



Holmes, E. A. et al. (2018) The Lancet Psychiatry Commission on psychological treatments research in tomorrow's science. *Lancet Psychiatry*, 5(3), pp. 237-286. (doi:[10.1016/S2215-0366\(17\)30513-8](https://doi.org/10.1016/S2215-0366(17)30513-8))

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Psychological Treatments Research in Tomorrow's Science: Seeing Further

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Authors:

Emily A. Holmes*, DClinPsych, PhD, Division of Psychology, Department of Clinical Neuroscience, Karolinska Institutet, SE-171 77 Stockholm, Sweden

Ata Ghaderi, PhD, Division of Psychology, Department of Clinical Neuroscience, Karolinska Institutet, SE-171 77, Stockholm, Sweden

Catherine J. Harmer, DPhil, University of Oxford, Department of Psychiatry, Warneford Hospital, Oxford OX3 7JX, UK

Paul G. Ramchandani, DPhil, Centre for Mental Health, Imperial College, Commonwealth Building, Hammersmith Campus, Du Cane Road, London W12 0NN

Pim Cuijpers, PhD, Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health Research Institute, Vrije Universiteit Amsterdam, the Netherlands

Anthony P. Morrison, PhD, School of Psychological Sciences, University of Manchester, Oxford Road, Manchester, M13 9PL, UK

Jonathan P. Roiser, PhD, University College London, Institute of Cognitive Neuroscience, 17 Queen Square, London, WC1N 3AR, UK

Claudi L. H. Bockting, PhD, University of Amsterdam, Academic Medical Center, Department of Psychiatry, Amsterdam, The Netherlands.

Rory C. O'Connor, PhD, Institute of Health & Wellbeing, University of Glasgow, Glasgow, G12 0XH, UK

Roz Shafran, PhD, University College London Great Ormond Street Institute of Child Health, 30 Guilford Street, London, WC1N 1EH, UK

Michelle L. Moulds, PhD, School of Psychology, The University of New South Wales, UNSW Sydney, Sydney UNSW 2052, Australia

Michelle G. Craske, PhD, Department of Psychology and Department of Psychiatry and behavioural Sciences, University of California, Los Angeles, 405 Hilgard Avenue, Los Angeles, CA USA 90095-1563

*Corresponding author: Emily A Holmes, DClinPsy, DPhil, Division of Psychology, Department of Clinical Neuroscience, Karolinska Institutet, SE-171 77 Stockholm, Sweden

Executive 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 disorders 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. This Commission is comprised of ten parts that each outline an area in which we see significant opportunity and scope for advancements that will move psychological treatments research forward.

Part 1: **Why** do existing treatments work? *Making the case for mechanisms of psychological treatments.* Beyond knowing that an intervention is efficacious, we need research initiatives that elucidate the key mechanisms through which the intervention effects change. An experimental psychopathology approach enables the identification of mechanisms. Research on mechanisms has significant scope to facilitate treatment innovation.

Part 2: **Where** can psychological treatments be deployed? *Research to improve mental health worldwide.* We outline a number of factors to facilitate access to psychological treatments worldwide. Future research initiatives need to continue to develop and evaluate the efficacy of brief, flexible interventions that can be adapted to meet the needs of individuals across cultural contexts, delivered and disseminated in a sustainable way.

Part 3: **With what?** *The potential for synergistic treatment effects: using and developing cross-modal treatment approaches.* The combination of psychological and pharmacological treatments needs to be better understood both in terms of clinical impact and underlying shared/different mechanisms. Efforts to develop and investigate the efficacy of novel cross-modal treatments may contribute to treatment innovation.

Part 4: **When in life?** Psychological science, prevention and early intervention: *getting it right from the start.* The social and economic toll of mental health problems early in life

render the development of effective prevention and early intervention approaches a priority. The adoption of both a preventive focus and a developmental approach is needed to identify risk factors for psychopathology, as well as the optimal time at which to offer prevention approaches to increase the likelihood of setting vulnerable young people on a path to positive mental health.

Part 5: Technology: *Can we transform the availability and efficacy of psychological treatment through new technologies?* New technologies provide exciting and timely means by which to disseminate and extend the efficacy and global reach of evidence-based interventions. eHealth and mHealth approaches that use information technology (e.g., the Internet, virtual reality, serious gaming) and mobile and wireless applications (e.g., text messaging, apps) are examples of ways in which technology has been harnessed to innovate psychological treatments, their availability and evaluation.

Part 6: Trials to Evaluate Psychological Therapies. The findings of randomised controlled trials that evaluate psychological therapies critically inform policy and practice. Accordingly, the design and conduct of RCTs warrant scrutiny and ongoing efforts for quality improvement (e.g., reporting standards, specification of protocols and inclusion/exclusion criteria, choice of outcome measures, measurement of adverse effects, prevention of bias in design and analysis). We outline a number of opportunities for further improvement which will ultimately enhance the credibility of quality of trials.

Part 7: Training: *Can we foster a vision for interdisciplinary training across mental health sciences to improve psychological treatments?* Early examples of collaboration between basic scientists and practitioners translated to historical steps in psychological treatment innovation. Such synergy is less apparent in more recent years. Improving links between clinical psychology, psychiatry, and basic research has the potential to again deliver advances in psychological treatments. We propose opportunities to improve training in interdisciplinary mental health sciences as an important initial step in forging the links between scientists and practitioners in the next generation, in order to bridge the extant gap between clinical practice and the basic research programs that underpin psychological treatments.

Part 8: **Who** should we treat for what and with what? *Embracing the complexity of mental disorders from personalised models to universal approaches*. Mental health disorders are inherently complex (e.g., heterogeneity in symptoms across disorders, high rates of comorbidity). Evidence-based treatments must address this complexity. Potential solutions to the complexity of mental health disorders include considering both highly individualized ‘personalised’ approaches as well as ‘universal’/‘transdiagnostic’ approaches that target common mechanisms. A goal of future research will be to examine whether these approaches improve treatment effectiveness.

Part 9: **Target: Suicidal behaviour: Protecting lives**. This topic illustrates one of many areas in which advances are needed. Despite recent developments in our understanding of risk factors that predict suicide attempts, as well as the treatment and prevention of suicidal behaviour, many outstanding questions remain. We specify areas for future research; e.g., use of new technologies, the role of culture, input from individuals with lived experience of suicidal behaviour, and employing a team science approach in develop, evaluate and disseminate prevention efforts.

Part 10: **Trafalgar Square and The Empty Plinth** - *A space for active innovation and scrutiny of psychological treatments research of the future*. The task of improving psychological treatments presents an exciting prospect for scientists and clinicians with an interest in the ‘science of mental life’. Clinicians, researchers, service users, carers, funders, commissioners, managers, policy-planners, ‘change’ experts –all have a part to play. Some long held ideas need examination, from the branding of psychological treatment types to considering what it is that people actually want treatment for. Scrutiny of new ideas should be rigorous yet encourage innovation.

Introduction [Section type heading]

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 research². Psychological treatments offer great promise for continued innovation, not least owing to the development of scientific methods and perspectives from many allied fields.

While researchers and industry struggle to produce new drugs for mental disorders: psychological treatments might have the potential to deliver acceptable, effective, and safe treatment options more quickly³. 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?

In the following sections, we use the term ‘mental disorder’. We note that in the wider literature many terms are used including mental health disorder, psychological disorder, psychiatric disorder, mental health problem, as well as other forms of psychological treatments terminology such as mental health difficulties, behavioural difficulties and so forth. For consistency the term mental disorder is used in the current commission.

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

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 treatments⁴, 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. For example, a 2014 commentary on improving psychology treatments stated “By the end of 2015, representatives of the leading clinical and neuroscience bodies should meet to hammer out the ten most pressing research questions for psychological treatments. This list should be disseminated to granting agencies, scientists, clinicians and the public internationally...reconsider the proportion of investments in mental health relative to other diseases”².

Panel 1. Methodology and approach used in preparing this Commission

This commission arose from an initial consultation meeting in December, 2015, in which researchers from a variety of backgrounds with interests or expertise in psychological treatments research met to discuss challenges in the field, and to lay out possibilities for a future research agenda for advancing the science of psychological treatments. The group's common interest was captured by Kazdin's call to arms to "reboot psychotherapy research and practice to reduce the burden of mental illness"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. We have cited only 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 perspectives, and that this is a start for necessary and continued discussion.

The commission is comprised of ten parts, each of which contains a theme that we consider critical to the development and improvement of research on psychological treatments: 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 disorder⁶, and more than 750,000 people die by suicide⁷. 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. The tremendous impact of these disorders is ongoing³⁹⁷. 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 disorders⁹.

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 expenditures¹⁰⁻¹². 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 2030¹³. 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-manage¹⁴.

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, however, these 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 treatment¹⁵. Coverage (i.e., the proportion of people who receive a consultation for a mental disorder) is 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%³⁹⁸. According to the 2014 Adult Psychiatric Morbidity Survey, there has been a welcome increase in people with common mental health disorders receiving treatment, largely attributed to the use of psychotropic medication¹⁶. Unfortunately, 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-base¹⁷.

Patient preference for psychological treatment options alongside restricted availability

In the USA, psychotherapy has assumed a less prominent role in mental health care²⁰. For example, in the USA the use of antidepressants almost doubled between 1996 and 2005¹⁸, (from 13 to 27 million individuals), whereas among antidepressant users the percentage of people who underwent psychotherapy declined from 31.50% to 19.87%.¹⁸ From 1999 to 2010, on average 8.6% of adult depression visits included the prescription of a Second-Generation Antipsychotic¹⁹ – this rate doubled during this period from 4.6% to 12.5%. By contrast, 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 treatment⁴. Meanwhile, clearly some patients prefer pharmacological treatment, and some might have no preference. We do not seek to reinforce what we believe to be a misplaced dichotomy between biological and psychological approaches (see *Part 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 the majority of patients prefer psychotherapies to medications, the availability of such treatments is a major problem in many if not most countries⁵, because of financial constraints, or because there are not enough trained psychotherapists to deliver the evidence-based treatments. This means that psychotherapies are mostly delivered in high-income countries, to those who can afford it and know the ways to find therapists. In low-income and middle-income countries, psychological treatments are scarce with notable exceptions²¹ (see also *Part 2, Worldwide*).

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 therapies⁹⁸. Internet-based interventions (see *Part 5*) can help in making psychotherapies available to those who need them because they can be offered relatively inexpensively and with a low threshold for access. Another important development to make therapies more accessible is to use lay-health counsellors (see *Part 2, Worldwide*).

Psychological treatment research in tomorrow's science

Improved psychological treatments are needed to help reduce the burden of mental disease worldwide. The psychological treatment research landscape is ripe for invigoration – it offers truly exciting and opportune areas for mental health sciences. Recruiting insights from multiple areas of science might allow us to ‘stand on the shoulders’ (to borrow a well-used metaphor from Isaac Newton)³⁹⁵ of existing evidence-based psychological treatments and ‘see further’ in order to improve psychological interventions. Greater collaborative endeavours between clinical and basic researchers of many disciplines will help in this regard².

Here we discuss opportunities to focus future research efforts to improve mental health. Ripe areas of enquiry include understanding the mechanisms that underlie psychological treatments, increasing their worldwide access, developing cross-modal treatment approaches, and (4) enhancing a preventative focus and developmental approach. To do this we need to harness tools provided by new technologies, improved trials methodology, and improved training in interdisciplinary mental health sciences to name but a few. The targets of psychological treatments should embrace challenging areas, such as the inherent complexities of mental health disorders and of suicide prevention, as illustrated here. We have addressed each of these ten key themes in separate parts of the Commission. The array of challenges ahead to which a psychological perspective can contribute will require fresh innovation.

Such research requires ideas to be tested, rejected, or developed in line with scientific method and the mental health challenges of the time (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 that we need change. 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 (figure 1). 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 resultant sculptures tend to be shown for a year, sometimes only months – sometimes there are gaps.

But the momentum and scrutiny continues. Some art works stand the test of time, some may not. 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 robust critical debate need to be a clear part of the way forward. The objects of enquiry might change, but the principles of seeking to improve our research efforts towards improved mental health will persist. Rather than being prescriptive regarding the future of psychological treatments research, this Commission sets out various suggestions and principles to guide the research that should apply across different mental disorders and transdiagnostic processes, approaches, countries and, indeed, to the new and future generations of mental health researchers. These principles might change over time and how best to strengthen psychological treatments should be subject of research, debate and discussion involving both the psychological treatments and mental health science fields, and many of those beyond.

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, 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, see Part 5) and that some psychological techniques can be effective when delivered by lay workers with modest training (see part 2). Moreover, neuroscience continues to reveal how efficiently the mind can work under various parameters (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, such as, why do effective psychological treatments work? The identification of specific targets for mechanistic questions might be facilitated not only by quantitative methods but also by qualitative methods, such as detailed narratives of individuals' experiences as they undergo psychological treatments. Once

potential targets have been identified in this way, they could be subjected to experimental investigation to establish causality for therapeutic change.

We 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.

Part 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). 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.

Introduction

It is known that certain psychological treatments are effective but we know little about the processes through which therapeutic change occurs. As Alan Kazdin has stated “Although there are many EBTs (*evidence based therapies*) available, there is little understanding of the mechanisms of change (i.e., precisely how they work)²³. Understanding mechanisms of action may be extremely important...”. Knowledge of mechanisms is essential to deriving and honing treatment strategies to target agents of change more directly, 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 to improve outcomes.

Mechanisms research presents exciting opportunities for psychological treatment research. However, most neuroscientific studies in psychopathology have taken simply described differences between groups of individuals with and without a diagnosis – an approach that cannot identify causal mechanisms. To move the field toward causality, we

should optimize research on mechanisms by framing it within a clinical treatment context to: a) understand how existing treatments work; b) improve these treatments; and c) derive new treatments.

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 functioning²⁴ 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 behaviours.

The processes through which psychological treatments produce change often overlap with, or complement, mechanisms that are responsible for the onset or particularly the maintenance of psychopathology (hereafter referred to as mechanisms of psychopathology). The NIMH Research Domain Criteria (RDoC) initiative is directing the search for mechanisms of psychopathology away from the constraints of categorical diagnostic criteria and towards dimensions of observable behavior and neurobiological measures²⁷². 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 comprising more specific subconstructs²⁵. 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.

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Mechanisms of psychopathology vary from being predominantly distal (e.g., effects of early life adversity that might have occurred many years previously upon inflammatory markers for depression²⁶) to predominantly proximal (e.g., ongoing biases in autobiographical memory for depression²⁷) (see²⁸ 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: for example, attention bias modification training for anxious individuals who exhibit selective bias of attention towards threat-relevant stimuli²⁹. Alternatively, psychological treatments may target factors that differ from but compensate for mechanisms of psychopathology, for example compensatory cognitive training for psychosis³⁰. Although 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 autism³¹.

What is the state of the field?

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 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 disorder³²⁻³⁴. Psychological treatments were developed to target those mechanisms precisely in the form of interoceptive exposure³⁵ (i.e., repeated exposure to interoceptive stimuli in the absence of aversive outcomes) and cognitive restructuring³⁶ (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 disorder³⁸. In this conceptualization, the distress-reducing effects of compulsive washing in response to obsessive thoughts of being contaminated reinforce and therefore increase 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 depression⁴⁰. This approach aims to increase access to positively rewarding stimuli and, more recently, achieve actions that are value driven and overcome task-related avoidance⁴¹. Behavioural activation for depression is highly effective relative to comparison control interventions, which included waitlist and nontargeted psychological control conditions (Hedges $g = 0.87$, CI 95% $0.60 \sim 1.15$ when collapsed across control conditions)⁴² [Overall, this mechanistic approach has 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 sizes⁴³, 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 controls⁴⁴ might indicate the importance of common factors (such as goal consensus, therapeutic alliance, empathy, expectations and therapist effects) that are relevant to all

psychotherapies⁴⁵. 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, the majority of studies to date have not evaluated mechanisms of treatment. Even the study of mediation is limited and often hindered by insufficiently rigorous methodology²³. 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. Similarly, while behavioural activation for depression might 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 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 is it 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 developed⁴⁶. Also, those therapeutic strategies that do not affect the critical processes can be removed, making

treatments more efficient as well as more effective⁴⁶. Moreover, by refuting 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 (panel 1).

<u>Panel 2. Reasons for Understanding Mechanisms of Psychological Treatments</u>
<ul style="list-style-type: none"> • Hone treatments to target processes responsible for change more directly and efficiently
<ul style="list-style-type: none"> • Uncover essential moderators of treatments outcome and improve precision in treatment matching
<ul style="list-style-type: none"> • Develop training programs for prevention of and recovery from psychopathology
<ul style="list-style-type: none"> • Eliminate wasteful and inefficient treatments
<ul style="list-style-type: none"> • Provide evidence for specificity above and beyond nonspecific factors responsible for the “dodo bird” effect

Knowledge of psychological treatment mechanisms might uncover moderators of treatment outcome, and thereby lead to greater precision in matching treatments to individual needs⁴⁴. For example, initial interest in attention bias modification training for anxious individuals waned as a result of mixed findings and small effect sizes⁴⁷. More recent research has provided some indication that the effects of attention bias modification training are larger for individuals with greater attentional bias at baseline²⁹ 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 might function in part by enhancing prefrontal cortex (PFC) inhibitory regulation over amygdala responding⁴⁹. 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 hyperactivation⁵⁰. If it can be established that exposure therapy works at least partially through enhancing PFC regulation of the amygdala, then exposure therapy might be more effective for the former

set of individuals with posttraumatic stress disorder compared to the latter. These examples simply illustrate ways in which the field could progress. Conclusive findings will depend upon replication with substantially larger samples.

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 mechanisms⁴⁶. To follow the prior example, by studying 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 serves 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). 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 example of such speculation is the hypothesis that behavioral activation for depression⁴¹ (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 ill health. Such attempts include training in mindfulness techniques to reduce affective memory bias and reduce development of, or relapse into, depressive ruminative states⁵¹. Another example is the delivery of cognitive behavioural therapy (CBT) as an adjunct to usual primary care for individuals who are depressed and have not responded well to medication alone⁵². In one study, short-term focused CBT was associated with significantly lower scores on depression three to five years later relative to usual care alone⁵². Similarly, cognitive therapy decreased recurrence of depression relative to

treatment as usual over a ten-year interval in remitted patients with histories of recurrent depression⁵³. 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 continued 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 for which psychological treatments (existing and newly developed) “hit” which processes. This evidence-base can and should include common factors as well as specific factors of psychotherapies²⁵. 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 effects⁵⁵. 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.

<u>Panel 3. Recommendations for Identifying Potential Mechanisms of Psychological Treatments</u>
<ul style="list-style-type: none"> • Develop a model of explanatory specificity • Experimental investigation of an explanatory construct to establish causal validity <ul style="list-style-type: none"> 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

Experimental psychopathology

As reviewed by Kazdin²³, 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 outcomes²³. Once theoretical mechanisms have been 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 neuroscience⁴⁶. 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 development⁵⁶. These findings could inform strategies aimed at increasing effective parenting to reduce the risk of mental health problems in offspring.

