Australian Government
National Mental Health Commission

NATIONAL MENTAL HEALTH RESEARCH STRATEGY

BACKGROUND PAPER: Anxiety disorders (Session 6A)

Professor Ron Rapee
Centre for Emotional Health
Macquarie University

With gratitude to: Yair Bar-Haim, Tel Aviv University; Philip Boyce, University of Sydney; Cathy Creswell, Oxford University; Toshiaki Furukawa, Kyoto University; Philip Kendall, Temple University; Lisa Lampe, University of Newcastle; Peter Lovibond, University of NSW; Jürgen Margraf, Ruhr University Bochum; Richard McNally, Harvard University; Donna Pincus, Boston University; Rick Richardson, University of NSW; Silvia Schneider, Ruhr University Bochum; Mikael Thastum, Aarhus University; Allison Waters, Griffith University; Maureen Whittal, University of British Columbia

Introduction

Anxiety disorders affect around 6-8% of youth and adults,[1,2] making them the most common group of mental disorders across the lifespan. Impact from anxiety disorders is pervasive, affecting relationships, career, and physical health and above all, producing extensive personal distress. While the intensity of their impairment is, on average, less than for several other disorders, its pervasiveness and the high prevalence of anxiety disorders makes them one of the higher sources of mental health disease burden. Scientific research into anxiety disorders has a long and impressive history and has ranged from classification and assessment through understanding of causes and maintenance, to treatment and prevention. There is a great deal we now know about anxiety disorders and their management – in fact treatment outcomes for anxiety disorders are among the strongest of all mental disorders. Nonetheless, there is a great deal we still don't know. Probably the most telling statistic is that despite all of our apparent advances, the population prevalence of anxiety disorders has not meaningfully changed.

In preparing this background paper, I briefly surveyed a random group of leading international researchers with expertise in anxiety (acknowledged above). Their views were surprisingly consistent and several core themes emerged as outlined below. It is important to point out that many of the issues described below are not specific or unique to anxiety disorders and in fact make more sense when considered transdiagnostically.

Classification/assessment

One of the greatest challenges facing the anxiety disorders field is the difficulty distinguishing "normal" from "abnormal". This is likely for two main reasons: a) the fact that anxiety (with all of the features of anxiety disorders) is a core aspect of normal human experience and b) the fact that levels of overall anxiousness tend to be chronic (long-standing) across a person's life. In fact the main distinction between normal anxiety and anxiety disorders is in impact – both distress and impairment. Studies that compare clinical and non-clinical populations on symptoms of anxiety, generally demonstrate only quantitative differences, and even these are quite inconsistent.

For this reason, assessment of anxiety disorders is a challenge and is an area that warrants constructive research. Early research argued for the importance of multi-modal assessment.[3] However,

psychophysiological measures have proven to show poor reliability and specificity and behavioural measures are also unreliable and are impractical for general clinical use. Cognitive and reaction time tasks, while perhaps the most scientifically exciting, are especially poor, psychometrically. Further work to strengthen the psychometric properties of cognitive and behavioural measures of anxiety could be especially important. Currently, the psychometrically strongest (and most practical) measures of anxiety are self- (or therapist) report. However, most current (symptom-based) measures show retest reliabilities of perhaps .6-.7, even over relatively short periods. If we accept that anxiety disorders are chronic, certainly over 1-2 weeks, then a strong measure of the pure construct needs to be far more reliable. Clearly there is a lot of "noise" in these measures (or in the construct) and this impacts all research efforts in anxiety.

At a practical level, advances in the field would be assisted by a shared agreement between experts on the core measures to use. A wide variety of instruments has been developed and at present there is little consistency between studies. This is particularly true when comparing across interest areas. For example, the outcome measures used in pharmacological studies are generally very different from the measures used in psychological studies, reducing any ability to compare. Some attempts at consensus statements are emerging, but these are not yet widely accepted.

Finally, one of the most critical issues (and certainly not specific to anxiety disorders) is the conceptualisation of the fundamental nature of psychopathology and how best it should be compartmentalised. To put it a different way, it is possible that "anxiety disorders" are not the best classification to describe nature. Several recent directions have been proposed as alternatives to the DSM structure (e.g., the HiTop system) and these suggest new directions of research to determine their implications for management of mental disorders. At a more focused level, the distinctions between anxiety and depression (as much as they exist) are still quite poorly understood, especially from the perspective of causes. For example, anxiety commonly precedes depression developmentally, but which youth and why some develop depression while others remain purely anxious is not known. Considerably more understanding of the factors that are responsible for both their overlap and differences would help to fine tune interventions as would a greater understanding of the fundamental nature of different forms of emotional distress and their relationships.

