' daily life, for instance by using an application on a mobile phone (*see also Section 5, Technology*). Given that ESM gathers numerous assessments for each individual, individualised analyses can generate an individualised model on the dynamics of the network of psychopathology for each person. Hereby, for instance the centrality (or the strength) of a specific symptom or mechanism for one specific person can be defined (e.g., loss of interest may be a central symptom for one individual with MDD, while for another individual a central symptom could be sad mood)[298].

This would offer new insights into mental health disorders and personalised models of psychopathology. Several recent systematic reviews have stressed the value of ESM for assessing symptom fluctuations and interactions over time in anxiety disorders[299], depressive disorders[300], and substance use[301]. Studying transient processes of emotions, cognitions, symptoms and stress (and other relevant factors) in daily life can be done both in prospective studies, as well as in experimental studies, such as a RCT (*see Section 6, Trials*). For instance, alongside a RCT of the effectiveness of three relapse prevention treatments in depression, an EMA study was incorporated in a subset of participants who had remitted from recurrent depression ($N = 51$). This EMA study involved assessing participants' emotions, cognitions, symptoms and imagery-based processing ten times a day, three days a week, for eight weeks using the "*Imagine your mood*" Application on a mobile phone[302]. Given these EMA studies are self-report questionnaires, it may be useful to add physiological and behavioral measures to such investigations.

Personalised treatment approaches

Research on personalised models might disentangle the complexity of mental health conditions, including co-morbidity, and optimise psychological treatments (*see Panel 19*). The goal of the personal medicine approach is to optimise the most efficient and favorable response to treatment based on an individual's unique characteristics (a wide range of characteristics ranging from genetic and neurobiological factors to symptoms) and underlying mechanisms (*see Panel 19*). EMA (i.e., assessing daily fluctuations of change over time within a person) might improve our insight into the specific diagnosis[303,304] and also offer valuable information that might improve patient-treatment matching. For instance, assessing daily fluctuations in positive and negative emotions using ESM in depression predicts response to treatment in depression[305]. In addition, assessing individual change over time in emotions (and other processes) while undergoing therapy (for instance in the context of a randomized controlled trial) might offer valuable empirical information on patterns of change and mechanisms of change during treatment.

An alternative route to improve patient-treatment matching is to use a machine learning approach to identify characteristics of the individual, based on group-based studies, which predict differential response to existing treatments using methods *to transform predictive information for a specific person*. A recent demonstration is the computation of a

Personalised Advantage Index score[306] comparing psychological versus pharmacological treatments for depression. Future studies should examine whether treatment matching can be improved for the substantial group of individuals with comorbid mental health disorders. Related approaches include clinical risk scoring, as currently used within the medical field[307]. For example, treatments for lung cancer are further improved by molecular testing for targeted therapies that can overcome resistance to first-generation drugs[308]. Within the field of mental health conditions we need more studies to examine the relevant variables for these index scores to optimize patient-treatment matching and incorporate the help of, for instance, machine learning.

In addition, as described in *Section 1 (Mechansims)*, research on mechanisms of psychological treatments might reveal crucial moderators of treatment outcome that leads to better patient-treatment matching, such as a biological marker (for instance larger effects of an attentional bias training in anxiety disorders for the group of individuals with a specific polymorphism of the serotonin transporter gene 5-HTTLPR).

Apart from enhancing patient-treatment matching, feedback to the clinician and the patient on daily fluctuations might be used to adapt treatment and thereby improve treatment outcome(s). Feedback on daily fluctuations of change within a person might enable us to adapt the interventions immediately within the sessions by giving real-time feedback on the progress to the clinician as well as the patient[277]. For instance, a RCT in 102 depressed patients showed that the efficacy of pharmacological treatment could be enhanced by adding ESM-derived feedback on personalized patterns of positive affect to the clinician and the patient[309]. Collecting EMA data with comparable assessments within clinical settings (*as suggested in Section 6, Trials*) on patterns of daily fluctuation of change over time within a person while undergoing treatment in a large population with mental health disorders (including outcomes after treatment) would be of great value. Mobile devices and applications could increasingly be used for person tailored, in-the-moment interventions. In the future, researchers could make empirical data available to clinicians and patients, which may help them to work together on improving treatment outcome as a team. Close collaboration will be needed with computer science and mathematics, drawing on advances in these fields (for instance areas of complexity, dynamical systems, and dealing with big data). Future research is needed on the dynamics of symptom outcome rather than simply static

assessments, for example using time series analysis on of daily mood data in bipolar disorder[310], and using the same method within the context of a randomized controlled trial. For now, more studies are needed to examine whether personalised treatments are indeed more effective than traditional treatments. A critical question for the coming years will be: *can we personalise our psychopathological models to the level that we can adjust our treatment and thereby improve outcomes?* (*see Panel 20 and Section 6, Trials*).

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 section 1 on *mechanisms of psychological treatments*). Apart from traditional disorder-specific approaches and personalized approaches, the opposite – although not incompatible - approach is to consider commonalities between mental disorders and a more "universal" approach (*see Panel 19*). For example, adverse life events are consistent predictors of the onset of most mental health conditions[311]. A risk factor, for instance, stress sensitisation, might prove to be a valuable target for treatment, since changing sensitization might influence the other symptoms in the network as well, such as rumination or sleeping problems[312]. Alternatively, changing stress sensitization might reduce a latent factor (such as neuroticism) and thereby reduce symptomatology. We might focus research efforts on trying to identify universal underlying mechanisms across numerous mental health conditions, and try to target these mechanisms by universal interventions (*see Panel 20*). This transdiagnostic approach, for instance in eating disorders, has begun to yield very promising results [313, 314].