The direct application of identified mechanisms of psychopathology to mechanisms of psychological treatment is well-represented in fear learning and exposure therapies for

anxiety disorders. 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 therapy⁵⁷ (although there are some mixed effects, possibly due to mechanistic moderators⁵⁸). Another example derives from the evidence that retrieving already stored memories induces a process of reconsolidation⁵⁹. 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. 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 trauma⁶³. Pharmacological agents (sch as propranolol) and behavioural techniques (extinction) have been shown to interrupt the reconsolidation process in humans, albeit with some mixed results⁶⁰, limiting boundary conditions and conceptual challenges⁶².

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 depression²⁷. More mechanistic research is needed in general and particularly in young people, where there is great need for innovative psychological treatments that precisely target narrowly specified mechanisms consistent with developmental models of aetiology (*see also Part 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. 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 or dependence⁶⁵. 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 extinction⁶⁶. Advances in understanding the neurobiology of rodent self-grooming may identify potential treatment mechanisms for repetitive behaviours such as compulsions⁶⁷.

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 rodents⁶⁸. 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 punishment in rodents⁶⁹.

In spite of these examples of iterative reciprocal information flow between experimental studies in humans and animals, for the most part a huge gap exists between basic and clinical researchers, which 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.

Evaluation of mechanisms

Once a mechanism has been identified through careful experimental demonstration, for example via experimental psychopathology studies, then it can be evaluated within the context of adequately powered clinical trials. 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.

Kazdin²³ 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). Kazdin²³ lists several 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 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. Although for certain mechanistic questions appropriately powered experimental studies of small samples can be informative, the demonstration of these criteria will require large samples, so collaborative, multi-site studies will be needed, which will require a strong investment from funders and collaboration among researchers, focusing on common goals.

Finally, the field would be advanced by a listing of the various therapeutic elements that comprise psychological therapies, as has already been initiated⁷⁰. Psychological treatments are mostly packages of different elements, such as cognitive restructuring, self-monitoring, problem solving, relaxation training, or assertiveness training. The more elements that are combined in a psychological treatment, the harder it is to establish mechanistic specificity. Greater precision is likely from evaluating the mechanisms of particular procedural elements rather than combinations of elements⁷¹ (*see*

Panel 4). Greater collaboration between clinical researchers and basic scientists combined with new methods and technologies position us to make more headway than ever before in understanding the mechanisms of change in evidence-based psychological treatments.

<u>Panel 4. Recommendations for Evaluation of Mechanisms of Psychological Treatments</u>
<ul style="list-style-type: none"> • Evaluate within the context of adequately powered clinical trials
<ul style="list-style-type: none"> • 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)
<ul style="list-style-type: none"> • Establish mediation by showing change in mediator over treatment and that change in the mediator precedes and predicts clinical outcome
<ul style="list-style-type: none"> o Temporal precedence (change in mediator precedes and predicts subsequent change in symptoms); value of repeated measurement
<ul style="list-style-type: none"> o Specificity of mediation to a single or limited number of mediators
<ul style="list-style-type: none"> 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 theoretical relevance
<ul style="list-style-type: none"> o Dose response relationship between degree of change in mediator and degree of clinical improvement
<ul style="list-style-type: none"> o Consistency in independent replication
<ul style="list-style-type: none"> • Evaluate mediation for elements or specific therapeutic strategies rather than packages of treatment elements

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

Introduction

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

many people in high-income countries. Brief, flexible, modular and efficacious treatments derived from mechanistic research could enable us to adapt such treatments more efficiently 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.

Psychological treatments from an international perspective

As discussed, mental disorders constitute a significant part of the overall burden of disease worldwide^{8,73}. Mental disorders also interact with other serious health conditions such as cardiovascular diseases, ischemic stroke, and HIV, increasing the risk of premature death^{75,77}. Efficacious psychological treatments for a wide range of mental disorders have mainly been developed in North America or Europe, and are typically designed for delivery through one-to-one psychotherapy by highly trained professionals. However, at a global level, 90% of individuals with mental health problems do not receive treatment⁷⁸. 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 countries⁸⁰. 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.⁵

<u>Panel 5. What Increases Access to Psychological Treatments Worldwide?</u>
<ul style="list-style-type: none"> • Existence of low cost, simple, specific and effective treatments Task shifting: educating people without prior experience of work within mental health services to deliver psychological interventions
<ul style="list-style-type: none"> • 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
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| <ul style="list-style-type: none">• Cultural adaptation: rooting the treatment in sociocultural context (traditions, expectations, norms, symbols, etc.) to make sure that it is perceived as intended |
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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 LAMICs⁸¹. WHO estimated a shortage of 1.18 million mental health workers for 144 LAMICs⁸². 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 care⁸³.

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 5). Characteristics of psychological treatments would be advantageous for the successful scale-up of psychological treatments would be that they are brief, flexible, modular and efficacious, streamlined to remove any and all complexities unnecessary for treatment gains. Such treatments will be aided by research into mechanisms of action in psychological treatments (*see Part I*), and a consideration of the core psychopathology of, and across, mental disorders. Large and complicated psychological treatment packages can be delivered only 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. For example, if one of the major maintaining factors in depression concerns lack of positive reinforcement in daily life (*c.f. Part I, 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 in LAMICs has typically focussed on availability and access, and researchers have taken a pragmatic approach to treatment development itself. Future research will harness scientifically driven developments. Developing psychological treatments on the basis of sound psychological theories and empirical knowledge gained from research on the processes of action in treatment may afford particular strengths by opening opportunities for cultural adaptation and psychological treatment across international contexts. Research that has tested theories about the mechanisms of action of various forms of exposure therapy for anxiety disorders⁸⁸ 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 the findings of research on basic mechanisms will indicate potential for brief and highly efficacious psychological treatments². Future research needs to move such work into intervention formats and modules 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^{81,94-95}. Nevertheless, empirical questions remain: how best can we train people to become lay counsellors in a sustainable way, and what barriers might there be to such sustainability? The delivery of therapy in group rather than one-to-one has clear benefits for delivery efficiency since the therapist to patient ratio is decreased.

Other research questions include how many training, supervision, and booster sessions will be needed to ensure high quality delivery of treatments? The majority of studies

in which potential treatment group leaders have received brief training (1-4 weeks) have shown effective outcomes,⁹⁷ 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, IAPT⁹⁸ 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? Models of training inexperienced clinicians with the aid of computerized guides have been employed in primary care clinics in the USA, albeit on a much smaller scale than IAPT¹⁰⁰. 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 treatments⁹³ (*see also Part 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 high-income countries¹⁰² but few studies have tested such interventions in LAMICs¹⁰⁷. More research is required, particularly as mobile phones are rapidly becoming available worldwide, as is the availability of the Internet¹⁰⁸.

Low-intensity treatments delivered by computerized or mobile-based guided self-help technologies present an ideal early option in a stepped care model of treatment. National guidelines are starting to propose the use of low intensity treatments as a first option to improve the availability of efficacious treatments (e.g., for bulimia nervosa and binge eating disorder¹⁰⁹). Countries such as Sweden and Australia have led the way in research on Internet-based treatment and the implementation of low-intensity treatments with examples from eating disorders¹¹² to parent training¹¹¹ - for a meta-analysis for mental and somatic disorders, see¹¹⁰. Such work provides models and lessons that can be used or developed for improving access to care worldwide. For example, the internet may offer enhanced possibilities for long-term follow-up after a standard course of psychological treatment has ended and the implementation of booster sessions.

Contextual factors 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 sustainability¹¹⁸. 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 persecution¹¹⁹. 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 media such as radio and TV to combat the stigma related to mental health and seeking treatment for mental health problems warrants investigation. 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 Mexico¹²⁰ is a good example of the effective application of such strategies to reduce stigma. . The “Headspace” initiative in Australia (<https://www.headspace.org.au>) 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. Evidence from the UK¹²¹ 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). 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 Part 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.

<u>Panel 6. Example Directions for Future Research to Improve Access to Psychological Treatments Worldwide</u>
<ul style="list-style-type: none">• Build brief, flexible, modular and efficacious treatments which are streamlined based on knowledge from research on mechanisms of action in psychological treatments
<ul style="list-style-type: none">• 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
<ul style="list-style-type: none">• 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
<ul style="list-style-type: none">• Investigate how new models of delivery of psychological treatments can be scaled up in a <i>sustainable</i> way since the long-term sustainability of most models is unclear
<ul style="list-style-type: none">• Investigate the use of media such as TV, Radio, and Internet to combat the stigma related to mental illness

There is a need to continue to work towards increasing global access to psychological treatments – both for individuals in LAMICs, but also those in high income nations. Research on psychological treatments will position us to continue to develop and evaluate the efficacy

of brief, flexible interventions which could be focussed on precise mechanisms of action that in turn can be adapted to meet the needs of individuals in different cultural contexts. Training lay people to deliver such interventions and scaling treatments for delivery in a manner that is sustainable in the long-term are two key directions for future work.

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

Introduction

Both pharmacological and psychological interventions are commonly recommended as first line treatments in psychiatry and the potential for enhancing treatment action through combination approaches has started to attract research interest. However, the optimal method for treatment combination is far from clear and requires dedicated research in preclinical, 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 programmes.

Creating synergy and avoiding harm with combination treatments

An individual with a mental health disorder(s) 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 (panel 7). However, current clinical guidelines include little about combination treatments and the vast majority of research 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. The generalisation of research based on single treatments to the typical clinical reality of combination in practice lacks validity. Exciting basic and clinical science questions arise about what does happen when psychological treatment is combined with other therapeutic approaches.

Empirical studies suggest that there might be small benefits, for example, when a psychological treatment (such as CBT) and a pharmacological treatment (such as a selective

serotonin reuptake inhibitor, SSRI) are combined in the acute treatment of emotional disorders including depression¹²⁶. 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 Part 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 CBT's benefits⁵⁸, although see¹²⁹. 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 discontinuation¹²⁸
- 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 has utilised recent developments in neuroscience and experimental psychology⁸⁸. Understanding the molecular basis of memory processes provides targets that might 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}. Drug treatments that facilitate extinction of fear associations, reduce reconsolidation of troublesome aversive memories, or enhance retention of more positive memories or experiences during therapy might be useful 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 disorder⁵⁸. 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 disorders¹²⁹. 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 volunteers¹³¹. 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 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 models⁵⁸ (*see also Part 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 Part 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. 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. We 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 treatments¹³² and employing psychological outcome measures to explore the effects of drug treatment¹³³.

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 2*). 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}.

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. Shiroma et al.¹³⁶ reported that increased positive bias induced with antidepressant drug treatment interacted with interpersonal support in the patients' environment to predict therapeutic response (*figure 3*). This kind of inter-disciplinary approach 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 intervention¹³⁴ which has the potential to increase interaction with the environment (such as behavioural activation), may remove a barrier to successful antidepressant drug treatment (*figure 2*).

To facilitate interdisciplinary combination approaches, 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 strategy¹³⁷. We need to build on this exciting initiative, call researchers across fields and set strategic funding to strengthen this early promise.

Testing the efficacy of combination treatments

Developing and assessing the efficacy of combination treatment also raises complexities for trial design and methodology (*see also Part 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 drug¹³⁸. This field of combination treatments will therefore benefit from a variety 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 pharmacological¹³⁹ and psychological¹⁴⁰ 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 dorsolateral prefrontal cortex was assessed using reactivity to a stressor as a proxy marker of efficacy in healthy volunteers¹⁴¹. The effects of cognitive bias modification and SSRI treatment alone and in combination have 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 volunteers¹⁴². Early changes in these measures are associated with later therapeutic benefit in patient groups¹³⁶ 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 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 might 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 ?*). Promising

treatment combinations and timing of treatment combinations might be isolated by pattern analysis from large data sets. To facilitate this, it is important to standardise assessments and the treatment elements (*see also Part 8 and Panel 18*). 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

Finally and importantly, patient preference should be considered when evaluating the effects of combination treatment. Individuals often express a preference for either psychological or pharmacological treatment, so the combination might 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 concepts¹³³. Challenging these assumptions and creating more synergy at multiple levels (including the public, clinicians and scientists) will be a critical step towards optimal development of treatments. The ethical implications of combination treatments and their development should be incorporated along with these areas for research strategy. Finally, we 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 lessened¹⁴³. 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 (panel 8).

<p style="text-align: center;"><u>Panel 8. Example directions for Future Research in Combination Treatment Approaches</u></p>
<ul style="list-style-type: none">• Development and validation of preclinical animal and human models for proof of principle studies and mechanistic focus in combination treatment research

<ul style="list-style-type: none"> • Elucidating the optimal parameters for enhanced learning with drug treatment approaches and the consideration of individual differences in this response
<ul style="list-style-type: none"> • 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.
<ul style="list-style-type: none"> • Clinical studies informed by proof of principle work to test the efficacy of treatments alone and in combination across disorders
<ul style="list-style-type: none"> • 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.
<ul style="list-style-type: none"> • 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 2: *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 depression¹³³. 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.*

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

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

Introduction

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

Prevention of mental disorders is 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 emerged¹⁶⁸. 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^{144,145}. 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, 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 years¹⁴⁷. There is enormous potential to either prevent mental health problems or to intervene early to reduce the 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 present time, there is a potentially greater role in early life for psychological approaches than for 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 and scientific and clinical challenges have to be met².

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 disorder¹⁴⁸. 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 programmes 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 areas¹⁴⁹; 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 intervention¹⁵⁰).

Requirements and challenges for prevention and early intervention

Preventive approaches in childhood and adolescence (panel 9) require the identification of risk factors or at-risk groups (unless an intervention is going to be delivered to the whole population).¹⁴⁴ Key early-life risk factors include 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 parent¹⁵¹. 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. However, many early interventions do not have sufficient evidence to be considered to be effective. Developing and testing early interventions that might reduce 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 but this is not the case: almost any intervention that 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 disorders¹⁵². 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 effects¹⁵³.

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 intervention¹⁵⁶). Disentangling these challenging problems is made more difficult when the components of a psychological intervention are not clearly specified or publically available, perhaps for commercial or some other protective reason.

A further challenge is a lack of understanding of the mechanisms by which intervention occurs in many preventive and early interventions. As set out in Part 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 be 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 Part 8 *Complexities*). There are relatively few well-studied examples of this, although some are emerging. For example, research has found that there is no significant evidence that young children at risk of anxiety disorders possess the specific cognitive biases for emotional stimuli¹⁵⁷, where such biases have been identified in adults with anxiety. In early childhood there will also be a need to go beyond the individualised mechanisms suggested in the RDoC explanatory constructs (*see Part 1, Mechanisms*). For example, other mechanisms, existing in the social world of young children, might 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. Parental sensitivity has been shown to be a key mechanism of change, for example in the context of attachment¹⁵⁹, although the detailed processes which might then lead to the development of psychopathology remain to be elucidated. A better understanding of mechanisms underlying treatment gains will also be critical for any step-change in effectiveness of prevention and early intervention.

Making interventions stick - persistence of effects

Another challenge for preventive and early intervention approaches, which is shared with many other forms of psychological intervention, is how to make interventions “stick” - 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. Relatively few psychological interventions have convincing evidence of sustained benefit. We need developments in psychological science to inform how 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 Part 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 technologies¹⁶¹. A further approach is to take interventions into schools¹⁶². 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

Three groups of interventions illustrate that preventive intervention and early intervention are possible from very early in life, and that longer-lasting benefits are possible (panel 10). All three interventions are derived from scientifically rigorous, sustained approaches to intervention development, 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 or early

interventions do exist, with varying levels of research evidence to support them in a range of psychological or psychiatric conditions.

Panel 10. Examples of Promising Preventive and Early Intervention Approaches

Example 1: During infancy, brief, focussed interventions such as ViPP (Video Feedback to Promote Positive Parenting: for example, see¹⁶⁴) 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 11 years later, although only convincingly in girls, and shown to be cost-effective using Australian criteria for cost-effectiveness¹⁵⁰.

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 behaviour¹⁶⁶. Longer-lasting benefits have been demonstrated, and economic modelling studies point to societal, financial and individual health gain¹⁶⁷.

Prevention of mental disorders in adults

In the past two decades, randomized controlled trials have shown that it is 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 CBT or interpersonal psychotherapy (IPT), have 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. Meta-analyses confirm

these interventions effectively reduce the incidence of new cases of depressive disorders by about 20 to 25%^{169,170}, and prevent or delay 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). Preventing the onset of mental disorders is one of the most promising areas in which research on psychological interventions can help to reduce the disease burden of mental disorders.

The challenges ahead

Clearly, more research is essential to expand our repertoire of approaches and the range of mental health disorders that can be addressed. This includes early preventive approaches focussed on infancy and childhood, and interventions through adolescence, when young people begin to present with many of the common mental health problems that will affect them through adult life. These approaches need to be theory-driven and rigorously trialled (*see Part 1 Mechanisms and Part 6 Trials*).

Particular attention should be paid to ensuring that interventions can produce effects with 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 scale¹⁷³ (*see Part 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 examples considered above provide optimism for future developments, but we 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) (panel 11). 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 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. Research questions 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?

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

Introduction

Internet-based psychological treatments have been applied across a broad range of mental 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 psychological assessment and treatments. In brief, technological innovations offer considerable possibilities to innovate psychological treatments, to adjust them to daily life and to the persons using them, and improve access to treatment. Such knowledge could be used to better understand how therapies work and to make them easier to use, so that more people can benefit from psychological treatments. Developments should be theory driven and properly evaluated.

Internet-based psychological treatments

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, learning how to apply a psychological treatment to themselves with the help of a coach or psychologist¹⁰¹. 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. Direct comparisons between face-to-face interventions and guided Internet interventions suggest that there are no major differences in efficacy between the two treatment formats¹¹⁰. The efficacy of Internet-based therapies (*see panel 12*) has been shown for a broad range of mental health problems: depression¹⁷⁴, anxiety disorders¹⁷⁵, sleep problems¹⁷⁶, bulimia¹⁷⁵, and alcohol problems¹⁷⁸.

Panel 12. What Do We Mean by New Technologies?

- Internet intervention: can be defined as any therapy that is delivered with the help of technology (for example through chat sessions, skype, or email), but most research has focused on Internet-based self-help interventions, so we focus on these treatments. If we refer to Internet interventions, we mean these treatments, unless we explicitly say otherwise.
- 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)
-
- 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 objectives¹⁸⁰.

Internet interventions 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 travelling time, reduce the stigma of going to a therapist, and ease psychological help for individuals who are hard of hearing¹⁸¹. Furthermore, they might reach patients who cannot be reached with more traditional forms of treatment. Interventions can 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, Internet interventions have numerous advantages. One major advantage is that recruiting patients and conducting RCTs of Internet interventions is much easier and more cost effective and efficient than conducting RCTs of traditional face-to-face psychotherapies (*see Part 6, Trials*). ~~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 by allowed larger scale trials powered to examine complex questions (*see Part 8, Complexities*) or to test for weaker effects (e.g. prevention trials).

Internet interventions also have limitations. 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). Drop-out rates are higher in Internet-based interventions than in face-to-face therapies¹⁸³ and it is not known whether patients who drop out get worse because of the intervention. Internet interventions might 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 alliance¹⁸⁴. Relatively little research has focused on the long-term effects of Internet interventions (the same is true for face-to-face psychological treatments). We also acknowledge that Internet interventions might have unknown disadvantages, such as misunderstandings due to reduced communication channels in unguided interventions and schematization of contents. Data security as well as privacy should be well-guarded for any intervention that is offered through the Internet. Finally, despite increasing access, the Internet is not yet accessible to many potential users around the world, and dissemination will depend on the attitudes of possible

users and health care professionals. However, even in LAMIC countries access to the internet and/or mobile phone is expanding exponentially (*see Part 2, Mental Health Worldwide*), although creative solutions (e.g., regarding literacy) may need to be taken into consideration.