Causes and maintenance of anxiety

Within the anxiety disorders field there is probably general consensus that we know almost nothing about predictors (or causes) of the development of anxiety. Behaviour genetic research has clearly demonstrated the importance of heritability. But aside from this extremely broad truism, this doesn't tell us very much – research into specific genetic loci is scattered and inconsistent. Yet this is the only preceding factor (along with parent psychopathology) that has received consistent support. For every study that identifies a putative "cause" (e.g., parent overprotection; peer relationship difficulties), there are three that fail to replicate. To a large degree, this may be a result of the issues identified above – especially, the chronicity (and early development) and "normality" of anxiety. When supposedly "causal" factors are investigated longitudinally, they inevitably show bi-directional relationships. For example, peer rejection predicts anxiety, which predicts peer rejection. Hence, the field is far more advanced in identifying maintaining factors. A number of widely accepted theoretical models exist and there is extensive empirical evidence for most aspects of these. Nonetheless, as several of the group surveyed for this paper agreed, much of this evidence remains correlational and there is a desperate need to invest in more longitudinal and experimental research to identify factors that maintain (or trigger) anxiety.

Harking back to earlier comments about distinguishing anxiety disorder from normal human experience, identification of factors that maintain anxiety disorders is commonly hampered by the difficulty in

distinguishing “normal” from “abnormal”. For example, cognitive biases toward threat are a widely accepted maintaining mechanism. But a cognitive bias toward threat can also be seen as a core characteristic of the anxious state. So is it an independent factor that maintains the problem, or is it a feature of the problem? Similarly, an early temperamental style characterised by withdrawal and inhibition is widely accepted as one of the main precursors to anxiety disorders. But the extent to which this is an independent causal factor rather than simply an early manifestation of the disorder is extremely difficult to determine.

Treatment efficacy

Anxiety disorders show some of the greatest treatment response among the mental disorders. There is general consensus in the field that both psychological treatments (primarily CBT) and pharmacotherapy (primarily SSRI) lead to consistent and reasonable reductions. Following sufficient treatment around 40-60% of people, across all ages, are remitted from their main, presenting anxiety disorder.[4] However: a) at least half do not remit fully (although many of these do show small to large symptom reductions); b) many comorbid disorders (including other forms of anxiety disorder) remain; c) there is commonly continued, residual anxiety (and impairment) even if it does not meet full diagnostic criteria for a DSM anxiety disorder. These are the clear challenges that remain in our field.

In addition to these “big-picture” issues, the surveyed experts for this paper identified a range of focused questions that need to be addressed to move the field forward. First, the anxiety disorders field, as in many other areas, is starting to grapple with the issue of “personalised health”. The common catchphrase among researchers is “which specific treatments, work for which particular people, under which specific circumstances”? This is not a new concept. There have been extensive attempts over the decades to “fine-tune” treatments for anxiety disorders to specific subgroups – e.g., cognitive vs somatic responders; people reporting muscular tension vs avoidance – in fact, even diagnostic-specific treatments are a form of personalisation. Across the years, the fashion has swung between highly specific treatments for separate anxiety disorders to broad, transdiagnostic treatments. In fact, the original method from the earliest behaviour therapists – individualised functional analyses – is the ultimate form of personalisation. Yet there has been no consistent evidence that any of these methods has led to better outcomes for anxiety than our current treatments. The allure of personalised health is seductive and it appears to be producing some impressive effects in areas of physical health and with use of pharmacotherapies. But a great deal more work is needed before we can begin to recommend personalisation of treatments for anxiety disorders beyond the diagnostic level.

Several directions are also being discussed with respect to minor adjustments to current treatments to increase their efficacy. There is widespread consensus that, broadly speaking, this is a crucial direction to follow. Current treatments are strong and so we should not be throwing the baby out with the bathwater. Rather, research is needed to identify minor additions and variations that can increase their impacts (see next paragraph). Similarly, we have little knowledge about long-term maintenance of treatment effects among those who do show initial benefits. This issue is studied much more extensively in depression, which is known to be a recurrent disorder. However, among people with anxiety disorders (especially adults), we have very little information about how long benefits typically last, what proportion will show recurrence, what predictors might indicate risk for relapse, what treatments to offer those who relapse, and how to potentially prevent (reduce) relapse. One issue that has received some investigation is the use of booster or additional sessions following the end of standard treatment. However, the optimal number and spacing of these sessions is unknown. Similarly, the use of technologies (e.g. smartphone; internet) to assist with generalisation, contextualisation, and maintenance of effects needs much more exploration.