Another example of a transdiagnostic psychological treatment approach is Barlow's "Unified Protocol" for the transdiagnostic treatment of emotional disorders. 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)[315]. Within developments of this approach, a more personalised approach is included which assesses a personalised model for each patient's dysfunction related to underlying mechanisms (profiling). The personal profile can be used to select additional interventions that are specific to the mechanisms underlying the patient's symptomatology[316].

More studies are needed that examine whether these unified approaches are indeed more effective than traditional disorder specific treatments.

Despite the apparent contrast between a personalised versus universal approach, we suggest that the research agenda ahead needs to embrace complexity, including co-morbidity, and consider both ends of the treatment spectrum – i.e., to both examine approaches which could offer cross-cutting universal treatment approaches and, if necessary, add disorder-specific interventions, alongside personalised treatment solutions (*see Panel 19*). Mental health researchers – and those who conduct research on psychological treatments specifically - should embrace the variety of complexities (including the enormous variety between individuals, as well as co-morbidity) that are inherent in studying mental health. Solutions to complexity of mental health disorders need to consider both highly individualised 'personalised' approaches as well as 'universal' / 'transdiagnostic' approaches to target common mechanisms (*see Panel 20*).

Panel 20. Example Directions for Future Research Regarding Complexities
• Embrace the complexity of mental health disorders, including co-morbidity, by studying inter- and intra-individual differences in daily life: investigate individual processes of emotions, cognitions, symptoms and stress (and other relevant mechanisms) in prospective studies, as well as in experimental studies, such as a RCT
• Study models that explain co-morbidity in mental health disorders and treatment approaches for co-morbid disorders
• Investigate whether we can personalise our psychopathological models to the level that we can adjust treatments and thereby improve treatment outcomes
• Investigate who we should treat with what: a disorder-specific treatment, a personalized treatment and/or transdiagnostic/unified treatment
• Examine the effects of transdiagnostic/unified treatments for several mental health conditions including the co-morbid conditions in comparison to current evidence based disorder-specific treatments

9. Target: *Suicidal behaviour: Protecting lives*

Overview: Suicide

In this section we illustrate how many of the principles outlined earlier in the Commission could usefully be applied to the development, evaluation and implementation of treatments to reduce suicidal behaviour. Although the causes of suicide and suicidal behaviour are complex, they are psychological phenomena at their core as an individual who attempts suicide makes a decision to end their life. In the past 25 years, there have been significant advances in understanding who is most at risk of suicide and what factors increase this risk in some individuals but not in others. Moving forward, we can build upon the growing evidence base for psychological treatments to reduce the risk of suicidal behaviour. Despite these recent advances, however, there are key gaps in knowledge that require urgent attention. Addressing these gaps represents an excellent opportunity to develop more effective treatments that are replicable, more precise, and can reach those who are most vulnerable irrespective of who they are or where they live.

Introduction

Suicide and suicide attempts are the most tragic outcomes that result from our failure to effectively treat those with mental health problems. In this section we illustrate how many of the principles outlined earlier in this Commission can be applied to the development, evaluation and implementation of treatments to reduce suicidal behaviour. Suicide is a major public health concern: at least 804,000 people die by suicide globally each year[317]. Given the scale of the challenge of suicide prevention, we are strongly of the view that suicidal behaviour warrants inclusion as a standalone section in this commission. Indeed, as the latter is a transdiagnostic phenomenon associated with a myriad of mental health problems, we believe that it is uniquely placed to be a 'test case' of how what we have learned elsewhere in this Commission can be applied to a specific problem. Indeed, it may well become a distinct diagnostic phenomenon in the future (as suicidal behaviour disorder was included in Section 3 of DSM 5, in areas requiring further research). In addition, given that suicidal behaviour

research (which includes tailored psychological treatments research) attracts only a fraction of the funding that mental health research receives - and mental health research only receives 6% of the total UK spend on health research, (MQ Research; https://www.mqmentalhealth.org/research/research-funding-landscape) - its standalone status is warranted. However, we do acknowledge that not all of the recommendations herein are directly applicable to suicidal behaviour.

In addition to the personal tragedy associated with every death by suicide, the economic cost of suicide is enormous. In Scotland, for example, the economic cost of suicide in a single year was estimated to have been in excess of £1 billion in 2004[318]. Although the science of suicide research is still relatively new, there have been welcome advances in the understanding, treatment and prevention of suicidal behaviour in recent decades[319], *see Panel 21 for key terms*. These advances include a better understanding of the common risk factors for suicidal behaviour[320-323], evidence that some psychological treatments reduce suicidal ideation and behaviour[324-331] and growing evidence that public health interventions are associated with reductions in suicide[330, 331]. In this section we describe the advances that relate to psychological treatments in more detail but also identify a number of urgent calls to action (*see Panel 22*). Although we focus on psychological treatments, we should also keep in mind how the principles outlined in this Commission can relate to the primary prevention of suicide.