Other technological opportunities

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 Part 8, Complexities*). Such information might 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 than traditional forms of outcome monitoring such as pen and paper questionnaires¹⁸⁶. Several virtual reality treatments have been developed, mainly for anxiety disorders,. 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 with some evidence of effectiveness,¹⁸⁸ although many of the trials are small and of suboptimal quality. A considerable number of studies have demonstrated that telephone-supported therapies are effective in the treatment of common mental disorders¹⁹⁰.

There is a rapid proliferation of mental health ‘apps’ which offer a range of psychological interventions,¹⁹¹ however, most lack health behaviour theory and evidence for the effectiveness¹⁹². Future research must 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 developments¹⁹⁵. Widely available and untested products pose risks to the public. In this young field, while efforts have started, international approaches are 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 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 delivery¹⁹⁶. 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 CBT for the treatment of adolescents seeking help for depression.

At some point, the automated support of these new technologies might in some cases replace the therapist altogether ('therapist-free therapy'¹⁹⁷), and lead to better, personalised treatments (*see also Part 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 ideation¹⁹⁸, and there is evidence that certain phrases and the use of personal pronouns for example predict depression status in blogs (*see also Part 9, Suicide*), although we acknowledge that this may raise ethical concerns¹⁹⁸. 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.

Finally, 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) are examples of ways in which technology has been harnessed to innovate psychological treatments, their availability and evaluation. Technological advances need to go along advances in psychological theory and understanding of mechanisms of change. Future technological innovations offer considerable possibilities to innovate psychological treatments (*see 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

Part 6 Trials to evaluate psychological therapies

Introduction

Several key issues in the design and conduct of clinical trials for the evaluation of psychological therapies must be addressed in the development of evidence-based psychological therapies. These issues present 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 prevention of bias

in trial design and analysis. The opportunities include the increasing role of service users and carers in all aspects of trial design and conduct, the 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).

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 trial to evaluate CBT 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 people¹⁹⁹. This trial 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: a small trial conducted to determine whether a larger clinical trial can be done e.g. capacity to recruit a specific sample[Joan: this is tautologous, can you give some examples of what might be tested for feasibility?].
 - A pilot study: a small trial that 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 contribute to a larger trial assuming there are no changes required, or an external pilot, where the data are analysed and set aside.

- A randomised controlled trial: a study in which participants are allocated to a particular condition (usually a treatment ‘arm’) on the basis of random assignment to produce an equal distribution of measured and, crucially, unmeasured variables. Ideally, treatment allocations are hidden from recruiters, participants, and assessors. The ‘controlled’ nature refers to using comparators (the conditions to which an intervention 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: 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 guideline²⁰⁰, 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: many potential sources of bias 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), amount of missing data and selective reporting of outcomes
- Blinding: This refers to whether participants or staff are aware of the treatment allocation. Note single blinding versus double blinding is a key difference between psychological versus pharmacological trials.
- Protocolised treatment: an attempt to standardize the delivery of a psychological therapy, 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

Clinical trials are the cornerstone of evidence-based approaches to decisions about access to healthcare but in the field of mental health, such trials often have significant methodological shortcomings that result in low quality evidence. Many psychotherapy trials are not registered in an international database before recruitment starts²⁰¹. This means that we cannot be certain that the outcomes reported 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 psychotherapy trials did not attempt to maintain blinding in the raters,²⁰¹ 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. 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 methodologies²⁰². In the past decade, for psychological treatment trials, there has been substantial improvement in the adoption of clinical trial registration and pre-specification of primary outcome including CONSORT criteria (panel 14). Such procedures are increasingly required by the leading journals and by ethical review boards. Particular adaptations for psychological trials need to be 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 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 SAEs²⁰⁷. Negative effects that require recording

range from worsening of existing symptoms to issues such as novel symptoms, poor therapeutic relationship, and perceived coercion²⁰³. Such adverse events are present in both traditional psychotherapies and internet-based interventions²⁰⁴. 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 practice²⁰⁵. Formalized measures of possible harms (side effects) of treatment trials should be the rule rather than 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 could ensure superior trial design, conduct and reporting, that other fields could aspire to meet. Since the introduction of the CONSORT guidelines,²⁰⁰ many 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. Yet, not all criteria can be met given that, for instance, double blinding in these types of studies is not usually possible. However, double blinding can be problematic for pharmacological treatments – despite best intentions, aspects of the treatments can break the blind, for example the rapid and dramatic weight gain and parkinsonian side effects with both first and second generation antipsychotics. Another possibility is that subjective cognitive effects²⁰⁸ unblind participants.

A set of reporting standards specifically tailored to psychological therapy trials are being developed as an extension of the original CONSORT guidelines²⁰⁹. 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.

Conflicts of interest

The conduct of a clinical trial by the developer of a psychological therapy could be considered equivalent in terms of bias to industry-sponsored trials of pharmacological therapies and investigator allegiance effects have been observed in psychological therapy trials^{210, 211}. A focus has been more on allegiance to a given type of psychotherapy than finance. The obstacles to obtaining funding to conduct the trial are likely to be greater for psychological therapies than for industry-sponsored pharmaceutical trials, and although trials of psychological therapies may be conceived and conducted by the originator, they are rarely funded by the originator. Steps can be taken to reduce bias, such as 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. 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 an entry criterion, 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 Part 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 depression²¹²). Even trials that have focused on mechanisms of change, such as whether reducing worry processes results in reduction in

paranoid thinking, have allowed comorbidities²¹³. 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 *Part 8 Complexity*, for further discussion of these issues).

Better integration of research trials within clinical settings would facilitate the generalisability of results to the real world. One goal is for every individual who attends a hospital clinic, 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.

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, 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 condition²¹⁴, perhaps across trial sites, 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 depression²¹⁷, although CBT is superior in the case of psychosis²¹⁸.

Clinical psychological trial experts such as Kazdin have formulated models 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 alone²¹⁹). If the question is whether one form of psychotherapy is better than another, then a head to head comparison may be required. 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. Findings from meta-analyses suggest that waiting list controls should 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 therapy⁴³.

Outcome measures

Most trial methodologists would recommend a single primary outcome and a single time point pre-specified at which this main outcome should be measured (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, as well as to track the time course of the response. However, there may be times when more than one primary outcome is justified (e.g., in psychosis studies, clinicians prefer psychiatric symptoms whereas service users prefer social outcomes),²²⁰ 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 latter²²⁰ Consensus regarding outcome measures for a specific condition would enable individual participant data meta-analyses²²¹⁻²²³, which can hopefully inform the moderators and mediators of treatment response (i.e., what works for whom; *see also Part 8, Complexities*). Integration with and adoption of routinely collected service outcome data would also facilitate this. As part of 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 psychosis²²⁴. 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. 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, this would increase confidence in findings.

Another important consideration when selecting outcomes is the time required to complete the overall battery of assessments. Psychological therapy trials often include numerous secondary outcome measures, which might be of significant interest. However, the greater the assessment burden on participants, the more likely it is to impair retention in the trial and subsequently result in missing data in the outcomes, reducing the internal validity of the trial. Limiting the selection of outcome measures is likely to minimise attrition, but limits opportunities for understanding processes of change. Similarly, agreement regarding the frequency of assessment occasions and length of follow-up would facilitate the pooling of data and the capacity for comparisons across trials. 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 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 *Part 8 Complexity*).

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 clinical trials, including identification of the most important and relevant research questions and thus outcome measures. 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). The assessment of acceptability of psychological therapies, as well as exploration of potential adverse effects, can be 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).

Public and patient involvement can be via consultancy groups (which was the case for the COMPARE trial), via priority setting partnerships that identify and prioritise the top ten unanswered questions (the James Lind Alliance facilitate the development of such partnerships; see <http://www.jla.nihr.ac.uk/>) which has been done for the treatment uncertainties related to a diagnosis of schizophrenia²²⁸, 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 recovery²²⁹ and identifying treatment priorities and preferences²³⁰).

Mechanisms and mediators of change

Trial design should also attempt to facilitate the identification of potential mechanisms and mediators of change (*see Part 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 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 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 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 help with the accurate identification of mechanisms of change and mediators of treatment outcome. Traditional approaches to mediation analysis²³¹ 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 might 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 CBT²³⁴ 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 session²³⁵ (*see Part 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 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 provides an opportunity to improve such meta-analyses.

Collaboration between research groups, investigators, and methodologists with regard to future pooling of data could be facilitated by the establishment of collective research groups recognised by group authorship, which would incentivise such involvement and co-operation.

At times, there is a need for alternative approaches to the traditional two-arm randomised controlled trial, such as multi-arm multi-stage trials²³⁶.

New methodologies, including adaptive designs, preference trials, and sequential, multiple assignment, randomised trials (SMART trials), 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 future clinical advantages such as more rapidly arriving at a suitable treatment for an individual. 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 or medication that would jeopardise recruitment, generalisability 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 proved to be inferior. Cohort multiple randomised controlled trial design²³⁹ 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 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. In all cases, collaboration among experts in trial design and analysis, experts in the development of psychological therapies and experts by lived experience will be essential.

Better detection of responders and non-responders would allow us to identify what works for whom (see *Part 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 *Part 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.

Finally, it is important to recognise that research to identify successful interventions is not just about RCTs, 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. 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. Another example would be developing methodologies for pragmatic studies in real world settings that encompass co-morbidities both mental and physical and allow us to move beyond standard RCTs.

Finally, 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, increase the confidence in and acceptance of their findings (see panel 15). Developments in three areas could dramatically improve trial quality in the evaluation of psychological therapies. 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, creation 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 enhance the credibility of the results of our clinical trials. Psychological treatment trials stand to benefit from advances in trials in other areas of medicine. Increased attention to and innovation in clinical trial methodology is to be welcomed.

<u>Panel 15. Directions and Priorities for Future Research in Clinical Trials of Psychological Treatments</u>
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • We need to routinely build into the design of clinical trials the ability to analyse for mechanisms (see <i>Part 1, Mechanisms</i>)
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • We need to ensure quality trial design and valid, reliable analysis of data by routine, early engagement with Clinical Trials Units, trials 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
<ul style="list-style-type: none"> • 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

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

Introduction

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 USA. 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 treatment²⁴¹. 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. 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, by taking a scientist practitioner approach, training in psychological treatment becomes far more than just learning to deliver the treatment described in a manual. By understanding the principles on which a treatment was derived this can help the practitioner best deliver the treatment and adapt to a given situation or patient. An example of where basic training is important includes 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 Part 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 extinction²⁴⁴. 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. Since this can also be counterintuitive from the perspective of some other therapeutic approaches, it can be important to understand the principles behind exposure techniques. Another example of practitioners benefiting from understanding the underlying science via their training is in the context of depression; namely the influential “learned helplessness” model²⁴⁵, and its later modifications in relation to hopelessness²⁴⁶. This model originated from the finding that animals exposed to inescapable aversive stimuli subsequently failed to escape when they had the option to do so²⁴⁷. Learned helplessness theory made important contributions to our understanding of risk factors for depression, especially relating to the roles of attributional style and perceived controllability²⁴⁸. 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 treatment²⁴⁹.

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 work in the same building as, for example, social scientists, economists, neuroscientists or geneticists. This reduces the opportunity to interact and share ideas. 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 limited².

Renewing the links between basic research and psychological treatments

Clinicians providing psychological treatments need training in basic research

In most countries, relatively little teaching of contemporary basic research (for example, experimental psychology, neuroscience, genetics, physiology, pharmacology, data science, social science, economics) is incorporated into the clinical syllabuses of clinical psychology or psychiatry, or of allied professional training in mental health treatment. The USA 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 USA has been emphasised²⁵⁰, although there is recognition within the profession that further such training would be desirable^{251, 396396}. 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. 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. 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.

Basic researchers need training in clinical conditions and psychological treatments

Most basic researchers, despite enthusiasm for the notion that their research might contribute to improved mental health treatments, 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 experience². 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 an elementary 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 16. An Example of How Linking Training in Neuroscience to Clinical Need 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 treatment²⁵², and psychological treatments⁴⁰⁰. Clinicians appreciate this as an area of specific need in which current treatments are inadequate.
- 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 circuits²⁵³, 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 systems²⁵⁵.
- 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 depression²⁵⁶

that were originally motivated by ideas derived from behaviourism⁴⁰, and that are known to increase responsivity in the brain's reward system²⁵⁷. 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 activities¹⁶. 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} (though not depression overall) This type of focussed approach has been incorporated 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. In the UK, 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, 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 MRC [Joan: leave here for Production to insert as margin links: <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>]. This provides a valuable springboard for a clinical research career, but there is scope for much

greater 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 USA, which emphasizes the science of clinical psychology in training and internships, would also be an effective way of increasing research training opportunities. A 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.

Culture change needed 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 in terms of both clinical accreditation and funding. A huge amount of research talent exists 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. 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. 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. 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

Finally, even amongst those clinical psychologists who do enter academia, few forums exist 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, some clinical psychologists and neuroscience researchers have started to work together to produce new ideas for intervention. A good example is the adoption of ideas from the literature on the neuroscience of reconsolidation – the modification of old memories during their reactivation - in the formulation of new treatment approaches for PTSD²⁶⁰. 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 trauma⁶³. Although this line of research requires considerable further work to demonstrate robust clinical efficacy^{263, 264} (*see Part 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 16*).

In the 1950s and 1960s, 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 (*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.

<u>Panel 17. Example Directions for the Future of Training and Links between Clinical and Basic Science</u>
<ul style="list-style-type: none"> • Opportunities for integrated clinical and academic training in psychology, through extended programmes, targeted at those clinicians with the greatest research potential
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Provision of “next steps” seminars focused on academic training as a standard part of mental health clinical training programmes

<ul style="list-style-type: none"> • 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/)
<ul style="list-style-type: none"> • Training programmes on which clinical psychology, psychiatry and basic research trainees have the opportunity to learn alongside each other
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Use of the continuing professional development framework to enhance the understanding of basic science understanding among psychological treatment practitioners

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

Introduction

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. Leading clinical guidelines recommend specific treatments for each mental health disorder, usually categorically defined by symptomatology^{e.g.265,266}. However, the reality of mental health conditions is more complex, and characterised by an enormous individual variety. Heterogeneity in symptomatology across mental health conditions is very common²⁶⁷ and many individuals suffer from more than one mental health disorder (i.e., co-morbidity^{268, 269}). 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 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. More studies are needed to examine whether these approaches improve the effectiveness of treatments for mental health disorders.

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 another as presumed by the network approach²⁷⁰. 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 factor²⁷⁰.

Mental health conditions are dimensional in nature, yet most mental health researchers use a categorical model to study the effects of treatments. The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5²⁷¹) 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. In the last few years, initiatives have been taken, for instance by the RDoC initiative²⁷², to stimulate research on dimensions of observable behavior and neurobiological measures instead of categorical diagnostic criteria of mental health disorders (see Part 1).

An additional complexity factor is individual differences at the level of psychopathology. 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 gone²⁷⁴. 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.

Mental health conditions are complex to study due to the interplay between individual emotions, cognitions, and physiology (and other factors) and their interactions with the environment, which change over time (*see Part I* 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 (such as the death of a loved one) are consistent risk factors for onset of the first episode, while less stressful events (for instance getting a minor traffic ticket) are sufficient to trigger a subsequent depressive episode for individuals who have experienced one or two previous depressive episodes²⁷⁷. Enormous individual differences have also been found in emotional fluctuations – an important component of many mental health disorders - and how emotions change over time within mental health disorders²⁷⁵.

Further, at least 45% of people suffering from mental health disorders have more than one disorder, i.e., co-morbidity (*see Panel 18*), while many more have sub-syndromal symptoms of other conditions²⁶⁸. 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 2016, including co-morbidity of mental health conditions, has risen substantially²⁷⁸. Co-morbidity is consistently associated with a greater demand for professional help, a poorer prognosis, greater interference with everyday life, and higher suicide rates^{e.g. 281, 282}. 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^{287, 289}. Dimensional models have been proposed to explain co-morbidity, and mostly suggest shared factors for the concurrent disorders (such as neuroticism²⁹¹), and some dimensional models add specific factors that differentiate among disorders^{e.g.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. As shown in Figure 5, the dimensional tri-level hierarchical model of co-morbidity between MDD and generalized anxiety disorders 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).

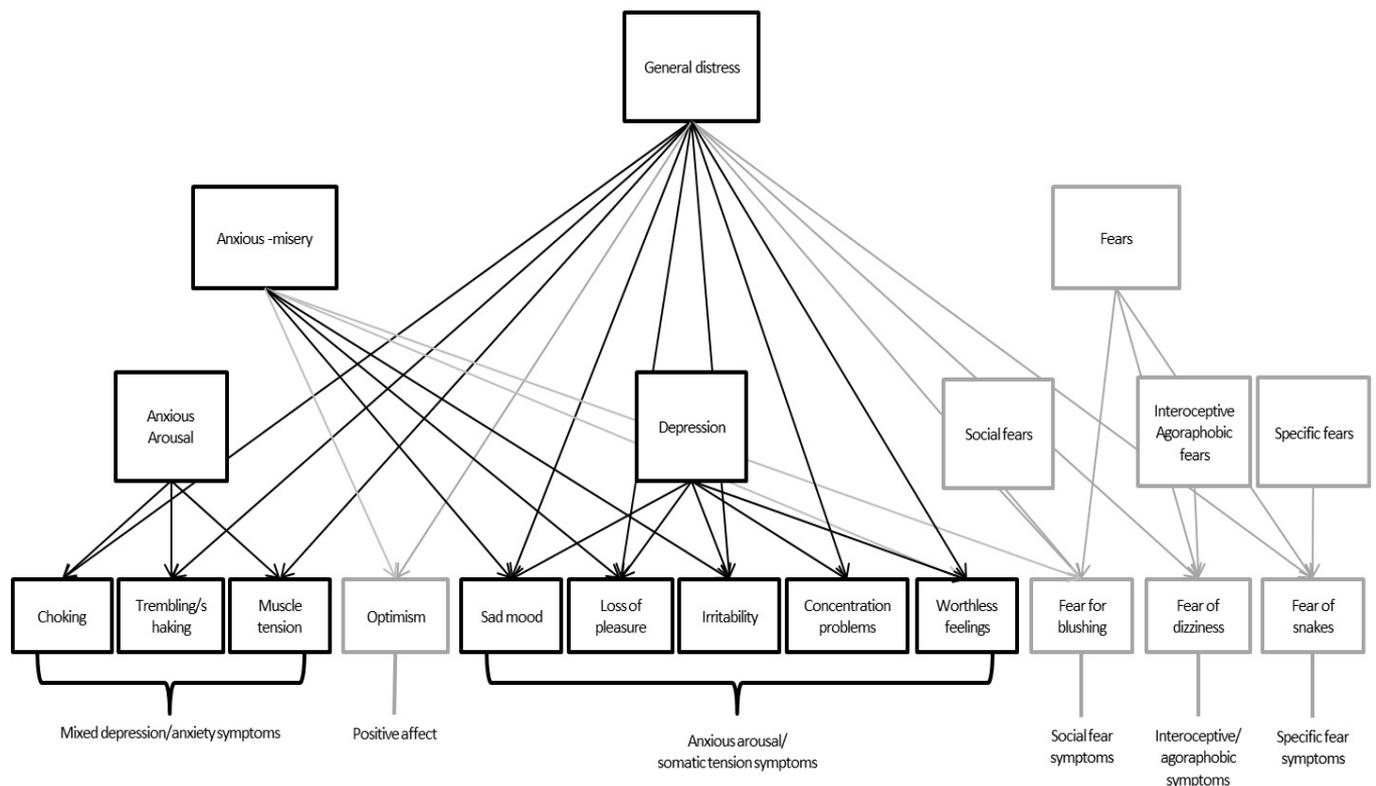


Figure 5. Co-morbid Major Depressive Disorder and Generalized Anxiety Disorder symptomatology explained by tri-level hierarchical model of depression and anxiety (based on²⁹⁴). Black boxes and lines represent factors and symptoms related to the co-morbidity.