One of the most exciting directions of enquiry in the anxiety field in recent years has been the identification of experimentally-derived methods that appear to have some potential therapeutic value. Two of the most promising examples are the use of the pharmacological agent, d-cycloserine (dCS) to enhance the impact and generalisation of in vivo exposure, and use of computerised cognitive bias modification methods to shift the automatic biases toward threat that are characteristic of anxious individuals. To date neither of these methods has demonstrated sufficient, consistent effects in real world applications to provide a recommended adjunct to current treatments. But the principles are promising and it is very possible that greater investment in research on these or derivative procedures will bear fruit. Along similar lines, it is possible that exploration of novel targets for therapy (not anxiety per se but targeted toward specific behaviours, cognitive processes, or neurological processes) might lead to greater specificity of effects, novel interventions, and greater efficacy. Similarly, greater investment in encouraging multidisciplinary research between human psychopathology experts, animal behaviour, and neuroscientists would be critical to uncover innovative advances. Several findings from work on fear learning in animals (such as the dCS research mentioned above, other methods of enhancing memory reconsolidation, or demonstrations of developmental differences in fear (un)learning, have powerful potential implications for human anxiety.

The relationship between psychotherapies and pharmacotherapies is a critical area that has received surprisingly little attention. Traditionally, researchers have argued from a theoretical stance about whether use of pharmacological agents would enhance or detract from the processes critical to the success of psychological treatments. There has been surprisingly little empirical evaluation of whether combining these treatments leads to better outcomes – the few studies have shown quite inconsistent effects – and interestingly there appears some indication that the effects differ between anxiety disorders. Much more evidence is needed, not only broadly about whether combined pharmacotherapy and psychotherapy can increase efficacy, but more importantly how to best and most effectively combine them. From a personalisation perspective, it is very possible that different people will respond better to one or other of these treatments (or to their combination), but to date there is virtually no investigation of this question and practitioners have no empirically-based guidelines by which to recommend either or both treatments to their patients.

More broadly, this also relates to a core challenge in our field – how to deal with so-called "treatment non-responders". The latest clinical treatment guidelines for anxiety disorder in Australia and New Zealand[4] recommend switching treatments in cases of non-response (and of course, in the absence of evidence to the contrary, this is most logical). But at present, there is no empirical evidence. In other words, there are no well-conducted clinical trials that have evaluated whether switching a person who fails to respond to either psychotherapy or pharmacotherapy to the other form of treatment will produce improvement. Even within modalities, there is little empirical evidence on which to base a change of treatment. For example, for anxious individuals who do not respond to a sufficient course of SSRI, the RANZCP guidelines recommend trying a different SSRI, SNRI or perhaps benzodiazepine. But there is little empirical basis for this recommendation. Within psychotherapy there is even less choice – there are very few treatments, other than CBT, that have been empirically validated for anxiety disorders and there is no current evidence that non-responders to one form will respond to a different form of psychotherapy. Investment in such research would be expensive and would rely on multi-site collaborations since it requires very large samples. But it is a critically important issue to address for the mental health of our population since at present, practicing clinicians have little validated recourse if 1st line treatments fail. Within this issue, one of the first questions that needs to be addressed is to determine how to define "sufficient treatment". The vast majority of clinical trials for anxiety disorders at present specify a pre-determined duration of treatment, often for the convenience of the trial (usually 8-15

weeks). There is very little empirical evidence that evaluates the optimum, minimum, and/or maximum durations for "sufficient" treatment, either for pharmacotherapy or psychotherapy. Related to all of these points is the use of stepped care. Stepped care has been recommended as a cost-effective and logical method of service delivery for anxiety disorders (and a range of other conditions) by several influential bodies.[5] Good empirical evidence has tested stepped care delivery for depression.[6] However, for anxiety, there is very little empirical evidence. More importantly, it is not the issue of whether stepped care works that is critical. Rather funding needs to be invested to determine the optimal combination of steps to produce the most cost-effective outcomes.