Panel 21. Suicidal Behaviour and Protecting Lives - What is Meant by Key Terms
• Suicide refers to a death in which an individual intentionally ends their own life
• Suicidal behaviour refers to thoughts and behaviours related to an individual intentionally taking their own life. These thoughts include suicide ideation, when an individual has thoughts about intentionally taking their own life; they also include suicide attempt, which refers to engagement in a potentially self-injurious behaviour in which there is at least some intention of dying
• Consistent with the UK National Institute for Health and Care Excellence guidance, self-harm is defined as intentional self-poisoning or self-injury, irrespective of motive[332]

Although suicide most often occurs in the context of mental health disorder[333, 334] there is widespread recognition of the need to move beyond diagnostic categories in order to explain and treat suicidal behaviour[335]. In addition, the central role of psychological factors in the aetiology and course of suicidal behaviour is now well recognized[323]. Arguably, suicide is the cause of death that is most closely related to psychological factors given that an individual makes a decision to end their own life[323]. Despite advances in our knowledge, our ability to predict who is most likely to kill themselves is limited because we do not have sufficiently specific markers of suicide risk. For example, although depression is the disorder most commonly associated with suicide risk, less than 5% of people treated for depression die by suicide[323, 336, 337].

New psychological models of suicide have been developed which have identified more proximal and specific markers of suicide risk[337-343] (*see also Section 1, Mechanisms*). In addition to the theoretical importance of identifying proximal markers of the final common pathway to suicidal behaviour, proximal markers are vitally important clinically and should be treatment targets. Specifically, constructs including defeat, entrapment, belongingness, burdensomeness, future thinking, goal adjustment, reasons for living and fearlessness about death[323, 339-341, 344, 345] are among the key predictors of suicide attempts we have as yet, and should, therefore, be targeted in psychological treatments and suicide prevention activities more generally. To date, there has been insufficient focus on these suicide-specific psychological proximal markers. Moreover, we know little about which factors are responsible for the observed effectiveness of suicide prevention approaches (*see also Section 1, Mechanisms).* Psychological treatment trials for suicidal behaviour should routinely assess theoretically-derived mechanisms (both psychological and biological) which may explain the treatment effect. A concerted focus on potential biomarkers, for example, salivary cortisol or the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA), ideally tested in combination with other factors is also required[346, 347].

Evidence for psychological treatments and suicidality

Psychological treatments reduce suicidal ideation and suicide attempts[324, 326, 348] although there is little evidence that they have a marked effect on subsequent suicide[349]. Indeed, suicide rates have stayed the same or have increased by more than 10% in 51% of 172 member states of the World Health Organisation between 2000 and 2012[317], including

the USA. So, one interpretation is that (if effective) the increased availability of psychological treatments should have contributed, in part, to a reduced suicide rate in these countries. Although that is one interpretation, given that most people who die by suicide are not in contact with clinical services in the 12 months before death, until we expand the reach of psychological treatments beyond those already in contact with clinical services, it is unlikely that their effectiveness will have a direct impact upon national suicide rates. Moreover, given the complexity of the risk factors for suicide, multilevel interventions offer most promise[350] and psychological treatments on their own will not make a sizeable dent in suicide rates.

Nonetheless, meta-analyses indicate that cognitive behaviour therapy (CBT) is effective in reducing suicidal behaviour in adults, although not in adolescents[327]. Indeed, this is consistent with a systematic review and meta-analysis of psychosocial interventions following self-harm in adults which concluded that CBT "seems to be effective in patients after self-harm" as is dialectical behaviour therapy for individuals with borderline personality[351], and individual studies provide support for psychodynamic interpersonal therapy[352] and mentalization-based therapy[353] (although the need for replications of single studies is noted). Evidence for the collaborative assessment and management of suicidality (CAMS), a therapeutic framework for suicidality, is also growing[354]. More recently, there are encouraging findings for the attempted suicide short intervention program (ASSIP) which is a brief integrated therapy and personalized letters intervention[355]. However, the low number of intervention studies overall underscores the need to develop the research agenda in this area.

A meta-analysis of therapeutic interventions for suicide attempts and self-harm in adolescents concluded that therapeutic interventions are effective in reducing self-harm (when it is treated as a global category which includes suicidal and non-suicidal self-harm), but that the effects are weaker when suicidal and non-suicidal behaviour are examined separately[356]. The latter is consistent with the newly published Cochrane review of interventions for children and adolescents who self-harm[329]. The review authors found relatively few trials (n = 11), most of which were single trials, from which they concluded that therapeutic assessment, mentalization, and dialectical behaviour therapy "warrant further evaluation"[13] *(see also Section 4, Prevention).* Treatments that target depression are also not effective in reducing suicidal thoughts or attempts[357]. It is important to highlight that there is

marked heterogeneity across treatment studies in the field, that many studies have relatively small sample sizes and that there is clear evidence of publication bias with no published studies reporting negative findings[327]. Replications of the existing treatments by independent groups will strengthen the evidence base. The development of evidence-based assessment measures that are clinically useful is also lacking in the suicide treatment research field (*see also Section 6, Trials*).