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)²⁷⁰. Thus, co-morbidity might be the result of shared symptoms across mental health disorders, so called bridge symptoms.

Figure 6 represents an example of a dynamic network of MDD symptoms that mutually reinforce other symptoms of MDD and co-morbid Generalized Anxiety Disorder symptoms (adapted figure, based on²⁷⁰). 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 Generalized Anxiety Disorder^{270, 295}. Additionally, there might 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., 270, 295}. The network approach does not explain why some individuals are more prone to co-morbidity (having more symptoms) than others.

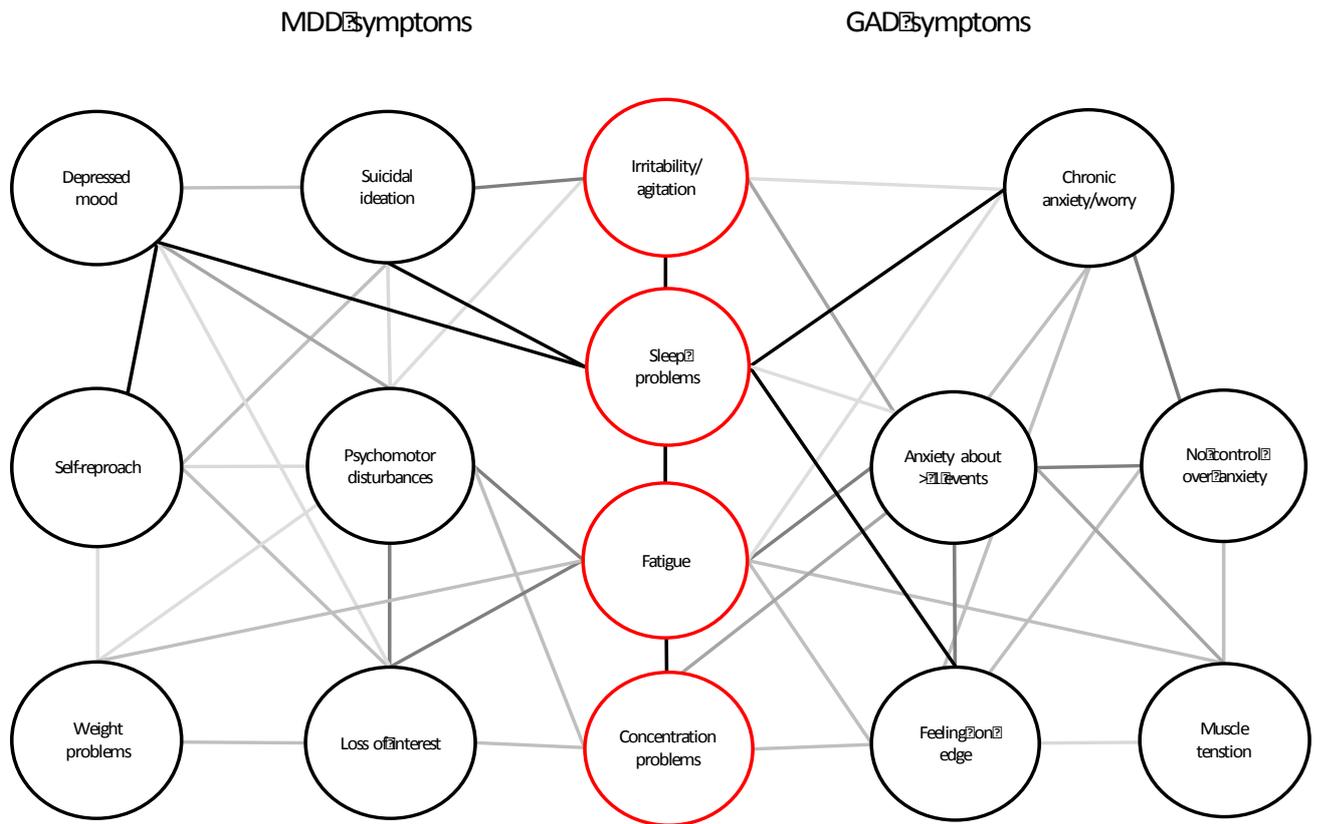


Figure 6. Hypothetical dynamic network of Major Depressive Disorder (MDD) symptoms that mutually reinforce other symptoms of MDD and comorbid Generalized Anxiety Disorder Symptoms (GAD, adapted from²⁷⁰). Nodes represent symptoms and edges denote the causal relationship between symptoms. Darker edges 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 18. 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 mechanisms²⁹⁶
- 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 CBT for specific anxiety disorders also reduce depressive symptomatology²⁹⁷), 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 method or ecological momentary assessment can be used to develop personalized models of psychopathology²⁹⁸. Experience sampling method refer to a collection of research methods by which a client repeatedly reports on symptoms, affect, behaviour, and cognitions close in time to experience and in the clients' daily life, for instance by using an application on a mobile phone (*see Part 5, Technology*). Given that experience sampling method gather 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. Systematic reviews have stressed the value of experience sampling method for assessing symptom fluctuations and interactions over time in anxiety disorders²⁹⁹, depressive disorders³⁰⁰, and substance use³⁰¹. Studying transient processes of emotions, cognitions, symptoms and stress (and other relevant factors) in daily life can be done in prospective studies, as well as in experimental studies, such as a RCT (*see Part 6, Trials*). For instance, alongside a RCT of the effectiveness of three relapse prevention treatments in depression, an ecological momentary assessment study was incorporated in a subset of participants who had remitted from recurrent depression. This assessed 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 phone³⁰². Given these ecological momentary assessment studies are self-report questionnaires, it might be useful to add physiological and behavioural 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 18*). The goal of the personal medicine approach is to optimise the response to treatment based on an individual's unique characteristics (ranging from genetic and neurobiological factors to symptoms) and underlying mechanisms (*see Panel 18*). Ecological momentary assessment might improve our insight into the specific diagnosis^{303,304} and offer valuable information that might improve patient-treatment matching. For instance, assessing daily fluctuations in positive and negative emotions using experience sampling method in depression predicts response to treatment in depression³⁰⁵. Assessing individual change over time in emotions (and other processes) while undergoing therapy (for instance in the context of an RCT) 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 score³⁰⁶ comparing psychological versus pharmacological treatments for depression. Future studies should examine whether treatment matching can be improved for individuals with comorbid mental health disorders. Related approaches include clinical risk scoring, as currently used within the medical field³⁰⁷. For example, treatments for lung cancer are further improved by molecular testing for targeted therapies that can overcome resistance to first-generation drugs³⁰⁸. 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 *Part 1 (Mechanisms)*, 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)⁴⁸.

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 patient²⁷⁷. For instance, an RCT in 102 depressed patients showed that the efficacy of pharmacological treatment could be enhanced by adding experience sampling method -derived feedback on personalized patterns of positive affect to the clinician and the patient³⁰⁹. Collecting ecological momentary assessment data with comparable assessments within clinical settings 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 (see *Part 6, Trials*). 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 of daily mood data in bipolar disorder³¹⁰, and using the same method within the context of RCTs. 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 19* and *Part 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 (*Part 1, 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 18*). For example, adverse life events are consistent predictors of the onset of most mental health conditions³¹¹. 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 problems³¹². 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 19*). 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.³¹⁵ 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). 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 symptomatology³¹⁶. More studies are needed that examine whether these unified approaches are indeed more effective than traditional disorder specific treatments.

Finally, despite the apparent contrast between a personalised versus universal approach, we suggest that the research agenda embrace complexity, including co-morbidity, and consider both ends of the treatment spectrum – i.e., examine approaches which could offer cross-cutting universal treatment approaches and, if necessary, add disorder-specific interventions, alongside personalised treatment solutions (*see Panel 18*). 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 19*).

<u>Panel 19. Example Directions for Future Research Regarding Complexities</u>
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Study models that explain co-morbidity in mental health disorders and treatment approaches for co-morbid disorders
<ul style="list-style-type: none"> • Investigate whether we can personalise our psychopathological models to the level that we can adjust treatments and thereby improve treatment outcomes
<ul style="list-style-type: none"> • Investigate who we should treat with what: a disorder-specific treatment, a personalized treatment and/or transdiagnostic/unified treatment
<ul style="list-style-type: none"> • 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

Part 9 Target: Suicidal behaviour: Protecting lives

Introduction

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.

Suicide and suicide attempts are the most tragic outcomes that result from our failure to effectively treat those with mental health problems. Suicide is a major public health concern: at least 804,000 people die by suicide globally each year³¹⁷. As suicidal behaviour 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.

In addition to the personal tragedy associated with every death by suicide, the economic cost of suicide is enormous. For example, in EU countries, the average lifetime cost associated with a suicide is estimated to be approximately two million euros³¹⁸. 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 decades³¹⁹. These advances include a better understanding of the common risk factors for suicidal behaviour³²⁰⁻³²³, evidence that some psychological treatments reduce suicidal ideation and behaviour³²⁴⁻³³¹ 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 and identify a number of urgent calls to action (*panel 20*). Although we focus on psychological treatments, we should keep in mind how the principles outlined in this Commission can relate to the primary prevention of suicide.

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 behaviour³³⁵. The central role of psychological factors in the aetiology and course of suicidal behaviour is now well recognized³²³. 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 life³²³. 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}

New psychological models of suicide have been developed which have identified more proximal and specific markers of suicide risk³³⁷⁻³⁴³ (*see also Part 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, 345} are among the key predictors of suicide attempts 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 Part 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 required³⁴⁷.

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 suicide³⁴⁹. Indeed, suicide rates stayed more or less the same or increased by more than 10% in half of the 172 member states of the WHO between 2000 and 2012³¹⁷. Most people who die by suicide are not in contact with clinical services in the 12 months before death, so until we expand the reach of psychological treatments beyond those already in contact with clinical services, it is

unlikely that they will have a direct impact upon national suicide rates. Given the complexity of the risk factors for suicide, multilevel interventions offer most promise³⁵⁰ and psychological treatments on their own will not make a sizeable dent in suicide rates.

Nonetheless, meta-analyses indicate that CBT is effective in reducing suicidal behaviour in adults, although not in adolescents³²⁷. A systematic review and meta-analysis of psychosocial interventions following self-harm in adults concluded that CBT “seems to be effective in patients after self-harm”, and specific studies provide support for dialectical behaviour therapy for individuals with borderline personality disorder³⁵¹ psychodynamic interpersonal therapy³⁵² and mentalization-based therapy³⁵³ (although the need for replications of those which are single studies is noted). There are also recent efforts to determine whether the collaborative assessment and management of suicidality, a therapeutic framework for suicidality, is feasible and clinically effective³⁵⁴. The attempted suicide short intervention program (ASSIP), a brief integrated therapy and personalized letters intervention, showed encouraging findings in patients who have attempted suicide³⁵⁵.

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 separately³⁵⁶. The latter is consistent with the Cochrane review of interventions for children and adolescents who self-harm³²⁹. The review authors found only 11 trials, most of which were single trials, from which they concluded that therapeutic assessment, mentalization, and dialectical behaviour therapy “warrant further evaluation”¹³ (*see also Part 4, Prevention*). Treatments that target depression are not effective in reducing suicidal thoughts or attempts³⁵⁷. 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 findings³²⁷. Replications of the existing treatments by independent groups are needed, as is the development of evidence-based assessment measures that are clinically useful in the suicide treatment research field (*see also Part 6, Trials*).

The development, evaluation and implementation of psychological treatments for suicidality must be 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 Part 8, Complexities*). The sex-specific research is especially important, because more men die by suicide than women in all countries in the world³¹⁷, but many more women participate in suicidal behavior treatment trials³²⁸. 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. For those psychological treatments that are effective, overall the effect sizes have tended to be small^{328, 358, 399}. Also, psychological treatments reach only 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 peers³⁵⁹), 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.

Most suicides occur in low- and middle-income countries (LAMICs)³¹⁷, so the extent to which treatments developed in high-income countries are generalizable to LAMICs needs very careful consideration (*see also Part 2, Worldwide*). When developing and evaluating treatment trials, consideration should 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 Part 8, Complexities*). More fundamentally (*as noted in Part 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. An appreciation of mechanisms will help explain why treatments that are expected to be effective fail to be so.

Challenges and opportunities for research

The Calls to Action panel (*see Panel 20*) 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 treatment³⁶⁰, 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 Part 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 treatment³⁶¹, 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 Part 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. However, potential iatrogenic effects ought to be monitored in such studies (as well as in mono-treatment studies, *see also Part 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-Harm³⁵⁸. 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 Part 6, Trials*). There has been some movement in this regard in the USA³²⁵, 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 suicide³⁶⁶. 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 Part 1, Mechanisms*).

We 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. For example, could gaming technology be harnessed to engage young people in help-seeking and treatment? Mobile apps offer 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 but must be developed with the same rigor as traditional means of psychological treatment delivery (*see also Part 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 efforts³⁶⁹⁻³⁷⁰.

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 development³⁷². 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 Part 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 Part 7, Training*). However, given 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.

<u>Panel 20. Calls to Action for Psychological Treatments Suicide Research</u>
<ul style="list-style-type: none"> ▪ More large-scale psychological treatment trials (including psychotherapeutic and brief contact interventions) targeting suicidal ideation/behaviour are urgently required
<ul style="list-style-type: none"> ▪ 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)
<ul style="list-style-type: none"> ▪ More rigorous investigation of those at imminent risk of suicide
<ul style="list-style-type: none"> ▪ Conduct replications of psychological treatments by independent groups
<ul style="list-style-type: none"> ▪ 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
<ul style="list-style-type: none"> ▪ 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
<ul style="list-style-type: none"> ▪ Use techniques derived from experimental psychopathology to determine whether hypothesized mechanisms account for changes in symptoms or wellbeing (<i>see Part 1</i>, recommendations for identifying potential mechanisms)
<ul style="list-style-type: none"> ▪ Determine active ingredients of psychological treatments (including the role of therapeutic alliance)

<ul style="list-style-type: none"> ▪ 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
<ul style="list-style-type: none"> ▪ Determine the barriers to treatment seeking in men, in particular
<ul style="list-style-type: none"> ▪ Investigate the extent to which new technologies may be useful to engage difficult to reach populations (e.g., men, adolescents)
<ul style="list-style-type: none"> ▪ 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

Part 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’ 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.

In the Introduction, we used the metaphor “The Fourth Plinth” in Trafalgar Square. A plinth here is a metaphor to make contemporary ideas visible and to give them critical consideration. Some pieces will be preserved for longevity, others may not. Particular psychological treatments or research ideas should not stand on a plinth forever, though some may stand the test of time. 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 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. One problem for our field is the need to sustain the adoption of evidence-based treatments by practitioners, who may rather ignore the evidence and use the 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 effectiveness⁸⁴⁻⁸⁸ (*see Part 1, Mechanisms*), however, in practice a substantial proportion of therapists do not use this effective therapeutic technique³⁷³. This reluctance and lack of uptake of empirically supported interventions, or aspects of them, is an issue that needs to be understood and rectified.

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. Many broader issues that affect the whole psychological treatment field 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) as well as many issues that are relevant to science more generally - from reproducibility to open data. Psychological science is a young discipline compared to many other fields - emphasis on the history of psychological treatments over the last century could be of benefit here. 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 fields (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 Empty Plinth approach 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. The metaphor could be adapted to fit the range of outlets, and journal editors and conference organisers 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.

Arguably, in some areas 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 falling³⁷⁶. There is an understandable current emphasis on increasing access to existing psychological treatments⁹⁸ given the large unmet need and changing models of service delivery^{5,93,378,379}. 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}. We also see a pressing need for multiple solutions, given the scale of the challenge before us. There is clearly 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. 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

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 intervention³⁸³. 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.

As reflected in the previous Section 7 on training, 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 in Section 1, Mechanisms), 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. Innovation benefits from creativity – including taking ideas from one area and seeing if they apply to another for treatment benefits.

Communication between clients, clinicians and across the health services as a whole needs improvement. 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 world³⁸⁴. 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 attention³⁸⁵, 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 Part 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.

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 RDoC³⁸⁷ 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 for proof of concept studies in psychological therapies could be especially important to the field; the level of funding for mental health research internationally, and psychological treatments in particular is far too low: ^{388, 389} increased funding is essential for progress in order to take risks in new areas.

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 rigorous research 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 disorders, from

impairments in social and occupational functioning through to quality of life (e.g., using instruments such as WHODAS 2.0³⁹⁰). 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 innovation³⁹¹. 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 disorders³⁹² (*see Part 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 initiative³⁸⁷. The value to patients of focussing on functioning (rather than disorder) would benefit from more attention. 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 in ways they value 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 progress³⁸¹. 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. More ideas will be needed. This is not a specific road map - we need to rethink across relevant areas what matters to gain traction. Innovations arising from thoughtful effort 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.

Acknowledgements

Additional contributors who also attended Lancet Psychiatry meeting, December 2015

include E. Barley, N. Balmer, S. E. Blackwell, N. Boyce, M. Browning, K. Carroll, S.

Cartwright-Hatton, C. Creswell, T. Dalgleish, M. Di Simplicio, S. Dix, B. Dunn, P. Fearon,

C. Hirsch, J. M. Hooley, L. Iyadurai, S. Jones, S. Kamboj, A. Milton, J. Powell, A. Reinecke,

and U. Schmidt.

We thank Dr Richard Emsley, Senior Lecturer in Biostatistics, University of Manchester, for his consultancy regarding clinical trial methodology. We would also like to thank L. Iyadurai and E. L. James for help preparing the manuscript.

Sources of Funding: We are grateful for support from MQ: Transforming Mental Health for travel expenses to the Commission meeting held at *Lancet Psychiatry, December 2015*.

EH is currently supported by the Karolinska Institutet and the Lupina Foundation of Toronto. EH has recently received support from the Medical Research Council (United Kingdom) intramural programme [MRC-A060-5PR50] and the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre Programme. The views expressed in this publication are those of the authors and not necessarily the views of the funders.

AG is supported by the Swedish Foundation for Humanities and Social Sciences (RJ). The views expressed in this publication are those of the authors and not necessarily those of the RJ.

CJH has current research funding from the Wellcome Trust, Medical Research Council and the NIHR Oxford Health Biomedical Research Centre.

PGR has funding from the UK National Institute of Health Research (NIHR) to develop and evaluate early interventions in randomised controlled trials, and receives support from the Imperial NIHR Biomedical Research Centre (BRC).