In brief, therefore, although the psychological treatments evidence-base for suicidal behaviour is growing, there are many gaps in knowledge. It is absolutely critical that the development, evaluation and implementation of psychological treatments for suicidality are prioritised. Moreover, we need to determine the extent to which psychological treatments are effective for different sociodemographic populations (males vs females, adolescents vs older adults, individuals from different ethnic backgrounds, etc.) as well as in different healthcare settings (e.g., primary/secondary care versus acute settings) and patient groups (e.g., psychiatric in- versus out-patients) (*see also Section 8, Complexities*). The former is especially important given that although more men die by suicide than women in all countries in the world, many more women participate in treatment trials. As a consequence, we do not know whether the existing treatments are effective for men. We also do not know whether treatments that have been shown to be effective in one setting generalize to other settings or patient groups. It is also not clear when it is optimal to deliver treatment interventions to reduce risk of future suicidal behaviour among those who have attempted suicide.

Needless to say, psychological treatments are not a panacea. It is important to note that for those psychological treatments that are effective, overall the effect sizes have tended to be small[358]. This suggests, in part, that we require a better understanding of the mechanisms that comprise psychological treatments. Also, psychological treatments only reach a minority of people who take their own lives or who are suicidal (for many reasons including access and suitability). Given the established inequality gradient for suicide (people from lower socio-economic backgrounds are significantly more likely to die by suicide compared to their more affluent peers[359]), we need to challenge the structural inequalities (e.g., poverty) that contribute to the excess in suicide mortality evident in those from more socially disadvantaged backgrounds.

Given that most suicides occur in low- and middle-income countries (LAMICs)[317], the

extent to which treatments developed in high-income countries are generalizable to LAMICs needs very careful consideration (*see also Section 2, Worldwide*). When developing and evaluating treatment trials, consideration also needs to be given to whether a tailored or modular approach is desirable/feasible, whether the treatment is principles-based or manualized, and whether the interventions account for different risk profiles and inequalities (*see also Section 8, Complexities*). Even more fundamentally, though (*as noted in Section 1, Mechanisms*), we need to re-focus our efforts to ensure that we understand the mechanisms responsible for treatment successes when they do occur (e.g., does prevention of suicide depend on changes in reward sensitivity?). Without an understanding of mechanisms, our ability to tailor, target, extend and replicate treatments is limited. Indeed, an appreciation of mechanisms will help explain why treatments that are expected to be effective fail to be so. Furthermore, the identification of mechanisms will also improve precision in treatment-matching.

Challenges and opportunities for research

The Calls to Action panel (*see Panel 22*) highlights the key challenges and opportunities for suicide treatment research in the next decade and beyond. As those who are at imminent risk of suicide are usually excluded from treatment trials, we know little about which treatments may be effective in this patient group. Relatedly, most people who are suicidal do not receive treatment[360], therefore, we need to better understand the barriers to help-seeking or accessing treatment. It may be that people in distress are reluctant to seek psychological or psychiatric treatment for fear of stigma. Organisations such as Headspace (https://www.headspace.org.au) in Australia (*see also Section 2, Worldwide*) offer a promising stepped care treatment model which is low in stigma, set in the community and provides family members (as well as friends and health professionals) with an avenue to seek help for a relative. Another challenge is that suicidal patients are difficult to maintain in treatment[361], so in addition to better understanding the factors associated with disengagement, we need to maximize treatment delivery when patients are in healthcare settings. For example, innovative brief contact interventions[225, 362, 363] have been shown to offer some promise in acute settings. They should be considered as adjuncts to existing treatments and may be effective in reducing the likelihood that individuals act on their suicidal thoughts[362, 363].

Although some public health suicide prevention interventions have adopted a multi-level approach and explored synergies (by delivering a combination of interventions[364, 365]), there are few examples of exploring synergies by combining different psychological treatments (*see Section 3 on Combination Treatments*). Given the heterogeneity of those who attempt suicide or die by suicide, exploring the efficacy of treatment combinations is likely to be one fruitful avenue as we move forward. However, potential iatrogenic effects ought to be monitored in such studies (as well as in mono-treatment studies, *see also Section 6, Trials*). The potential for harm in psychological treatments has been highlighted in the Royal Australian and New Zealand College of Psychiatrists Guidelines for Deliberate Self-Harm[358]. We also need to focus on mechanisms and target those in developing new treatment approaches.

To facilitate the pooling of findings across different treatment studies, we urge suicide researchers to agree on a common set of core outcome measures (*see also Section 6, Trials*). There has been some movement in this regard in the US[325], however, an international consensus would be fruitful. To this end, it would be helpful to convene an international, interdisciplinary working group to agree such a set of measures. We also call for all psychological treatment trials to include a measure of suicidality as an outcome measure, even in studies in which this may only be a secondary focus. Although suicidal behaviour occurs transdiagnostically, we need to consider the differential prevalence of suicidal ideation and behaviour across psychiatric categories and better understand why, for example, individuals with bipolar disorder are at particularly high risk of suicide[366]. Psychological treatments research needs to embrace the assessment of potential mechanisms to account for treatment efficacy, as well as determine the active ingredients of effective treatments for suicidality (*see also Section 1, Mechanisms*).