PC has funding from the European Union (FP7 and H2020 programmes), ZonMw (Dutch Health Research Council) and the PFGV.

APM reports no current source of funding.

JPR is funded by the Wellcome Trust.

CLHB is supported by the department of Psychiatry at the Academic Medical Center of the University of Amsterdam and by the Netherlands Institute of Advanced Sciences (NIAS, 2017) supported by Royal Netherlands Academy of Arts and Sciences (KNAW).

ROC has funding from US Department of Defense, UK National Institute of Health Research, NHS Greater Glasgow & Clyde, NHS Health Scotland, the Medical Research Council, MQ Research and the Scottish Government. The views expressed in this publication are those of the authors and not necessarily the views of my current funders.

RS: All research at Great Ormond Street Hospital NHS Foundation Trust and UCL Great Ormond Street Institute of Child Health is made possible by the NIHR Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

MLM is supported by the National Health and Medical Research Council (NHMRC) (Australia). MM also receives support from the PLS Alliance Fellows Funding Scheme (UNSW Sydney, Australia). The views expressed in this publication are those of the authors and not necessarily the views of these funders.

MGC is currently funded by the National Institutes of Mental Health (1 R01 MH1001171, R01MH1014531, R34 MH101359, R01 MH102274), the Defense Advanced Research Projects Agency (R21 MH1010336), and the National Aeronautics and Space Administration (NNX15AP57G). The views expressed in this publication are those of the authors and not necessarily those of the NIMH, DARPA or NASA.

Contributors

All authors made an equal contribution to this paper.

Conflict of Interest Statements

EAH's primary affiliation is the Karolinska Institutet, Sweden where she is Professor and deputy head of department, and which provides her annual salary. She currently receives grant support from the Lupina Foundation of Toronto. EAH serves on the Board of the Charity "MQ; transforming mental health", and was formerly chair of the Fellows committee, and has received no remuneration for these roles. EAH is an Honorary Professor of Clinical Psychology at the University of Oxford, Department of Psychiatry and Visiting Scientist at the Medical Research Council (MRC) Cognition and Brain Sciences Unit, University of Cambridge and receives no remuneration for these roles. EAH is on the Board of Overseers for the charity "Children and War Foundation", Oslo, Norway; and on the editorial boards of 'Cognitive Behaviour Therapy' and 'Psychological Science'. She receives no remuneration for these positions. She does receive remuneration for the following roles: EAH is Associate Editor of *Behaviour Research and Therapy* and receives an honorarium. EAH has presented occasional clinical training workshops, and keynote / invited addresses at conferences, some of which include a fee. EAH receives royalties from her co-authored book on Imagery in Cognitive Therapy (Oxford University Press, 2011).

AG is a Professor of Clinical Psychology at the Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden. AG is on the editorial board of *Behaviour Research and Therapy* and has received no remuneration for this role. AG has presented clinical training workshops and provided supervision to clinicians at eating disorder treatment units, most of which include a fee, but are not related to the current contribution. AG also receives royalties from his co-authored books on eating disorders and body image.

CJH has received consultancy fees from P1vital, Lundbeck Johnson & Johnson and Servier. She has grant income from Johnson & Johnson, UCB, Lundbeck and Sunovion.

PGR is employed full-time by Imperial College London and Central and NorthWest London (CNWL) Foundation NHS Trust. He has been involved in the development and adaption of psychological interventions, but receives no payments from these.

PC is Head of the Department of Clinical, Neuro and Developmental Psychology at the VU University Amsterdam, for which he receives his annual salary. He is Deputy Editor of “Depression and Anxiety”, for which his university receives a fee. He receives expense allowances for his membership of the Board of Directors of “Mind”, the “Fonds Psychische Gezondheid” and “Korrelatie”, and for being Chair of the PACO Committee of the “Raad voor Civiel-militaire Zorg en Onderzoek” of the Dutch Ministry of Defense. He also receives royalties for books he has authored or co-authored and for occasional invited lectures. APM’s primary affiliation is the School of Psychological Sciences, University of Manchester. APM is also Director of the Psychosis Research Unit, Greater Manchester West NHS Trust. APM serves on several editorial boards and receives no remuneration for these roles. APM has presented keynote addresses at conferences and delivered clinical training workshops, some of which have included a fee. APM receives royalties from several co-authored and edited books. APM delivers CBT within the NHS and has received funding from both the MRC and NIHR to conduct evaluative research into the efficacy of psychological therapies.

JPR is a consultant for Cambridge Cognition and Takeda; these roles have no direct relation to the current contribution. JPR is an Associate Editor at Neuroimage: Clinical and receives an honorarium for this role, which has no direct relation to the current contribution.

ROC’s primary affiliation is the Institute of Health & Wellbeing, University of Glasgow where he heads the Mental Health and Wellbeing Research Group. He is also Director of the Suicidal Behaviour Research Laboratory at the University of Glasgow. He is Deputy Chief Editor of *Archives of Suicide Research* and Associate Editor of *Suicide and Life-Threatening Behavior*. He also serves on several editorial boards. He receives no remuneration for any of these additional roles. He was a member of the National Institute of Health & Care Excellence’s (NICE) guideline development group for the longer-term management of self-harm. He sits on the Scottish Government’s Suicide Prevention and Implementation Monitoring Group. He receives royalties from several co-authored/edited books, occasional workshops and invited addresses.

CLHB is Professor of Clinical Psychology at the Department of Psychiatry at the Academic Medical Center at the University of Amsterdam in The Netherlands (primary affiliation). CLHB has received a fellowship at the Netherlands Institute of Advanced Sciences (NIAS) supported by Royal Netherlands Academy of Arts and Sciences (KNAW) and this enabled her to work on this contribution. CLHB is Co-Editor of ‘*PlosOne*’ and of European Psychologist, she receives no honorarium for this role. CLHB is member of the Dutch multi-disciplinary guideline for anxiety and depression. She receives no remuneration for this role. She is advisor for the minister on National Health Care on forms of care for inclusion in the statutory insured package (Advies Pakket Commissie, ZIN). She receives an honorarium for this role and this role has no direct relation to the current contribution. CLHB has presented keynote addresses at conferences such as EABCT 2014 and European Conference of Psychology and received an honorarium. She has presented clinical training workshops, some

of which include a fee. CLHB receives royalties from her books and co/edited books.

RS served as a Senior Adviser for the 'MQ: PsyImpact' programme from Feb 2015-2016. She is a consultant for 'Big Health'. She also receives royalties for books she has authored or co-authored (American Psychological Association Books, Elsevier Press) and occasional workshops and invited addresses.

MLM's primary affiliation is the School of Psychology, The University of New South Wales, UNSW Sydney, Australia – where she is a Professor and PLS Alliance Fellow. She is a consulting editor of the *Journal of Experimental Psychology: Applied* and *Clinical Psychological Science*, and a member of four additional editorial boards. She receives no remuneration for these roles. MLM has presented keynote addresses at conferences and has received an honorarium for some of these.

MGC's primary affiliation is the UCLA Department of Psychology, where she is Vice Chair, which provides her annual salary, supplemented by summer funds from grants from NIMH or DARPA. She is Editor-in-Chief of *Behaviour Research and Therapy* and Associate Editor of *Psychological Bulletin*, for which she receives remuneration. She is Director of the UCLA Anxiety and Depression Center, co-Director of the UCLA Staglin Family Music for Behavioral and Brain Health, President of the Association for Behavior and Cognitive Therapy, Co-Chair of the Human Studies Section of the UCLA Grand Challenge for Depression, Member of DSM-5 Steering Committee for the American Psychiatric Association, Member of the Scientific Advisory Board for the Center of Excellence on Generalization Research at the University of Leuven in Belgium, Honorary Member of the Experimental Psychopathology Group (Dutch-Flemish Postgraduate School for Research and Education), and Honorary Fellow of the Department of Psychiatry at Oxford University; she receives no remuneration for any of these positions. She does receive remuneration for her awards as Eleonore Trefftz Guest Professorship (Technical University of Dresden) and the International Francqui Professor (Belgium). She also receives royalties for books she has authored or co-authored (American Psychological Association Books, Elsevier Press) and occasional workshops and invited addresses.

References

- 1 James W. *The Principles of Psychology*. New York: Henry Holt & Co.; 1890.
- 2 Holmes EA, Craske MG, Graybiel AM. Psychological Treatments: A call for mental-health science. Clinicians and neuroscientists must work together to understand and improve psychological treatments [Comment]. *Nature* 2014; **511**: 287-9.
- 3 Joyce C. Transforming our approach to translational neuroscience: the role and impact of charitable nonprofits in research. *Neuron* 2014; **84**: 526-32.
- 4 McHugh RK, Whitton SW, Peckham AD, Welge JA, Otto MW. Patient preference for psychological vs pharmacologic treatment of psychiatric disorders: a meta-analytic review. *J Clin Psychiatry* 2013; **74**: 595-602.
- 5 Kazdin AE, Blase SL. Rebooting psychotherapy research and practice to reduce the burden of mental illness. *Perspect Psychol Sci* 2011; **6**: 21-37.
- 6 Steel Z, Marnane C, Iranpour C, et al. The global prevalence of common mental disorders: A systematic review and meta-analysis 1980-2013. *Int J Epidemiol* 2014; **43**: 476-93.
- 7 Värnik P. Suicide in the world. *Int J Environ Res Public Health* 2012; **9**: 760-71.
- 8 Whiteford HA, Degenhardt L, Rehm J, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; **382**: 1575-86.
- 9 Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx B. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. *Am J Psychiatry* 2014; **171**: 453-62.
- 10 Chisholm D, Sweeny K, Sheehan P, et al. Scaling-up treatment of depression and anxiety: a global return on investment analysis. *Lancet Psychiatry* 2016; **3**:415-424.
- 11 Hu TW. Perspectives: an international review of the national cost estimates of mental illness, 1990-2003. *J ment Health Policy Econ* 2006; **9**: 3-13.
- 12 Gustavsson A, Svensson M, Jacobi F, et al. Cost of disorders of the brain in Europe 2010. *Eur Neuropharmacol: J Eur Col Neuropharmacol* 2011; **21**: 718-79.
- 13 Bloom DE, Cafiero ET, Jané-Llopis E, et al. *The Global Economic Burden of Noncommunicable Diseases*. Geneva: World Economic Forum, 2011.
- 14 Huber M, Knottnerus JA, Green L, et al. How should we define health? *BMJ* 2011; **343**: d4163.
- 15 Andrews G, Issakidis C, Sanderson K, Corry J, Lapsley H. Utilising survey data to inform public policy: comparison of the cost-effectiveness of treatment of ten mental disorders. *Brit J Psychiatry* 2004; **184**(6): 526-33.
- 16 McManus S, Bebbington P, Jenkins R, Brugha T. (eds.) (2016). *Mental health and wellbeing in England: Adult Psychiatric Morbidity Survey 2014*. Leeds: NHS Digital.
- 17 Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62**: 629-40.
- 18 Olfson M, Marcus SC. National patterns in antidepressant medication treatment. *Arch Gen Psychiatry* 2009; **66**: 848-56.

- 19 Gerhard T, Akincigil A, Correll CU, Foglio NJ, Crystal S, Olfson M. National trends in second-generation antipsychotic augmentation for nonpsychotic depression. *J Clin Psychiatry* 2014; **75**: 490-7.
- 20 Olfson M, Marcus SC. National trends in outpatient psychotherapy. *Am J Psychiatry* 2010; **167**: 1456-63.
- 21 Fairburn CG, Patel V. The global dissemination of psychological treatments: a road map for research and practice. *Am J Psychiatry* 2014; **171**: 495-498.
- 22 Greater London Authority [GLA]. (2016). Fourth Plinth. <https://www.london.gov.uk/WHAT-WE-DO/arts-and-culture/art-and-design/fourth-plinth> (accessed 4 May, 2016).
- 23 Kazdin AE. Moderators, mediators, and mechanisms of change in psychotherapy. *Ann Rev Clin Psychol* 2007; **3**: 1-27.
- 24 Brown LA, Wiley JF, Wolitzky-Taylor K, et al. Changes in self-efficacy and outcome expectancy as predictors of anxiety outcomes from the CALM study. *Depress Anxiety* 2014; **31**: 678-689.
- 25 Kozak MJ, Cuthbert BN. The NIMH research domain criteria initiative: background, issues and pragmatics. *Psychophysiol*, 2016; **53**: 286-297.
- 26 Miller GE, Cole SW. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. *Bio Psychiatry* 2012; **72**: 34-40.
- 27 Dalgleish T, Werner-Seidler A. Disruptions in autobiographical memory processing in depression and the emergence of memory therapeutics. *Trends Cog Sci* 2014; **18**: 596-604.
- 28 Roiser JP. What has neuroscience ever done for us? *Psychol* 2015; **28**: 284-287.
- 29 Fox E, Zougkou K, Ashwin C, Cahill S. Investigating the efficacy of attention bias modification in reducing high spider fear: the role of individual differences in initial bias. *J Behav Ther Exp Psychiatry* 2015; **49**: 84-93.
- 30 Twamley EW, Vella L, Burton CZ, Heaton RK, Jeste DV. Compensatory cognitive training for psychosis: Effects in randomized controlled trial. *J Clin Psychiatry* 2012; **73**: 1212-1219.
- 31 Smith T, Iadarola S. Evidence base update for autism spectrum disorder. *J Clin Child Adolesc Psychol* 2015; **44**: 897-922.
- 32 Barlow, D.H., & Craske, M.G. The phenomenology of panic. In S.J. Rachman & J.D. Maser (Eds.), *Panic: Psychological Perspectives* 1988, (pp. 11-36). Hillsdale, New Jersey: Lawrence Erlbaum Associates.
- 33 Bouton ME, Mineka S, Barlow DH. A modern learning theory perspective on the etiology of panic disorder. *Psychological Review* 2001; **108**: 4-32.
- 34 Clark DM. A cognitive approach to panic. *Behaviour Research and Therapy* 1986; **24**: 461-470.
- 35 Barlow, D.H. & Craske, M.G. *Mastery of your anxiety and panic*. 1988. Albany, New York: Graywind Publications.
- 36 Salkovskis PM, Clark DM, Hackmann A. Treatment for panic attacks using cognitive therapy without exposure or breathing retraining. *Behav Res Ther* 1991; **29**: 161-166.
- 37 Hofmann SG & Smits JA. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. *J Clin Psychiatry* 2008; **69**: 621-32.

- 38 Foa, EB, Steketee G, Grayson JB, Turner RM, Latimer, P. Deliberate exposure and blocking of obsessive-compulsive rituals: Immediate and long-term effects. *Behav Ther* 1984; **15**: 450-472.
- 39 Ost L, Havnen A, Hansen B, Kvale G. Cognitive behavioral treatments of obsessive– compulsive disorder. A systematic review and meta-analysis of studies published 1993–2014. *Clin Psychol Rev* 2015; **40**: 156-169.
- 40 Lewinsohn PM. A behavioral approach to depression. In RM Friedman and MM Katz (Eds). *The psychology of depression: contemporary theory and research*; 1974 (157-185). New York: Wiley.
- 41 Jacobson NS, Martell CR, Dimidjian S. Behavioral activation treatment for depression: returning to contextual roots. *Clin Psychol: Sci Prac* 2001, **8**: 255-270.
- 42 Cuijpers P, van Straten A, Warmerdam L. Behavioral activation treatments of depression: a meta-analysis. *Clin Psychol Rev* 2007; **27**: 318-326.
- 43 Mohr DC, Spring B, Freedland KE et al. The selection and design of control conditions for randomized controlled trials of psychological interventions. *Psychother Psychosom* 2009; **78**: 275-84.
- 44 Cuijpers P, Cristea I, Karyotaki E, Reijnders, Huibers MJH. How effective are cognitive behavior therapies for major depression and anxiety disorders? A meta-analytic update of the evidence. *World Psychiatry* 2016; **15**: 245-258.
- 45 Wampold BE. How important are the common factors in psychotherapy? An update. *World Psychiatry* 2015; **14**: 270-277.
- 46 Kazdin AE. Evidence-based psychotherapies I: qualifiers and limitations in what we know. *S Afr J Psychol* 2014; **44**: 381-403.
- 47 Cristea IA, Kok RN, Cuijpers P. Efficacy of cognitive bias modification interventions in anxiety and depression: Meta-analysis. *Br J Psychiatry* 2015; **206**: 7-16.
- 48 Fox E, Zougkou K, Ridgewell A, Garner K. The serotonin transporter gene alters sensitivity to attention bias modification: evidence for a plasticity gene. *Bio Psychiatry* 2011; **70**:1049-54.
- 49 Milad MR, Rosenbaum BL, Simon NM. Neuroscience of fear extinction: implications for assessment and treatment of fear-based and anxiety related disorders. *Behaviour Research and Therapy* 2014; **62**: 17-23.
- 50 Lanius RA, Vermetten E, Loewenstein RJ, Brand B, Schmahl C, Bremner JD, Spiegel D. Emotion modulation in PTSD: clinical and neurobiological evidence for a dissociative subtype. *Am J Psychiatry* 2010; **167**(6):640-7.
- 51 van Vugt MK, Hitchcock P, Shahar B, Britton W. The effects of mindfulness-based cognitive therapy on affective memory recall dynamics in depression: a mechanistic model of rumination. *Front Hum Neurosci* 2012; **6**: 257
- 52 Wiles NJ, Thomas L, Turner N, et al. Long-term effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: follow-up of the CoBaT randomised controlled trial. *Lancet Psychiatry* 2016; **3**: 137-144.
- 53 Bockting CL, Smid NH, Koeter MW, Spinhoven P, Beck AT, Schene AH. Euduring effects of preventive cognitive therapy in adults remitted from recurrent depression; A 10-year follow-up of a randomized controlled trial. *J Aff Dis* 2015; **185**: 188-94.