We also need to investigate the extent to which new technologies may be useful to engage so-called difficult to reach populations (e.g., men, adolescents)[367, 368]. For example, given the exponential growth in gaming, could this technology be harnessed to engage young people in help-seeking and treatment? As the roll-out of Internet-based psychological treatments continues, it is vital that they are developed with the same rigor as traditional means of psychological treatment delivery. Mobile apps also offer potential opportunities to monitor suicidal ideation and mood in real-time and have the potential to enhance our ability

to identify (and intervene) when individuals are at their most vulnerable (*see also Section 5, Technology*). Arguably, the field of suicide prevention has not given due consideration to the cultural influences and pressures (e.g., depictions of masculinity) on men and women. Given the scale of male suicide, it is vital that we better integrate such factors into our understanding of suicide risk as well as suicide prevention efforts in particular[369-371].

Those with lived experience of suicidal behaviour (e.g., individuals bereaved by suicide, and those with personal experience) should be involved in all stages of treatment development[372]. Consistent with other areas of psychological treatments research, as we know relatively little 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 also Section 4, Prevention*).

Finally, team science is key to the success of developing, evaluating and implementing psychological treatments to prevent suicide. As suicide is the end-product of the interplay between psychological, social, biological, clinical and cultural factors, interdisciplinarity should be the norm in psychological treatment research (*see also Section 7, Training*). However, given - as stated at the beginning of this section - that an individual 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.

To conclude, this is an exciting time to be working in psychological treatment research for suicide, as we have the theoretical and empirical foundations for promising treatments. In the next decade and beyond, however, we have to be innovative in our thinking and practice, to ensure that the promise of psychological treatments research is realized and leads to a reduction in suicidal ideation and suicide attempts.

Panel 22. Calls to Action for Psychological Treatments Suicide Research

- More large-scale psychological treatment trials (including psychotherapeutic and brief contact interventions) targeting suicidal ideation/behaviour are urgently required

▪ Determine whether psychological treatments work for different sociodemographic populations (males vs females, adolescents vs older adults, individuals from different ethnic backgrounds etc) as well as in different settings (e.g., primary/secondary care versus acute settings), patient groups (e.g., psychiatric in- versus out-patients) and countries (e.g., low- middle-income versus high-income countries)
▪ More rigorous investigation of those at imminent risk of suicide
▪ Conduct replications of psychological treatments by independent groups
▪ Agree on common measures of core outcomes (suicidal ideation and behaviour) and conduct multi-centre treatment studies and harness 'big data' techniques to determine whether psychological treatments can prevent suicide
▪ Assess potential mechanisms derived from psychological theories hypothesized to account for treatment effects in all trials (risk and protective mechanisms) as well as moderators of the effects
▪ Use techniques derived from experimental psychopathology to determine whether hypothesized mechanisms account for changes in symptoms or wellbeing (*see Section 1*, recommendations for identifying potential mechanisms)
▪ Determine active ingredients of psychological treatments (including the role of therapeutic alliance)
▪ All psychological and social treatments (irrespective of whether suicidality is the target) should include a measure of suicidal thinking/behaviour which could be harvested in 'big data' analyses
▪ Determine the barriers to treatment seeking in men, in particular
▪ Investigate the extent to which new technologies may be useful to engage difficult to reach populations (e.g., men, adolescents)
▪ Those with lived experience of suicidal behaviour (those bereaved by suicide, those with personal experience) should be involved in all stages of psychological treatment research

10. Trafalgar Square and The Empty Plinth - *A space for active innovation and scrutiny of psychological treatments research of the future*

Inspecting ideas - and making space for ideas of the future

Psychological treatments are highly effective for many patients but a large proportion either fail to respond to existing therapies, or the therapies that we have cannot reach them. To 'see further' [footnote#4] we need to innovate. To innovate, we need to generate ideas, and we need to engage in the critical inspection, progression as well as rejection of ideas, via the process of high quality, rigorous research.

Psychological treatment research needs to harness, innovate, and provide a counterforce against stagnation, while preserving ideas that stand the test of time. In the Introduction, we used the metaphor "The Fourth Plinth" in Trafalgar Square. This empty plinth is used for a series of temporary works of contemporary art by leading national and international artists. Ideas are of their time and are selected, then replaced. Some pieces will be preserved for longevity, others may not. A plinth here is a metaphor to make contemporary ideas visible and to give them critical consideration. Particular psychological treatments and/or research ideas should not stand on a plinth forever. Rather, numerous ideas 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, and the notion of innovation and turnover are critical parts of its future.

How might this work for psychological treatments? Let us consider the wide range of potential topics, how they could be selected, where they would be aired, how they could achieve visibility, and the need for a repeated cycle of this endeavour - with the ultimate aim to better air and debate the issues of our time in order to make a difference for mental health. Topics could include both novel ideas or longstanding challenging topics. Novel issues could include recent findings that would benefit from constructive and rapid scrutiny (such as therapeutic approaches that emerge from the findings of pre-clinical studies, new ideas from

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Footnote #4 "*If I have seen further it is by standing on ye shoulders of Giants*"; Letter from Isaac Newton to Robert Hook dated 5th February 1676, as transcribed in *The Correspondence of Isaac Newton*. (1959). H. W. Turnbull, Ed. (Vol. 1.) Cambridge: Cambridge University Press.

sister disciplines, technology and new ethical issues, and so forth). Exciting new directions that emerge in these and other contexts should be clearly formulated, considered and reflected upon – and most importantly, need to be subjected to rigorous debate within and beyond the field, as well as empirical evaluation in the context of scientifically-sound studies such as well-controlled RCTs.