- 54 Wampold BE, Mondin GW, Moody M, Stich F, Benson K, Ahn H. A meta-analysis of outcome studies comparing bona fide psychotherapies: Empirically, “all must have prizes.” *Psychol Bull* 1997; **112**: 203-215.
- 55 Marcus DK, O’Connell D, Norris AL, Sawaqdeh A. Is the dodo bird endangered in the 21st century? A meta-analysis of treatment comparison studies. *Clin Psychol Rev* 2014; **34**: 519-530.
- 56 Lee KH, Siegle GJ, Dahl RE, Hooley JM, Silk JS. Neural responses to maternal criticism in healthy youth. *Social Cognitive & Affective Neuroscience* 2015; **10**: 902-912.
- 57 Ressler KJ, Rothbaum BO, Tannenbaum L, et al. Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. *Arch Gen Psychiatry* 2004; **61**: 1136-1144.
- 58 Otto MW, Kredlow MA, Smits JA, et al. Enhancement of psychosocial treatment with d- Cycloserine: models, moderators, and future directions. *Biological Psychiatry* 2015;
- 59 Nader K, Schafe GE, Le Doux JE. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature* 2000; **406**: 722-726.
- 60 Kindt M. A behavioural neuroscience perspective on the aetiology and treatment of anxiety disorders. *Behaviour Research and Therapy* 2014; **62**: 24-36.
- 62 Treanor M, Brown LA, Rissman J, Craske MG. Can memories of traumatic experiences or addiction be erased or modified? A critical review of research on the disruption of memory reconsolidation and its applications. *Persp Psychol Sci* 2017; **12**: 290-305.
- 63 James EL, Bonsall MB, Hoppitt L, et al. Computer game play reduces intrusive memories of experimental trauma via reconsolidation-update mechanisms. *Psychol Sci* 2015; **26**: 1201-1215.
- 64 Davis M, Ressler K, Rothbaum BO, Richardson R. Effects of D-cycloserine on extinction: translation from preclinical to clinical work. *Bio Psychiatry* 2006; **60**:369–375
- 65 Schramm MJ, Everitt BJ, Milton AL. Bidirectional modulation of alcohol-associated memory reconsolidation through manipulation of adrenergic signaling. *Neuropsychopharmacology* 2011; **41**: 1103-1111.
- 66 Marvar PJ, Goodman J, Fuchs S, Choi DC, Banerjee S, Ressler KJ. Angiotensin type 1 receptor inhibition enhances the extinction of fear memory. *Bio Psych* 2014; **75**: 864-872.
- 67 Kalueff AV, Stewart AM, Song C, Berridge KC, Graybiel AM, Fentress JC. Neurobiology of rodent self-grooming and its value for translational neuroscience. *Nature Rev Neurosci* 2016; **17**: 45-59.
- 68 Hales CA, Stuart SA, Anderson MH, Robinson ES. Modelling cognitive affective biases in major depressive disorder using rodents. *Brit J Pharm* 2014; **171**: 4524-4538.
- 69 Parker RM, Paul ES, Burman OH, Browne WJ, Mendl M. Housing conditions affect rat responses to two types of ambiguity in a reward-reward discrimination cognitive bias task. *Behav Brain Res* 2014; **274**: 73-8
- 70 Michie S, Richardson M, Johnston M, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Ann Behav Med* 2013;**46**: 81-95.
- 71 England MJ, Stith-Butler A, Gonzalez ML. Psychosocial interventions for mental and substance use disorders: A framework for establishing evidence-based standards. *Institute of Medicine of the National Academies* 2014; Washington, DC.

- 73 Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2197-223.
- 75 Lawrence D, Kisely S, Pais J. The epidemiology of excess mortality in people with mental illness. *Can J Psychiatry* 2010; **55**: 752-60.
- 78 Wang PS, Angermeyer M, Borges G, et al. Delay and failure in treatment seeking after first onset of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry* 2007; **6**: 177-85.
- 79 Becker AE, Kleinman A. Mental health and the global agenda. *N Engl J Med* 2013; **369**: 66-73.
- 80 World Health Organization. Mental health: facing the challenges, building solutions — report from the WHO European Ministerial Conference. Geneva: World Health Organization; 2005.
- 81 Patel V, Chowdhary N, Rahman A, Verdeli H. Improving access to psychological treatments: lessons from developing countries. *Behav Res Ther* 2011; **49**: 523-8.
- 82 World Health Organization. Mental health atlas: 2011. Geneva: World Health Organization; 2011.
- 83 Saraceno B, van Ommeren M, Batniji R, et al. Barriers to improvement of mental health services in low-income and middle-income countries. *Lancet* 2007; **370**: 1164-74.
- 88 Vervliet B, Craske MG, Hermans D. Fear extinction and relapse: state of the art. *Annu Rev Clin Psychol* 2013; **9**: 215-48.
- 93 Kazdin AE, Rabbitt SM. Novel models for delivering mental health services and reducing the burden of mental illness. *Clin Psychol Sci* 2013; **1**: 170-91.
- 94 Bass J, Neugebauer R, Clougherty KF, et al. Group interpersonal psychotherapy for depression in rural Uganda: 6-month outcomes: randomised controlled trial. *Br J Psychiatry* 2006; **188**: 567-73.
- 95 Rahman A, Malik A, Sikander S, Roberts C, Creed F. Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: a cluster-randomised controlled trial. *Lancet* 2008; **372**: 902-9.
- 97 Dawson KS, Bryant RA, Harper M, et al. Problem Management Plus (PM+): a WHO transdiagnostic psychological intervention for common mental health problems. *World Psychiatry* 2015; **14**: 354-7.
- 98 Clark DM. Implementing NICE guidelines for the psychological treatment of depression and anxiety disorders: the IAPT experience. *Int Rev Psychiat* 2011; **23**: 318-27.
- 100 Craske MG, Rose RD, Lang A, et al. Computer-assisted delivery of cognitive behavioral therapy for anxiety disorders in primary-care settings. *Depress Anxiety* 2009; **26**: 235-42.

- 102 Andersson G, Titov N. Advantages and limitations of Internet-based interventions for common mental disorders. *World Psychiatry* 2014; **13**: 4-11.
- 1
- 107 Arjadi R, Nauta MH, Chwdhary N, Bockting CLH. A systematic review of online interventions for mental health in low and middle income countries: a neglected field. *Global Mental Health* 2015; **2**: 1-6.
- 108 Poushter J. Smartphone Ownership and Internet Usage Continues to Climb in Emerging Economies 2016. <http://www.pewglobal.org> (accessed 2016-04-29).
- 109 Hay P, Chinn D, Forbes D, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of eating disorders. *Aust N Z J Psychiatry* 2014; **48**: 977-1008.
- 110 Andersson G, Cuijpers P, Carlbring P, Riper H, Hedman E. Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. *World Psychiatry* 2014; **13**: 288-95.
- 111 Enebrink P, Hogstrom J, Forster M, Ghaderi A. Internet-based parent management training: a randomized controlled study. *Behav Res Ther* 2012; **50**: 240-9.
- 112 Ljotsson B, Lundin C, Mitsell K, Carlbring P, Ramklint M, Ghaderi A. Remote treatment of bulimia nervosa and binge eating disorder: a randomized trial of Internet-assisted cognitive behavioural therapy. *Behav Res Ther* 2007; **45**: 649-61.
- 118 Eaton J, McCay L, Semrau M, et al. Scale up of services for mental health in low-income and middle-income countries. *Lancet* 2011; **378**: 1592-603.
- 119 Nickerson A, Bryant RA, Silove D, Steel Z. A critical review of psychological treatments of posttraumatic stress disorder in refugees. *Clin Psychol Rev* 2011; **31**: 399-417.
- 120 Singhal A, Rogers EM. Entertainment-education: A communication strategy for social change. New Jersey: Erlbaum, 1999.
- 121 Knapp MRJ, McDaid D, Parsonage M, editors. Mental health promotion and mental illness prevention: the economic case. London: Department of Health, 2011.
- 124 Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, Reynolds III CF Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. *World Psychiatry*, 2014; **13**: 56-67.
- 125 Cuijpers P, van Straten A, Warmerdam L, Andersson G. Psychological treatment versus combined treatment of depression: A meta-analysis. *Depress Anxiety* 2009; **26**: 279-288.
- 126 Hollon SD, Jarrett RB, Nierenberg AA, Thase ME, Trivedi M, Rush AJ. Psychotherapy and medication in the treatment of adult and geriatric depression: which monotherapy or combined treatment? *J Clin Psychiatry* 2005; **66**: 455-468.
- 127 Barlow DH, Gorman JM, Shear MK, Woods SW. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: A randomized controlled trial. *JAMA* 2000; **283**:2529-36.
- 128 Otto MW, Bruce SE, Deckersbach T. Benzodiazepine use, cognitive impairment, and cognitive-behavioral therapy for anxiety disorders: issues in the treatment of a patient in need. *J Clin Psychiatry* 2005; **66**: 34—8.

- 129 Ori R, Amos T, Bergman H, Soares-Weiser K, Ipser JC, Stein DJ. Augmentation of cognitive and behavioural therapies (CBT) with d-cycloserine for anxiety and related disorders. *Cochrane Database Syst Rev* 2015; **10**:CD007803
- 130 Merlo E., Milton AL, Goozee ZY, Theobald DE, Everitt BJ. Reconsolidation and extinction are dissociable and mutually exclusive processes: behavioral and molecular evidence. *J Neurosci* 2014, **34**: 2422-2431
- 131 Guhn A, Dresler T, Andreatta M et al. Medial prefrontal cortex stimulation modulates the processing of conditioned fear. *Front Behav Neurosci* 2014, **8**:44.
- 132 Kennedy SH, Konarski JZ, Segal ZV et al. (2007) Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. *Am J Psychiat* 2007. **164**:778-788.
- 133 Warren MB, Pringle A, Harmer CJ. A neurocognitive model for understanding treatment action in depression. *Philos Trans R Soc Lond B Biol Sci.* 2015 **370**:20140213
- 134 Beck AT, Rush AJ, Shaw BF, Emery G. Cognitive Therapy of Depression. New York: Guildford, 1979
- 135 Disner SG, Beevers CG, Haigh EA, Beck AT. Neural mechanisms of the cognitive model of depression. *Nat Rev Neurosci* 2011 **12**:467-477.
- 136 Shiroma PR, Thuras P, Johns B, Lim KO. Emotion recognition processing as early predictor of response to 8-week citalopram treatment in late-life depression. *Int J Geriatr Psychiat* 2014; **29**:1132-1139.
- 137 Moss A, Freeman TP. Mind the gap: bringing together psychopharmacology and cognitive behavioural therapy. <https://thepsychologist.bps.org.uk/mind-gap-bringing-together-psychopharmacology-and-cognitive-behavioural-therapy> (accessed Oct 5, 2017).
- 138 Bouton ME. Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. *Biol Psychiatry* 2002. **52**:976-986.
- 139 Murphy SE, Downham C, Cowen PJ, Harmer CJ. Direct effects of diazepam on emotional processing in healthy volunteers. *Psychopharmacology (Berl)*. 2008 **199**:503-513.
- 140 Reinecke A, Waldenmaier L, Cooper MJ, Harmer CJ. Changes in automatic threat processing precede and predict clinical changes with exposure-based cognitive-behavior therapy for panic disorder. *Biol Psychiatry* 2013; **73**:1064-1070
- 141 Clarke PJ, Browning M, Hammond G, Notebaert L, MacLeod C. The causal role of the dorsolateral prefrontal cortex in the modification of attentional bias: evidence from transcranial direct current stimulation. *Biol Psychiat* 2014; **76**:946-952
- 142 Browning M, Grol M, Ly V, Goodwin GM, Holmes EA, Harmer CJ. Using an experimental medicine model to explore combination effects of pharmacological and cognitive interventions for depression and anxiety. *Neuropsychopharma* 2011; **36**:2689-2697.
- 143 Başoğlu M, Marks IM, Kiliç C, Brewin CR, Swinson RP. Alprazolam and exposure for panic disorder with agoraphobia. Attribution of improvement to medication predicts subsequent relapse. *Br J Psychiatry* 1994; **164**:652-259.
- 144 Champion J, Bhui K, Bhugra D. European Psychiatric Association. European Psychiatric Association (EPA) guidance on prevention of mental disorders. *Eur Psychiatry* 2012; **27**:68-80.

- 145 Heckman JJ. Skill formation and the economics of investing in disadvantaged children. *Science* 2006; **30**:312:1900-1902.
- 147 Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. *Arch Gen Psychiatry* 2003; **60**:709-717.
- 148 Warner KE, Boat TF, Beardslee WR, et al. Committee on the Prevention of Mental Disorders and Substance Abuse Among Children, Youth, and Young Adults: Research Advances and Promising Interventions. Washington DC, USA: National Academies Press; 2009.
- 149 Olds DL, Holmberg JR, Donelan-McCall N, Luckey DW, Knudtson MD, Robinson J. Effects of home visits by paraprofessionals and by nurses on children: follow-up of a randomized trial at ages 6 and 9 years. *JAMA Pediatr* 2014; **168**: 114-121.
- 150 Rapee RM. The preventative effects of a brief, early intervention for preschool-aged children at risk for internalising: follow-up into middle adolescence. *J Child Psychol Psychiatry* 2013; **54**:780-8.
- 151 Stein A, Ramchandani P, Murray L. Impact of Parental Psychiatric Disorder and Physical Illness Rutter's Child and Adolescent Psychiatry: Fifth Edition 2009, Pages 407-420. Blackwell Publishers.
- 152 Carter JC, Stewart DA, Dunn VJ, Fairburn CG. Primary prevention of eating disorders: might it do more harm than good? *Int J Eat Disord* 1997; **22**:167-172.
- 153 Fonagy P. Psychotherapy research: do we know what works for whom? *Brit J Psychiatry* 2010; **197**: 83-85.
- 154 Zhou X, Hetrick SE, Cuijpers P, et al. Comparative efficacy and acceptability of psychotherapies for depression in children and adolescents: a systematic review and network meta-analysis. *World Psychiatry* 2015; **14**: 207-22
- 156 Robling M, Bekkers MJ, Bell K, et al. Effectiveness of a nurse-led intensive home-visitation programme for first-time teenage mothers (Building Blocks): a pragmatic randomised controlled trial. *Lancet* 2016; **387**:146-55.
- 157 Ewing DL, Dash S, Thompson EJ, Hazell CM, Hughes Z, Lester KJ, Cartwright-Hatton S. No significant evidence of cognitive biases for emotional stimuli in children at-risk of developing anxiety disorders. *J Abnorm Child Psychol* 2016; **44**: 1243-52
- 159 Verhage ML, Schuengel C, Madigan S, et al. Narrowing the transmission gap: A synthesis of three decades of research on intergenerational transmission of attachment. *Psychol Bull* 2016; **142**:337-66.
- 161 Merry SN, Stasiak K, Shepherd M, Frampton C, Fleming T, Lucassen MF. (2012). The effectiveness of SPARX, a computerised self help intervention for adolescents seeking help for depression: randomised controlled non-inferiority trial. *BMJ* 2012; 344:e2598.
- 162 Araya R, Fritsch R, Spears M, et al. School intervention to improve mental health of students in Santiago, Chile: a randomized clinical trial. *JAMA Pediatr* 2013; **167**:1004-10.

- 164 Juffer, F., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (Eds.), *Promoting Positive Parenting: an attachment-based intervention*. New York: Lawrence Erlbaum Associates/Taylor & Francis Group, 2008
- 166 Scott S, Briskman J, O'Connor TG. Early prevention of antisocial personality: long-term follow-up of two randomized controlled trials comparing indicated and selective approaches. *Am J Psychiatry* 2014; **171**:649-57.
- 167 Dretzke J, Frew E, Davenport C, et al. The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children. *Health Technol Assess*. 2005 Dec;9(50):iii, ix-x, 1-233.
- 168 Cuijpers P, Beekman ATF, Reynolds CF. Preventing depression: a global priority. *J Am Med Assoc* 2012; **307**: 1033-4
- 169 Cuijpers P, van Straten A, Smit F, Mihalopoulos C, Beekman AT. Preventing the onset of depressive disorders: a meta-analytic review of psychological interventions. *Am J Psychiatry* 2008; **165**: 1272-80
- 170 van Zoonen K, Buntrock C, Ebert DD, et al. Preventing the onset of major depressive disorder: a meta-analytic review of psychological interventions. *Int J Epidemiol* 2014; **43**: 318-29
- 171 van der Gaag M, Smit F, Bechdolf A, et al. Preventing a first episode of psychosis: meta-analysis of randomized controlled prevention trials of 12 month and longer-term follow-ups. *Schizophr Res* 2013; **149**: 56-6231.
- 172 McGorry PD, Yung AR, Phillips LJ, et al. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Arch Gen Psychiatry* 2002;**59**: 921-928.
- 173 De Silva MJ, Ryan G. Global mental health in 2015: 95% implementation. *Lancet Psychiatry* 2016; **3**:15-7.
- 174 Richards D, Richardson T. Computer-based psychological treatments for depression: a systematic review and meta-analysis. *Clin Psychol Rev* 2012; **32**: 329-42.
- 175 Andrews G, Cuijpers P, Craske MG, McEvoy P, Titov N. Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis. *PloS One* 2010; **5**: e13196.
- 176 Cheng SK, Dizon J. Computerised cognitive behavioural therapy for insomnia: a systematic review and meta-analysis. *Psychother Psychosom* 2012; **81**: 206–16.
- 177 Beintner I, Jacobi C, Schmidt UH. Participation and outcome in manualized self-help for bulimia nervosa and binge eating disorder - a systematic review and metaregression analysis. *Clin Psychol Rev* 2014; **34**: 158–76.
- 178 Riper H, Blankers M, Hadiwijaya H, Cunningham J, Clarke S, Wiers R. Effectiveness of guided and unguided low-intensity internet interventions for adult alcohol misuse: a meta-analysis. *PloS One* 2014; **9**: e99912.
- 179 Eccleston C, Fisher E, Craig L, Duggan GB, Rosser BA, Keogh E. Psychological therapies (Internet-delivered) for the management of chronic pain in adults. *Cochrane Database Syst Rev* 2014;**2**:CD010152.
- 180 Kay M, Santos J, Takane M. mHealth; new horizons for health through mobile technologies. WHO Global Observatory for eHealth series Volume 3. Geneva: WHO, 2011

- 181 Andersson G, Cuijpers P. Pros and cons of on-line cognitive behaviour therapy. *Br J Psychiatry* 2008; **193**: 270–1.
- 182 Buntrock C, Ebert DD, Lehr D, Smit F, Riper H, Berking M, Cuijpers P. Effect of a web-based guided self-help intervention for prevention of major depression in adults with sub-threshold depression: A randomized clinical trial. *JAMA* 2016; **315**: 1854–63.
- 183 Van Ballegooijen W, Cuijpers P, Van Straten A, et al. Adherence to internet-based and face-to-face cognitive behavioural therapy for depression: a meta-analysis. *Plos One* 2014; **9**(7): e100674.
- 184 Sucala M, Schnur JB, Constantino MJ, Miller SJ, Brackman EH, Montgomery GH. The therapeutic relationship in e-therapy for mental health: a systematic review. *J Med Internet Res* 2012; **14**: e110.
- 185 Wenze SJ, Miller IW. Use of ecological momentary assessment in mood disorders research. *Clin Psychol Rev* 2010; **30**: 794–804.
- 186 Smits N, Zitman FG, Cuijpers P, den Hollander-Gijsman ME, Carlier IV. A proof of principle for using adaptive testing in Routine Outcome Monitoring: the efficiency of the Mood and Anxiety Symptoms Questionnaire -Anhedonic Depression CAT. *BMC Med Res Methodol* 2012; **12**:4.
- 187 Powers MB, Emmelkamp PMG. Virtual reality exposure therapy for anxiety disorders: a meta-analysis. *J Anx Dis* 2008; **22**: 561–9.
- 188 Turner WA, Casey LM. Outcomes associated with virtual reality in psychological interventions: where are we now? *Clin Psychol Rev* 2014; **34**: 634–44.
- 190 Mohr DC, Vella L, Hart S, Heckman T, Simon G. The effect of telephone-administered psychotherapy on symptoms of depression and attrition: A meta-analysis. *Clin Psychol Sc Pract* 2008; **15**: 243–53.
- 191 Anthes E. Pocket psychiatry. *Nature* 2016; **532**: 20-23.
- 192 Donker T, Petrie K, Proudfoot J, Clarke J, Birch MR, Christensen H. Smartphones for smarter delivery of mental health programs: a systematic review. *J Med Internet Res* 2013; **15**: e247.
- 193 Espie CA, Kyle SD, Williams C, et al. A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. *Sleep* 2012; **35**: 769-81.
- 194 Bucci S, Barrowclough C, Ainsworth J, et al. Using mobile technology to deliver a cognitive behaviour therapy-informed intervention in early psychosis (Actissist): study protocol for a randomised controlled trial. *Trials* 2015; **16**: 1-20.
- 195 Mohr DC, Schueller SM, Riley WT, et al. Trials of intervention principles: Evaluation methods for evolving behavioral intervention technologies. *JMIR* 2015; **17**: e166.
- 196 Merry SN, Stasiak K, Shepherd M, Frampton C, Fleming T, Lucassen MF. The effectiveness of SPARX, a computerised self help intervention for adolescents seeking help for depression: randomised controlled non-inferiority trial. *BMJ* 2012; **344**: e2598.
- 197 Therapist-free therapy. *The Economist* 2011; **398**: 82-83.
- 198 Christensen H, Cuijpers P, Reynolds CF. Changing the direction of suicide prevention research: a necessity for true population impact. *JAMA Psychiatry* 2016; **73**: 435-436.