Open and constructive debate needs to be encouraged, without new ideas being too swiftly "smashed down" by tradition and vested interests in maintaining the status quo. On the other hand, new ideas and vogues in thinking (for example, fashionable new forms of therapy) must be scrutinised prior to being accepted and delivered in clinical practice. Of note, one problem for our field is the need to sustain the adoption of evidence-based treatments by practitioners, who may rather cast the evidence aside for techniques for which they have a personal preference. For example, "exposure" is a theoretically-driven treatment technique with an excellent evidence-base and for which there is a strong scientific understanding of the mechanisms that underlie its effectiveness (*see Section 1, Mechanisms*). However, in practise a substantial proportion of therapists do not use this effective therapeutic technique[373]. This reluctance and lack of uptake of empirically-supported interventions, or aspects of them, is an issue that needs to be understood and rectified. To use the metaphor, we should continue to work on improving some older statues on solid plinths, moving them from an empty plinth to a more permanent venue when appropriate.

The plinth metaphor also provides a way in which to question older ideas that we now take for granted, and yet would benefit from further examination. There are many broader issues that affect the whole psychological treatment field which require discussion (such as our diagnostic systems, the quantity of academic publications versus their capacity to deliver patient impact, funding issues that are specific to psychological treatments, etc) as well as many issues that are currently relevant to science more generally - from reproducibility to open data. Psychological science is a young discipline compared to many other fields - further emphasis on the history of psychological treatments over the last century could be of benefit here. We note that there are parallels between some of our suggestions here and the 'Science in Transition' initiative in the Netherlands, which calls for a number of key reforms in science with the goal of scientists producing reproducible outcomes[374,375].

How can topics be selected? In the art world, the "Empty Plinth" is an open competition from artists and subject to a review panel – the winner places an object up on a platform for viewing and discussion. For psychological treatments research, there could be equivalent competition/selection process of having specific calls for people to raise challenging ideas which catalyse progress. This will generate topics beyond that what we can imagine now, and potentially create a way to capture the concerns and questions of younger generations in our field (e.g., why isn't neuroscience being used more?), or those of researchers with several decades of experience (e.g., why have effect sizes for psychological treatments not improved?).

The potential locations of where the "Empty Plinth" metaphor could be used could include a dedicated session at conferences and cross-disciplinary meetings, a type of journal article, in electronic media and so forth in areas which allow debate and scrutiny. Clearly the field does not have one place such as London's Trafalgar Square in which a metaphorical plinth would stand; rather, the metaphor could be adapted to fit the range of outlets, and journal editors and conference organisers alike could be encouraged to provide space for this. In order to bring attention to the resulting ideas, an annual prize could be awarded for topics that have attracted attention and made constructive progress.

The Plinth metaphor highlights the need for repetition in this process – so that novel psychological treatment ideas displayed in the Plinth will constantly be generated, tested, and disseminated (as indicated). This iterative process will not only encourage innovation, but will enable differentiation of those new treatments and ideas that will stand the test of time – and allow long held assumptions to be questioned in order to bring about progress. In some sense these are all processes that occur throughout the scientific process. But as we have argued throughout this commission, due to the scale of mental health problems, progress needs to speed up for psychological treatments research and borrowing an idea from the Arts may be just one way to catalyse this.

The early stage of our field (compared to many other scientific disciplines, e.g., medicine, biology, physics) also offers opportunities. Mental health and psychological treatments provide critical, fascinating and demanding targets for research enquiry. Creative but realistic solutions require communication, and meaningful multidisciplinary collaborations among researchers and funding agencies, and some 'blue skies' thinking from

outside the field. More psychological treatment researchers are needed across all disciplines – there remain a vast range of important questions that as yet have barely been addressed. This poses a great opportunity for example for many early career scientists to make landmark contributions, and more should be encouraged to the field (see *Section 7, Training*).

Stagnation versus innovation: the need for new treatments

Arguably, psychological treatment research has stagnated. Outcomes for many psychological disorders (including depression, obsessive compulsive disorder, schizophrenia and bipolar disorders) have not improved since the interventions were developed, and may even be falling[376]. While there are notable exceptions of disorders from which lessons can be learned such as for eating disorders[377], and others which are beyond the scope of this piece to list here, clearly more rapid advances are needed in numerous areas.

There is an understandable current emphasis on increasing access to existing psychological treatments[98] given the large unmet need and changing models of service delivery[5,93,378,379] (*see Section 2, Worldwide*). Relatedly, there are attempts to improve the efficiency of existing interventions via identification of mechanisms of treatment (*see Section 1, Mechanisms*) so that that existing interventions can benefit more patients. **There is, however, an equally strong need to develop 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 fall into one of these categories varies by disorder, age group and research study, but can be considered to be at least 50%[380, 381]. Given the large number of people for whom psychological treatments are not sufficiently effective to make a tangible difference to their lives, there is an urgent requirement to develop new treatments. The development of such treatments will be challenging for practical reasons (such as cost), as well as conceptual ones: it is hard to 'think differently' from within an existing and agreed framework. Existing organisations that are designed to facilitate improvement and innovation (such as NHS Improving Quality in the UK) will be helpful, as will initiatives such as 'Science in Transition'. The 'Science in Transition' initiative arose in the Netherlands and proposes that Science has 'gone wrong' and is in need of fundamental reform with an increased focus on real societal relevance with a modified reward system that creates reproducible and translatable research[374, 375]. **New treatments will require new research**

processes and methods combined with a strong determination and energy to make change a reality.