- 199 National Institute for Health and Care Excellence. Psychosis and schizophrenia in children and young people: Recognition and management. *NICE* 2013; **GC155**: <https://www.nice.org.uk/guidance/cg155> (accessed Oct 5, 2017)
- 200 Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; **340**: c332
- 201 Bradley H, Rucklidge JJ, Mulder RT. A systematic review of trial registration and selective outcome reporting in psychotherapy randomised controlled trials. *Acta Psychiatr Scand* 2017; **135**: 65-77
- 202 Dunn G, Emsley R, Liu H, et al. Evaluation and validation of social and psychological markers in randomised trials of complex interventions in mental health: a methodological research programme. *Health Technol Assess* 2015; **19**: 1-115
- 203 Rozental A, Kottorp A, Boettcher J, Andersson G, Carlbring P. Negative effects of psychological treatments: An exploratory factor analysis of the negative effects questionnaire for monitoring and reporting adverse and unwanted events. *PloS One* 2016; **11**: e0157503.
- 204 Boettcher J, Rozental A, Andersson G, Carlbring, P. Side effects in internet-based interventions for social anxiety disorder. *Internet Interv* 2014; **1**: 3-11.
- 205 Linden, M. How to define, find and classify side effects in psychotherapy: from unwanted events to adverse treatment reactions. *Clin Psychol Psychother* 2013; **20**: 286-296.
- 206 Arnberg FK, Alaie I, Parling T, Jonsson U. Recent randomized controlled trials of psychological interventions in healthcare: a review of their quantity, scope, and characteristics. *J Psychosom Res* 2013; **75**:401-8.
- 207 Jonsson U, Alaie I, Parling T, Arnberg FK. Reporting of harms in randomized controlled trials of psychological interventions for mental and behavioral disorders: a review of current practice. *Contemp Clin Trials* 2014; **38**: 1-8.
- 208 Longden E, Read J. Assessing and reporting the adverse effects of antipsychotic medication: a systematic review of clinical studies, and prospective, retrospective, and cross-sectional research. *Clin Neuropharm* 2016; **39**: 29-39.
- 209 Mayo-Wilson E, Montgomery P, Hopewell S, Macdonald G, Moher D, Grant S. Developing a reporting guideline for social and psychological intervention trials. *Brit J Psychiatry* 2013; **203**:250-4.
- 210 Munder T, Brüttsch O, Leonhart R, Gerger H, Barth J. Researcher allegiance in psychotherapy outcome research: An overview of reviews. *Clin Psychol Rev* 2013; **33**:501-11.
- 211 Lieb K, Osten-Sacken Jvd, Stoffers-Winterling J, Reiss N, Barth J. Conflicts of interest and spin in reviews of psychological therapies: a systematic review. *BMJ* 2016; **6**: e010606
- 212 van der Lem R, de Wever WW, van der Wee NJ, van Veen T, Cuijpers P, Zitman FG. The generalizability of psychotherapy efficacy trials in major depressive disorder: an analysis of the influence of patient selection in efficacy trials on symptom outcome in daily practice. *BMC Psychiatry* 2012; **12**:e192.
- 213 Freeman D, Dunn G, Startup H, et al. Effects of cognitive behaviour therapy for worry on persecutory delusions in patients with psychosis (WIT): a parallel, single-blind, randomised controlled trial with a mediation analysis. *Lancet Psychiatry* 2015; **2**:305-13.
- 214 Sensky T, Turkington D, Kingdon D, et al. A randomized controlled trial of cognitive-behaviour therapy for persistent symptoms in schizophrenia resistant to medication. *Arch Gen Psychiatry* 2000; **57**:165-72.

- 217 Cuijpers P, Driessen E, Hollon SD, van Oppen P, Barth J, Andersson G. The efficacy of non-directive supportive therapy for adult depression: a meta-analysis. *Clin Psychol Rev* 2012;**32**:280-91.
- 218 Turner DT, Gaag Mvd, Karyotaki E, Cuijpers P. Psychological Interventions for Psychosis: A Meta-Analysis of Comparative Outcome Studies. *Am J Psychiatry* 2014;**171**:523-38.
- 219 Morrison AP, French P, Stewart S, et al. Early Detection and Intervention Evaluation for people at risk of psychosis (EDIE-2): A multisite randomised controlled trial of cognitive therapy for at risk mental states. *BMJ* 2012; **344**: e2233.
- 220 Morrison AP, Shryane N, Beck R, et al. Psychosocial and neuropsychiatric predictors of subjective recovery from psychosis. *Psychiatry Res* 2013;**208**:203-9.
- 221 Riley R, Lambert P, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010;**340**:c221.
- 222 Vittengl JR, Jarrett RB, Weitz E, et al. Divergent outcomes in cognitive-behavioral therapy and pharmacotherapy for adult depression. *Am J Psychiatry* 2016; **173**: 481-90.
- 223 Weitz E, Hollon SD, Twisk J, et al. Baseline depression severity as moderator of depression outcomes between cognitive behavioral therapy vs pharmacotherapy: an individual patient data meta-analysis. *JAMA Psychiatry* 2015; **72**: 1102-9
- 224 Keeley T, Khan H, Pinfold V, et al. Core outcome sets for use in effectiveness trials involving people with bipolar and schizophrenia in a community-based setting (PARTNERS2): study protocol for the development of two core outcome sets. *Trials* 2015;**16**:1-9.
- 225 Morrison AP, Turkington D, Pyle M, et al. Cognitive therapy for people with schizophrenia spectrum disorders not taking antipsychotic drugs: a single-blind randomised controlled trial. *Lancet* 2014; **383**: 1385-1403.
- 226 Ennis L, Wykes T. Impact of patient involvement in mental health research: longitudinal study. *Brit J Psychiatry* 2013;**203**:381-6.
- 227 Brett J, Staniszewska S, Mockford C, et al. A Systematic Review of the Impact of Patient and Public Involvement on Service Users, Researchers and Communities. *Patient* 2014; **7**:387-95.
228. Lloyd K, Rose D, Fenton M. Identifying uncertainties about the effects of treatments for schizophrenia. *J Mental Health* 2006;**15**:263-8.
- 229 Law H, Morrison AP. Recovery in Psychosis: A Delphi Study With Experts by Experience. *Schiz Bull* 2014;**40**:1347-55.
- 230 Byrne R, Morrison AP. Service Users' Priorities and Preferences for Treatment of Psychosis: A User-Led Delphi Study. *Psychiat Serv* 2014;**65**:1167-9.
- 231 Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986;**51**:1173-82.
- 232 Van der Weele TJ. Marginal Structural Models for the Estimation of Direct and Indirect Effects. *Epidem* 2009;**20**:18-26.
- 233 Emsley R, Dunn G, White IR. Mediation and moderation of treatment effects in randomised controlled trials of complex interventions. *Stat Methods Med Res* 2010;**19**:237-70.

- 234 Freeman D, Dunn G, Garety P, et al. Patients' beliefs about the causes, persistence and control of psychotic experiences predict take-up of effective cognitive behaviour therapy for psychosis. *Psychol Med* 2013;43:269-77.
- 235 Goldsmith LP, Lewis SW, Dunn G, Bentall RP. Psychological treatments for early psychosis can be beneficial or harmful, depending on the therapeutic alliance: an instrumental variable analysis. *Psychol Med* 2015;45:2365-73.
- 236 Parmar MKB, Carpenter J, Sydes MR. More multiarm randomised trials of superiority are needed. *The Lancet* 2014;384:283-4.
- 237 Goldacre B. *Bad Pharma: How Medicine is Broken, and How We Can Fix It*. London: Foruth Estate, 2013.
- 238 Cuijpers P, Cristea IA. How to prove that your therapy is effective, even when it is not: a guideline. *Epidemiol Psychiatr Sci* 2015; 25: 428-435.
- 239 Relton C, Torgerson D, O’Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: introducing the “cohort multiple randomised controlled trial” design. *BMJ* 2010;340:c1066
- 240 Smith GC, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ* 2003;327:1459-61.
- 241 Frank G. The Boulder Model: History, rationale, and critique. *Prof Psycho Res Pract* 1984; 15: 417-35.
- 242 Abramowitz JS, Deacon BJ, Whiteside SPH. *Exposure Therapy for Anxiety: Principles and Practice*. New York: Guilford Press, 2012.
- 243 Mowrer OH. *Two-Factor Learning Theory: Versions One and Two*. Learning theory and behavior. Hoboken, NJ: John Wiley & Sons, 1960.
- 244 Foa EB. Cognitive behavioral therapy of obsessive-compulsive disorder. *Dialogues Clin Neurosci* 2010; 12: 199-207.
- 245 Abramson LY, Seligman ME, Teasdale JD. Learned helplessness in humans: critique and reformulation. *J Abnorm Psychol* 1978; 87: 49-74.
- 246 Abramson LY, Alloy LB, Metalsky GI. Hopelessness Depression - a Theory-Based Subtype of Depression. *PsycholRev*1989; 96: 358-72.
- 247 Seligman ME, Maier SF, Geer JH. Alleviation of learned helplessness in the dog. *J Abnorm Psychol* 1968; 73: 256-62.
- 248 Liu RT, Kleiman EM, Nestor BA, Cheek SM. The Hopelessness Theory of Depression: A Quarter Century in Review. *Clin Psychol* 2015; 22: 345-65.
- 249 Pryce CR, Azzinnari D, Spinelli S, Seifritz E, Tegethoff M, Meinlschmidt G. Helplessness: a systematic translational review of theory and evidence for its relevance to understanding and treating depression. *Pharmacol Ther* 2011; 132: 242-67.
- 250 Hoffman JL, Simon AB, Prasad KM, Truman CJ, Morrison J, Ernst CL. Neuroscience in psychiatry training: how much do residents need to know? *Am J Psychiatry* 2006; 163: 919-26.
- 251 Fung LK, Akil M, Widge A, Roberts LW, Etkin A. Attitudes toward neuroscience education in psychiatry: a national multi-stakeholder survey. *Academ psychiatry* 2015; 39: 139-46.

- 252 Uher R, Perlis RH, Henigsberg N, et al. Depression symptom dimensions as predictors of antidepressant treatment outcome: replicable evidence for interest-activity symptoms. *Psychol Med* 2012; **42**: 967-80.
- 253 Eshel N, Roiser JP. Reward and punishment processing in depression. *Biol Psychiatry* 2010; **68**: 118-24.
- 254 Gray JA. The psychophysiological basis of introversion-extraversion. *Behav Res Ther* 1970; **8**: 249-66.
- 255 Craske MG, Meuret AE, Ritz T, Treanor M, Dour HJ. Treatment for anhedonia: a neuroscience driven approach. *Depress Anx* 2016; **33**: 927-938.
- 256 Dimidjian S, Barrera M, Jr., Martell C, Munoz RF, Lewinsohn PM. The origins and current status of behavioral activation treatments for depression. *Annu Rev Clin Psychol* 2011; **7**: 1-38.
257. Dichter GS, Felder JN, Petty C, Bizzell J, Ernst M, Smoski MJ. The effects of psychotherapy on neural responses to rewards in major depression. *Biol Psychiatry* 2009; **66**: 886-97.
- 258 Blackwell SE, Browning M, Mathews A, et al. Positive imagery-based cognitive bias modification as a web-based treatment tool for depressed adults: a randomized controlled trial. *Clin Psychol Sci* 2015; **3**: 91-111.
- 259 Williams AD, O'Moore K, Blackwell SE, Smith J, Holmes EA, Andrews G. Positive imagery cognitive bias modification (CBM) and internet-based cognitive behavioral therapy (iCBT): a randomized controlled trial. *J Affect Disord* 2015; **178**: 131-41.
- 260 Schwabe L, Nader K, Pruessner JC. Reconsolidation of human memory: brain mechanisms and clinical relevance. *Biol Psychiatry* 2014; **76**: 274-80.
- 261 Brunet A, Orr SP, Tremblay J, Robertson K, Nader K, Pitman RK. Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. *J Psychiatr Res* 2008; **42**: 503-6.
- 262 Brunet A, Poundja J, Tremblay J, et al. Trauma reactivation under the influence of propranolol decreases posttraumatic stress symptoms and disorder: 3 open-label trials. *J Clin Psychopharmacol* 2011; **31**(4): 547-50.
- 263 Iyadurai, L., Blackwell, S. B., Meiser-Stedman, R., et al. Preventing intrusive memories after trauma via a brief intervention involving Tetris computer game play in the emergency department: a proof-of-concept randomized controlled trial. *Mol Psychiatry* 2017; **10.1038/mp.2017.23**.
- 264 Horsch, A., Vial, Y., Favrod, C. Harari, M. M., Blackwell, S. E., Watson, P., Iyadurai, L., Bonsall, M. B., & Holmes, E. A. (2017). Reducing intrusive traumatic memories after emergency Caesarean section: a proof-of-principle randomized controlled study. *Behav Res Ther* 2017; **94**:36-47
- 265 National Institute for Health and Clinical Excellence: Guidance. Depression the treatment and management of depression in adults (updated edition). *NICE* 2010; **CG90**.
- 266 American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder. 3rd edition. Washington, DC: American Psychiatric Publishing, 2010.
- 267 Cramer AO, Waldorp LJ, Van der Maas HL, Borsboom D. Comorbidity: A network perspective. *Behav Brain Sci* 2010; **33**: 137-150.
- 268 Lewinsohn PM, Zinbarg R, Seeley JR, Lewinsohn M, Sack WH. Lifetime comorbidity among anxiety disorders and between anxiety disorders and other mental disorders in adolescents. *J Anxiety Disord*. 1997;**11**:377-94.

- 269 Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, Severity, and Comorbidity of 12-Month DSM-IV Disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62**: 617–627.
- 270 Borsboom D, Cramer AO. Network Analysis: An Integrative Approach to the Structure of Psychopathology. *Ann Rev Clin Psychol* 2013; **9**: 91–121.
- 271 DSM-5: diagnostic and statistical manual of mental disorders. 5th edition. Washington, DC: American Psychiatric Publishing, 2013.
- 272 National Institute of Mental Health. A Report by the National Advisory Mental Health Council Workgroup on Tasks and Measures for Research Domain Criteria (RDoC). Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Mental Health <https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml>
- 273 van der Maas HL1, Molenaar PC. Stagewise cognitive development: an application of catastrophe theory. *Psychol Rev* 1992; **99**: 395–417.
- 274 Borsboom D, Rhemtulla M, Cramer AO, van der Maas HL, Scheffer M, Dolan CV. Kinds versus continua: a review of psychometric approaches to uncover the structure of psychiatric constructs. *Psychol Med* 2016; **21**: 1–13.
- 275 Kuppens P, Oravecz Z, Tuerlinckx F. Feelings change: Accounting for individual differences in the temporal dynamics of affect. *J Pers Soc Psychol* 2010; **99**: 1042–1060.
- 277 Bockting CLH. My Optimism Wears Heavy Boots: Towards Empirically Driven Tailored Interventions, Illustrated By Depression Research. Inaugural lecture. ZuidamUithof Drukkerijen, Utrecht, 2015
- 278 GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*, 2017;, No. 10100
- 279 Albert U, Rosso G, Maina G, Bogetto F. Impact of anxiety disorder comorbidity on quality of life in euthymic bipolar disorder patients: differences between bipolar I and II subtypes. *J Affect Disord* 2008; **105**: 297–303.
- 280 Brown TA, Antony MM, Barlow DH. Diagnostic comorbidity in panic disorder: Effect on treatment outcome and course of comorbid diagnoses following treatment. *J Consult Clin Psychol* 1995; **63**: 408–418.
- 281 Merikangas KR, He JP, Burstein ME, et al. Service utilization for lifetime mental disorders in U.S. adolescents: Results of the National Comorbidity Survey Adolescent Supplement (NCS-A). *J Am Acad Child Psychiatry* 2011; **50**: 32–45.
- 282 Nock MK, Hwang I, Sampson NA, Kessler RC. Mental disorders, comorbidity and suicidal behavior: Results from the National Comorbidity Survey Replication. *Mol Psychiatry* 2010; **15**: 868–876.
- 287 Kessler RC, Berglund P, Demler O, Jin R, Merikangas K, Walters EE. Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005a; **62**: 593–602.

- 289 Moffitt TE, Harrington H, Caspi A, et al. Depression and Generalized Anxiety Disorder. *Arch Gen Psychiatry* 2007; **64**: 651–660.
- 291 Zinbarg RE, Mineka S, Craske MG, et al. The Northwestern-UCLA youth emotion project: Associations of cognitive vulnerabilities, neuroticism and gender with past diagnoses of emotional disorders in adolescents. *Behav Res Ther* 2010; **48**: 347-58.
- 293 Caspi A, Houts RM, Belsky DW, et al. The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders? *Clinl Psychol Sci* 2014; **2**: 119–137.
- 294 Prenoveau JM, Zinbarg RE, Craske MG, Mineka S, Griffith JW, Epstein AM. Testing a hierarchical model of anxiety and depression in adolescents: a tri-level model. *J Anxiety Disord* 2010; **24**: 334–44.
- 295 Borsboom D, Cramer AO, Schmittmann VD, Epskamp S, Waldorp LJ. The small world of psychopathology. *PLoS One* 2011; **6**: e27407.
- 296 Fairburn CG, Cooper Z, Shafran R. Cognitive behaviour therapy for eating disorders: a "transdiagnostic" theory and treatment. *Behav Res Ther*. 2003;**41**: 509-28.
- 297 Stewart RE, Chambless DL. Cognitive-behavioral therapy for adult anxiety disorders in clinical practice: a meta-analysis of effectiveness studies. *J Consult Clin Psychol* 2009; **77**: 595-606.
- 298 Wichers M. The dynamic nature of depression: a new micro-level perspective of mental disorder that meets current challenges. *Psychol Med* 2014; **44**, 1349-1360.
- 299 Walz LC, Nauta MH, aan het Rot M. Experience sampling and ecological momentary assessment for studying the daily lives of patients with anxiety disorders: A systematic review. *J Anxiety Disord* 2014; **28**: 925–937.
- 300 aan het Rot M, Hogenelst K, Schoevers RA. Mood disorders in everyday life: A systematic review of experience sampling and ecological momentary assessment studies. *Clin Psychol Rev* 2012; **32**: 510–523.
- 301 Serre F, Fatseas M, Swendsen J, Auriacombe M. Ecological momentary assessment in the investigation of craving and substance use in daily life: A systematic review. *Drug Alcohol Depen* 2015; **148**: 1–20.
- 302 Bockting CL, Elgersma HJ, van Rijsbergen GD, de Jonge P, Ormel J, Buskens E, et al. Disrupting the rhythm of depression: design and protocol of a randomized controlled trial on preventing relapse using brief cognitive therapy with or without antidepressants. *BMC Psychiatry* 2011;**11**:8.
- 303 van Os J, Lataster T, Delespaul P, Wichers M, Myin-Germeys I. Evidence that a psychopathology interactome has diagnostic value, predicting clinical needs: an experience sampling study. *PLoS One* 2014; **23**;9: e86652.
- 304 Wigman JT, van Os J, Borsboom D, et al. Exploring the underlying structure of mental disorders: cross-diagnostic differences and similarities from a network perspective using both a top-down and a bottom-up approach. *Psychol Med* 2015; **45**: 2375–87.
- 305 Wichers M, Lothmann C, Simons CJP, Nicolson NA, Peeters F. The dynamic interplay between negative and positive emotions in daily life predicts response to treatment in depression: a momentary assessment study. *Brit J Clin Psychol* 2012; **51**: 206–222.
- 306 DeRubeis RJ, Cohen ZD, Forand NR, Fournier JC, Gelfand LA, Lorenzo-Luaces L. The Personalized Advantage Index: Translating Research on Prediction into Individualized Treatment Recommendations. A Demonstration. *PLoS ONE* 2014; **9**: e83875.