Whilst we have called for the need to develop new psychological therapies in order to address the prevalence of and global burden imposed by mental health problems, we also see a pressing need for multiple solutions, given the scale of the challenge before us. We foresee value in a range of approaches, including the dissemination of evidence-based therapies, initiatives to reduce stigma, and increasing the accessibility of evidence-based psychotherapies (e.g., through internet interventions or the training of lay-health counsellors in low and middle income countries). So whilst we see the need for a multi-pronged approach, we argue that the development of new therapies is one of the most promising approaches - given the scale of the problem of mental health disorders from a public health perspective.

What factors might foster stagnation and what innovation? Branding, communication and funding

It is striking how **the majority of psychological treatment researchers stick to what they know**. Such adherence is rewarded by strong CVs, grant funding and an unparalleled deep knowledge of a field. However, it can also lead to insularity. Fields that are highly relevant to psychological treatments from not only neuroscience, maths and pharmacology (as discussed earlier), but a diverse range disciplines such as 'medical geography'[382] could help clinical researchers and practitioners think differently. Communicating with colleagues in other areas of science and bringing their learning into our psychological treatments has huge potential. Jointly reviewing advances in areas such as cognitive and social science to identify which innovations will be relevant to improving psychological therapies is entirely feasible. Such an approach has tremendous potential to facilitate the introduction of new, scientifically sound ideas into treatment.

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 also stifles innovation by implying 'ownership' of an intervention[383]. A sustainable, not-for-profit model for the development of psychological

interventions is an alternative and potentially better way forward. The increasing pressure from 'knowledge transfer' departments at Universities for branding for uniqueness by one research group needs to be resisted where useful in favour of developments in psychological therapies that are more open, highlight shared common components, and are precisely described at a level at which they can benefit from examination by the wider the psychological treatment community. The issue is clearly complex due to concerns with regard to incentivising investment in psychological treatments from a range of sources, as well as the need for quality control within particular interventions. The development of 'citizen science' has the potential to counteract branding and provide a fertile ground for innovation. Examples need to be developed and shared.

Communication between clients, clinicians and across the health services as a whole needs improvement. As an example, mental and physical healthcare 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[384]. Improving communication between providers of these two services via shared training, resources or even co-location will be a fundamental step in innovation, with scope to yield significant benefits for the entire healthcare system. Drawing on multiple areas of expertise will be important; in particular, obtaining input from patients and carers – a topic that is receiving increasing attention (see[385], but requires more.

It is impossible to divorce the issues of innovation and improvement from those of dissemination and implementation. Innovations that stay localised will benefit some patients but the impact will be minimal (*see Section 2, Worldwide*). Furthermore, the length of time from 'bench to bedside' (currently estimated at 17 years, although some argue it will be quicker to develop psychological than pharmacological treatments[3,386]) will continue to be unacceptably high unless dissemination and implementation are part of the plan from the outset (*see also Section 5, Technology*). Communication between stakeholders is essential to ensuring the impact of innovations. It is only through the development of meaningful networks that genuine collaborations can be built – such as joint training, joint conferences and joint funding. Such networks need to be funded appropriately for the stage of development, with basic researchers and clinicians having a bi-directional conversation,

initially by email but then face-to-face in a relaxed atmosphere with time to think creatively, argue 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 an 'other' category on the RDoC[387] (*see also Section 1*) so that researchers are not restricted to only studying the known has the potential to facilitate new ideas. While researchers understand that funding agencies have a tendency to be risk averse, the funding of high risk studies is fundamental to the development of new treatments. More support akin to the funding of psychological therapies by 'MQ: Transforming Mental Health' for proof of concept studies in psychological therapies could be especially important to the field. However, the level of funding for mental health research internationally, and psychological treatments in particular is far too low[388, 389]. As has been argued elsewhere – and needs to continue to be argued - increased funding is essential for progress.

Globally, within larger funding organisations, mental health is often subsumed with other diseases or with for example, neuroscience. Representation by people with mental health research experience can be thin. Genuine expertise in mental health is needed on the decision making bodies of the major funding bodies. Clearer representation of expertise in psychological treatments would also be of benefit. It would be useful to have a review of international funding organisations which address mental health, and to determine the extent to which psychological treatment research is included and accommodated. Some charities fund research and this is of course welcomed, but unfortunately many smaller charities often do not have the capacity to conduct a research review process that is as rigorous as that which can be carried out by larger, well-established, well-connected national charities or research bodies. A number of factors may be responsible, including a lack of infrastructure to support peer review, lack of knowledge of the peer review process). The quality and impact of studies that fail to benefit from peer review and scientific support is often sub-optimal. Funding models whereby smaller charities supporting mental health research are supported by larger charities with regard to their commissioning and execution of research is likely to improve both the quality of research and value for money of the research project. 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 the area.

How can we assess the effectiveness of our efforts?