- 307 Barnett S, Moonesinghe SR. Clinical risk scores to guide perioperative management. *Postgrad Med* 2011; **87**: 535–541.
- 308 Politi K, Herbst RS. Lung cancer in the era of precision medicine. *Clin Cancer Res* 2015; **21**: 2213–2220.
- 309 Kramer I, Simons CJ, Hartmann JA, et al. A therapeutic application of the experience sampling method in the treatment of depression: a randomized controlled trial. *World Psychiatry* 2014; **13**: 68–77.
- 310 Holmes EA, Bonsall MB, Hales SA, et al. Applications of time-series analysis to mood fluctuations in bipolar disorder to promote treatment innovation: a case series. *Transl Psychiatry* 2016; **6**: e720.
- 311 Keller MC, Neale MC, Kendler KS. Association of different adverse life events with distinct patterns of depressive symptoms. *Am J Psychiatry* 2007; **164**: 1521–29.
- 312 Costantini G, Epskamp S, Borsboom D, et al. State of the aRt personality research: a tutorial on network analysis of personality data in R. *J Res Pers* 2015; **54**: 13–29.
- 313 Dalle Grave R, Calugi S, Sartirana M, Fairburn C. Transdiagnostic cognitive behaviour therapy for adolescents with an eating disorder who are not underweight. *Behav Res Ther* 2015; **73**: 79–82.
- 314 Fairburn CG, Cooper Z, Doll HA, et al. Transdiagnostic cognitive-behavioral therapy for patients with eating disorders: a two-site trial with 60-week follow-up. *Am J Psychiatry* 2009; **166**: 311–319.
- 315 Farchione TJ, Fairholme CP, Ellard KK, et al. Unified protocol for transdiagnostic treatment of emotional disorders: A randomized controlled trial. *Behav Ther* 2012; **43**: 666–678.
- 316 Thompson-Hollands J, Sauer-Zavala S, Barlow DH. CBT and the future of personalized treatment: a proposal. *Depress Anx* 2014; **31**: 909–911.
- 317 World Health Organization. Preventing suicide: a global imperative. Geneva: World Health Organization, 2014
- 318 McDaid D, Bonin E, Park A, Hegerl U, Arensman E, Kopp M, Gusmao R. Making the case for investing in suicide prevention interventions: estimating the economic impact of suicide and non-fatal self harm events. *Injury Prevention* 2010 **16** (Suppl 1):A257-A258319 O'Connor RC, Platt S & Gordon J. Achievements and Challenges in Suicidology: Conclusions and Future Directions. In R O'Connor, S Platt, & J Gordon (Eds.) *International Handbook of Suicide Prevention: Research, Policy and Practice*. Chichester: Wiley Blackwell, 2011.
- 320 Hawton K, van Heeringen K. Suicide. *Lancet* 2009; **373**: 1372–81.
- 321 Hawton K, Saunders KE, O'Connor RC. Self-harm and suicide in adolescents. *Lancet* 2012; **379**: 2373–82.
- 322 Turecki, G., & Brent, D. Suicide and suicidal behaviour. *Lancet* 2016; **387**: 1227–1239.
- 323 O'Connor RC, Nock MK. The Psychology of Suicidal Behaviour. *Lancet Psychiatry* 2014; **1**: 73–85.
- 324 Brown, GK, Jager-Hyman, S. Evidence-based psychotherapies for suicide prevention. *American J Prevent Med* 2014; **47**: S186–S194.
- 325 Inagaki, M., Kawashima, Y., Kawanishi, C. et al. Interventions to prevent repeat suicidal behavior in patients admitted to an emergency department for a suicide attempt: A meta-analysis. *J Aff Dis* 2015, **175**: 66–

78.

326 O'Connor E, Gaynes BN, Burda BU, Soh C, Whitlock EP. Screening for and treatment of suicide risk relevant to primary care: a systematic review for the US preventive services task force. *Ann Int Med* 2013; **158**: 741-754.

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

328 Hawton K, Witt KG, Taylor Salisbury TL, Arensman E, Gunnell D, Hazell P, Townsend E, van Heeringen K. Psychosocial interventions for self-harm in adults. *Cochrane Database Syst Rev* 2016; **CD012189**

329 Hawton K, Witt KG, Taylor Salisbury TL, Arensman E, Gunnell D, Townsend E, van Heeringen K, Hazell P. Interventions for self-harm in children and adolescents. *Cochrane Database Syst Rev* 2015; **12**: CD012013.

330 Zalsman G, Hawton K, Wasserman D, van Heeringen K, Arensman E, Sarchiapone M, Carli V, Hoschl C, Balazs J, Purebl G, Kahn JP, Saiz PA, Lipsicas CB, Bobes J, Cozman D, Hegerl U, Zohar J. Suicide prevention strategies revisited: 10 year systematic review. *Lancet Psychiatry* 2016; **3**:646-59

331 Van der Feltz-Cornelis, C.M., Sarchiapone, M., Postuvan, V., Volker, D., Roskar, Tancic Grum, A., Carli, V., McDaid, D., O'Connor, R., Maxwell, M., Ibelshausen, A., Van Audenhove, C., Scheerder, G., Sisask, M., Gusmão, R., Hegerl, U. Best practice elements of multilevel suicide prevention strategies. Review of systematic reviews. *Crisis. Journal of Crisis Intervention and Suicide Prevention* 2011; **32**: 319-333.

332 National Institute for Health and Care Excellence. Self-harm in over 8s: longer-term management. *NICE* 2011; **CG133**: <https://www.nice.org.uk/guidance/cg133> (accessed Oct 5, 2017)

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

334 Hawton K, Saunders KEA, Topiwala A, Haw C. Psychiatric disorders in patients presenting to hospital following self-harm: a systematic review. *J Aff Disord* 2013; **151**: 821-830.

335 Van Heeringen K. Towards a psychobiological model of the suicidal process. In K. van Heeringen (Ed.), *Understanding Suicidal Behaviour*. Chichester: John Wiley & Sons, 2001.

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

337 O'Connor RC. Towards an integrated motivational–volitional model of suicidal behaviour. In: O'Connor RC, Platt, S., Gordon, J., (Eds). *International handbook of suicide prevention: Research, policy and practice*. Chichester: Wiley Blackwell, 2011

338 Joiner TE. *Why people die by suicide*. Boston: Harvard University Press, 2005.

339 Van Orden KA, Witte TK, Cukrowicz KC, Braithwaite SR, Selby EA, Joiner TE, Jr. The Interpersonal Theory of Suicide. *Psychol Rev* 2010; **117**: 575-600.

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

341 O'Connor RC, Smyth R, Williams JMG. Intrapersonal positive future thinking predicts repeat suicide attempts in hospital treated suicide attempters. *J Consult Clin Psychol* **2015**; **83**: 169-176.

342 Klonsky ED, May AM. The Three-Step Theory (3ST): A new theory of suicide rooted in the "Ideation-

- to-Action" framework. *International Journal of Cognitive Therapy* 2015; **8**: 114-129.
- 343 Williams JMG. *The cry of pain*. London: Penguin, 2001.
- 345 O'Connor RC, O'Carroll RE, Ryan C, Smyth R. Self-regulation of unattainable goals in suicide attempters: A two year prospective study. *J Affect Dis* 2012; **142**: 248-55.
- 347 O'Connor DB, Green JA, Ferguson E, O'Carroll RE, O'Connor RC. Cortisol reactivity and suicidal behavior: investigating the role of the hypothalamic-pituitary-adrenal axis responses to stress in suicide attempters and ideators. *Psychoneuroendocrin* 2017;**75**: 183-191.
- 348 Comtois KA, Linehan MM. Psychosocial treatments of suicidal behaviors: a practice-friendly review. *J Clin Psychol Sess* 2006; **62**: 161-170.
- 349 Crawford MJ, Thomas O, Khan N, Kulinskaya E. Psychosocial interventions following self-harm: systematic review of their efficacy in preventing suicide. *Brit J Psychiatry: J Mental Sci* 2007; **190**: 11-7.
- 350 van der Feltz-Cornelis CM, Sarchiapone M, Postuvan V, et al. Best practice elements of multilevel suicide prevention strategies: a review of systematic reviews. *Crisis* 2011; **32**: 319-33.
- 351 Linehan MM, Comtois KA, Murray AM, et al. Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. *Arch Gen psychiatry* 2006; **63**: 757-66.
- 352 Guthrie E, Kapur N, Mackway-Jones K, et al. Randomised controlled trial of brief psychological intervention after deliberate self-poisoning. *BMJ* 2001; **323**:135-138.
- 353 Rossouw TI, Fonagy P. Mentalization-based treatment for self-harm in adolescents: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry* 2012; **51**: 1304-13.
- 354 Ryberg W, Fosse R, Zahl PH, Brorson I, Møller P, Landro NI, Jobes D. Collaborative Assessment and Management of Suicidality (CAMS) compared to treatment as usual (TAU) for suicidal patients: study protocol for a randomized controlled trial. *Trials* 2016; **17**: 481.
- 355 Gysin-Maillart A, Schwab S, Soravia L, Megert M, Michel K. A novel brief therapy for patients who attempt suicide: a 24-months follow-up randomized controlled study of the attempted suicide short intervention program (ASSIP). *PLOS Med* 2016; **13**: e1001968.
- 356 Ougrin D, Tranah T, Stahl D, Moran P, Rosenbaum Asarnow J. Therapeutic interventions for suicide attempts and self-harm in adolescents: Systematic review and meta-analysis. *J Am Acad of Child Adolesc Psychiatry* 2015; **54**: 97-107.
- 357 Cuijpers P, de Beurs DP, van Spijker BA, Berking M, Andersson G, Kerkhof AJ. The effects of psychotherapy for adult depression on suicidality and hopelessness: a systematic review and meta-analysis. *J Aff Disord* 2013; **144**: 183-90.
- 358 Carter G, Page A, Large M, Hetrick S, Milner AJ, Bendit N, Walton C, Draper B, Hazell P, Fortune S, Burns J, Patton G, Lawrence M, Dadd L, Robinson J, Christensen H. Royal Australian and New Zealand College of Psychiatrists clinical practice guideline for the management of deliberate self-harm. *Aus NZ J Psychiatry* 2016; **50**: 939-1000.
- 359 Platt, S. Inequalities and suicidal behavior. In R.C. O'Connor, J. Pirkis (Eds). *International Handbook of Suicide Prevention* (2nd edition, pp.258-283). Chichester: Wiley Blackwell, 2016

360. Bruffaerts R, Demyttenaere K, Hwang I, et al. Treatment of suicidal people around the world. *Brit J Psychiatry* 2011; **199**: 64–70.
- 361 Evans K, Tyrer P, Catalan J, Schmidt U, Davidson K, Dent J, Tata P, Thornton S, Barber J, Thompson S. Manual-assisted cognitive-behaviour therapy (MACT): a randomized controlled trial of a brief intervention with bibliotherapy in the treatment of recurrent deliberate self-harm. *Psychol Med* 1999; **29**: 19-25.
- 362 Milner, AJ, Carter G, Pirkis, J, Robinson J & Spittal MJ. Letters, green cards, telephone calls and postcards: systematic and meta-analytic review of brief contact interventions for reducing self-harm, suicide attempts and suicide. *Brit J Psychiatry* 2015; **206**:184-190.
- 363 Armitage CJ, Abdul Rahim W, Rowe R & O'Connor RC. An exploratory randomized trial of a simple, brief psychological intervention to reduce subsequent suicidal ideation and behaviour in patients hospitalised for self-harm. *Brit J Psychiatry* 2016; **208**: 1-7.
- 364 Hegerl U, Althaus D, Schmidtke A, & Niklewski G. The alliance against depression: 2-year evaluation of a community-based intervention to reduce suicidality. *Psychol Med* 2006, **36**, 1225-1233.
- 365 Harris F, Maxwell M, O'Connor R., et al. Exploring Synergistic Interactions And Catalysts In Complex Interventions: Longitudinal, Mixed Methods Case Studies Of An Optimised Multi-Level Suicide Prevention Intervention In Four European Countries (Ospi-Europe). *BMC Pub Health* 2016; **16**:
- 366 Chesin M, Stanley B. Risk assessment and psychosocial interventions for suicidal patients. *Bipolar Disord* 2013; **15**: 584-593.
- 367 de Beurs D, Kirtley O, Kerkhof A, Portzky G, & O'Connor RC. The role of mobile phone technology in understanding and preventing suicidal behavior. *Crisis* 2015; **36**: 79-82.
- 369 Cleary A. Suicidal action, emotional expression and the performance of masculinities. *Soc Sci Med* 2012; **74**: 498-505.
- 370 Colucci, E., & Lester, D. (2013) (Eds). *Suicide and culture. Understanding the context.* Gottingen: Hogrefe.
- 372 Lezine D. Lived experience and suicide prevention. In R.C. O'Connor & J. Pirkis (Eds.). *International Handbook of Suicide Prevention* (2nd edition). Chichester: Wiley, 2016
- 373 Becker CB, Zayfert C, Anderson, E. A survey of psychologists' attitudes towards and utilization of exposure therapy for PTSD. *Behav Res Ther* 2004; **42**: 277-292.
- 374 Dijkstra H, Huisman F, Miedema F, Mijnhart W. Why science doesn't work as it should and what to do about it. *Sci Trans* 2013. <http://www.scienceintransition.nl/wp-content/uploads/2013/10/Science-in-Transition-Position-Paper-final.pdf> (accessed March 15 2017).
- 375 Ioannidis JP. How to make more published research true. *PLoS Med* 2014; **11**: e1001747.
- 376 Johnsen TJ, Friberg O. The Effects of Cognitive Behavioral Therapy as an Anti-Depressive Treatment is Falling: A Meta-Analysis. *Psychol Bull* 2015; **141**: 747-768.
- 377 Fairburn CG, Cooper Z, Shafran R. Cognitive behaviour therapy for eating disorders: a "transdiagnostic" theory and treatment. *Behav Res Ther* 2003: 509-528

- 378 Bower, P., & Gilbody, S. Stepped care in psychological therapies: access, effectiveness and efficiency Narrative literature review. *Brit J Psychiatry* 2005; **186**: 11-17.
- 379 Wang PS, Aguilar-Gaxiola S, Alonso J, et al. Use of mental health services for anxiety, mood, and substance disorders in 17 countries in the WHO world mental health surveys. *The Lancet* 2007; **370**: 841-850.
- 380 Bockting CL, Hollon SD, Jarrett RB, Kuyken W, Dobson K. A lifetime approach to major depressive disorder: The contributions of psychological interventions in preventing relapse and recurrence. *Clin Psychol Rev* 2015; **41**: 16-26.
- 381 Loerinc AG, Meuret AE, Twohig MP, Rosenfield D, Bluett EJ, Craske MG. Response rates for CBT for anxiety disorders: Need for standardized criteria. *Clin Psychol Rev* 2015; **42**: 72-82.
- 382 Meade, M. S. (1988). *Medical geography*. John Wiley & Sons, Ltd.
- 383 Rosen GM, Davison GC. Psychology should list empirically supported principles of change (ESPs) and not credential trademarked therapies or other treatment packages. *BehavModific* 2003; **27**: 300-312
- 384 Naylor C, Parsonage M, McDaid D, Knapp M, Fossey M, Galea A. Report. Long-term conditions and mental health. The cost of co-morbidities. London: The King's Fund and Centre for Mental Health, 2012
- 385 Ennis L, Wykes T. Impact of patient involvement in mental health research: longitudinal study. *Brit J Psychiatry* 2013; **203**: 381-386.
- 386 Grant J, Cottrell R, Cluzeau F, Fawcett G. Evaluating “payback” on biomedical research from papers cited in clinical guidelines: applied bibliometric study. *BMJ* 2000; **320**:1107-1111.
- 387 Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry* 2010; **167**: 748-51.
- 388 Nature Editorials. Therapy deficit. Studies to enhance psychological treatments are scandalously under-supported. *Nature* 2012; **489**: 473-474.
- 389 MQ Landscape Analysis (April 2015). UK Mental Health Research Funding, 2015.
- 390 Bedirhan Üstün T, Chatterji S, Kostanjsek N, et al. Developing the World Health Organization Disability Assessment Schedule 2.0. *Bull World Health Organiz* 2010; **88**: 815–823.
- 391 Davidson L, O'Connell MJ, Tondora J, Lawless M, Evans AC. Recovery in serious mental illness: A new wine or just a new bottle? *Profess Psychol: Res Pract* 2005; **36**: 480.
- 392 Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62**: 617-627.
- 393 Rachman, S. Betrayal: a psychological analysis. *Behav Res Ther* 2010; **48**: 304-311.
- 394 Wykes T, Haro, JM, Belli, SR, et al. Mental health research priorities for Europe. *Lancet Psychiatry* 2015; **2**: 1036–42.

*******NEW REFS ADDED IN REVISED VERSION:**

395. 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.
396. Report of the UK Academy of Medical Sciences (2013). "Strengthening academic psychiatry in the UK"

397. GBD 2016 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet* 2017; **390**: No. 10100 DOI: [http://dx.doi.org/10.1016/S0140-6736\(17\)32130-X](http://dx.doi.org/10.1016/S0140-6736(17)32130-X)

398. Park-Lee E., Lipari RN, Hedden SL, Kroutil LA, Porter JD (2017). Receipt of services for substance use and mental health issues among adults: Results from the 2016 National Survey on Drug Use and Health. SAMSHA. <https://www.samhsa.gov/data/sites/default/files/NSDUH-DR-FFR2-2016/NSDUH-DR-FFR2-2016.htm>

399. Hawton, K., Witt KG, Taylor Salisbury TL, Arensman E, Gunnell D, Hazell P, Townsend E, van Heeringen K. Psychosocial interventions following self-harm in adults: a systematic review and meta-analysis. *Lancet Psychiatry* 2016; **3**: 740-750.

400. Craske MG, Meuret AE, Ritz T, Treanor M, Dour HJ. Treatment for anhedonia: a neuroscience driven approach. *Depression and Anxiety* 2016; **3**: 927-938.