Our broad aim in undertaking this commission was to identify ways in which research efforts have scope to improve mental health globally via advancements in the effectiveness and the global reach of psychological treatments. More specifically, we have outlined an agenda of some of the concrete areas in which we see real scope for improvements in treatment research and their delivery to translate to more effective interventions, and greater accessibility of such treatments, to individuals with mental health difficulties. Treatment protocols that more effectively treat, as well as prevent the onset of, mental disorders will in turn have a part to play among the many contributions needed to relieve the substantial worldwide burden imposed by mental ill health.

Our capacity to assess in a tangible and meaningful way whether the goal of improving mental health treatments has in fact been achieved remains a challenge for the field. The initial indicator of success on this front is at the level of trial outcomes – i.e., to examine whether effect sizes indicate improved efficacy of novel and refined psychological interventions. In the longer term, meta-analyses will delineate whether newer treatment approaches have made substantial gains in terms of improved effectiveness – and thus in turn, contribute to reducing the prevalence and indeed the burden of mental health problems. In the more distant future, the findings of epidemiological studies that illustrate rates of prevalence over time will speak to the success of treatment and prevention approaches. We acknowledge, however, that 'measurement' in this domain is indeed complicated and ambitious; e.g., changes in our diagnostic classification systems complicate these types of comparisons over time. We therefore see a need for research on how to define and quantify burden. We see scope for further progress to be made in not only examining prevalence rates, but also by investigating improvements in the functional impact of mental diseases, from impairments in social and occupational functioning through to quality of life (e.g., using instruments such as WHODAS 2.0[390]). Such a suggestion chimes with our earlier acknowledgement of the value of expanding conceptualizations of mental health beyond the

notions of disease and infirmity to outcomes with broader functional relevance (e.g., an individual's capacity to adapt, self-manage, etc; see *Introduction*).

Innovation to create new treatments. What ideas can we cast on the plinth in the first round?

Increasing access to existing effective psychological treatments is a priority, but it is equally important to invest in innovations that will energise the field of psychological treatment research and improve therapeutic outcome[5, 93]. There are many books and journal articles dedicated to the issue of innovation, and even an entire journal devoted to this topic ('Healthcare: The Journal of Delivery Science and Innovation'), which commenced in June 2013. It is clear that innovation is a challenging area and that what is presented as innovation can often be seen as 'old wine in a new bottle'. Innovation needs to be put in its historical context so that existing ideas are not repackaged with enthusiasm as an innovation[391.] As said, we need to engage in the critical inspection, progression as well as rejection of ideas via research; that is, to celebrate a metaphorical plinth with replenishing ideas, rather than to imagine therapy-brand statues which stand for ever. One approach is to change the nature of the questions are asking. Here we begin with two examples.

What matters to patients?

Arguably, most clinical research has focussed on single diagnoses despite the fact that many patients experience multiple co-existing disorders[392] (*see Section 8, Complexity*). Clinicians have guidelines for the treatment of specific diagnoses but almost no data to guide them with regard to evidence-based decision-making in cases where patients have common co-occurring disorders such as anxiety and depression. Patients' difficulties can alternatively be considered in terms of the problem they are experiencing rather than in diagnostic terms, for example 'loneliness', or 'betrayal'[393]. Linking with social psychology and having a **problem-based approach** to the development of psychological treatments, rather than a disorder-based approach, is likely to lead to new ways of thinking about, and addressing, mental health disorders, which was partly the intention of the RDoC[387]. Such approaches may increase engagement in and the acceptability of therapies, but would still have their challenges in terms of agreeing operationalised definitions of the problem, as well as ensuring

that such difficulties were impacting on people's lives, interfering with functioning and could be viewed within a psychological framework.

What matters to researchers?

Many things matter to researchers - but most scientists become curious about what does not work, not just what does. Data that do not obey 'the rules' are essential to scientific progress. For psychological treatments research, **defining non-responders**, identifying which people relapse, as well as those who fail to engage in treatment - are all necessary and critical steps that will enable our field to progress[381]. Conducting 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 impact and would bring generalizable benefits to existing as well as new treatments.

What next?

We see mental health as a significant global challenge, but at the same time recognise that in current times 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 country. Notwithstanding the fact that many such significant problems exist in our world today, in the domain of mental health, we call for increased research efforts in order to evolve psychological treatments, so that more effective interventions will serve as an important part of our armoury of approaches needed to make a significant impact upon the burden of mental disease worldwide.

We acknowledge that our call for developments in psychological treatments for mental health problems is but one endeavour in the context other timely such initiatives. For example, Wykes et al.[394] recently laid out six key priorities for a mental health research agenda for Europe and worldwide. Mental health is increasingly being recognised as a domain in which we need to move forward on a global scale. Furthermore, psychological interventions can be applied not only to mental health problems, but have been increasingly utilised across a range of areas; for example, in promoting health behaviour change, managing the psychological aspects and impact of physical health problems (e.g., pain

management and somatic concerns, psycho-oncology), instituting organisational change, to name just a few.

Clinicians, researchers, patients, carers, funders, commissioners, managers, policy-planners, ‘change’ experts and the wider public all have a part to play in innovating psychological therapies and a focus on any one of the above ideas presented in this paper has the potential to bring about dramatic and much-needed improvements. Such innovations have genuine potential to transform the science and practice of psychological therapies, as well as the lives of all of those affected by mental health problems.

Figure. The Forth Plinth, Trafalgar Square London, from different angles (photo by E. Holmes, 2016)

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