Finally, prevention of mental disorder is an understudied field right across the spectrum of psychopathology, perhaps especially so for anxiety disorders. True prevention of anxiety disorders is extremely difficult, largely due to the chronicity of these disorders described earlier and their early onset. Nonetheless, a few attempts at prevention from very early age have shown promise but considerably more research is needed. More common in the anxiety field is early intervention, which is commonly delivered to youth through schools. This work has shown promise but again, there is a lot that we don't know. Few early intervention studies have evaluated longer-term effects and almost none beyond two years. Yet in the context of prevention, long-term impact into the adult years is critical. Most studies to date have also evaluated "researcher-led" interventions (both classroom and online) in the context of isolated clinical trials. Research now needs to begin to evaluate translation to the real world. In particular, sustainability of programs, systematic use by schools and education systems, and alternate models of delivery (e.g., delivery through school psychologists, teachers, or school nurses) need to be considered.

Treatment mechanisms

Greater understanding of the mechanisms underpinning treatments, both pharmacological and psychological, can suggest directions to increase efficacy. Unfortunately, there is broad consensus across the anxiety research field that we either don't understand how treatments work or that our beliefs about putative mechanisms have not been demonstrated. Some potentially useful conceptual directions include understanding mechanisms underpinning incidence (onset of disorder) and remission (recovery from disorder) and whether these are opposites or distinct processes, and similarly increasing our understanding of whether mental disorder (e.g. anxiety) and positive mental health are simply opposing states or are independent, with different maintaining mechanisms. Greater knowledge about moderators of treatment efficacy is important to both target treatments and to personalise them. At present, there are very few identified moderators that have been consistently replicated among treatments for anxiety. In fact the lack of consistent moderators is a fascinating issue in itself – current anxiety treatments appear to work similarly across ages, between sexes, despite comorbidities, and even across cultures and socioeconomic levels. However, the lack of extensive research in these latter two areas is a challenge for the field. The vast majority of treatment outcome research for anxiety is conducted with white, educated, and high functioning individuals. Far more research is needed in non-Western cultures and especially at the extreme end of disadvantage. Similarly, developmental differences in the mechanisms underpinning extinction demonstrated in animal models suggest that the mechanisms underlying anxiety treatment likely differ with development. Greater understanding of these differences may help to unlock more developmentally targeted interventions with greater efficacy.

Studying mediators of treatment is a particular challenge. First, good measures of many proposed mediators (especially for psychological treatments) have not been developed. Second, the time-course for proposed mechanistic changes is hard to determine, but probably occur relatively quickly. Therefore, innovative

methods of assessment that can be repeated frequently, are required. Finally, investigation of both moderators and mediators requires large samples that are difficult to obtain at a single site. Combining data across sites would be useful, but variations in treatments and processes across different sites adds unnecessary noise to the data. Therefore, large studies need dedicated funding, which is very difficult to obtain.

Treatment implementation

Despite the fact that current treatments for anxiety disorders are moderately efficacious, relatively few people in the community have access to empirically validated treatments, especially psychotherapy. Many practitioners are either poorly skilled or are unwilling to use empirically validated treatment packages. Better education and stigma reduction for both the public and professionals is seen as critical. Further, within the Australian context (and many other countries), good treatments for anxiety are primarily delivered by private clinicians, who are mostly accessed by educated, affluent, urban individuals. We need better methods to disseminate empirically validated treatments for anxiety (and their eventual improvements) to a much broader cross-section of the community. The recent explosion of research interest into online delivery of CBT can help to mitigate this problem to some extent. Online interventions provide a consistent product to all customers and they have the potential to be widely disseminated at lower cost (to the consumer). At present, online interventions are still not widely known or accepted by consumers and more research is needed into barriers to their uptake. Increased incorporation of economic analyses into clinical trials (for all forms of treatment) for anxiety should also help to demonstrate their cost effectiveness as well as guide efforts to maximise cost effectiveness. In turn, an increasing database on the cost effectiveness of treatments for anxiety disorders will help to convince policy makers to invest in broader public access.

Research investment is also needed to explore the most efficient and effective public models. Stepped care as one example was described above. But evidence is also needed about the types of skills and qualifications from practitioners that are needed to provide best practice, as well as methods to encourage uptake of best practice in public and private services. As an example, the British Improving Access to Psychological Therapies (IAPT) system publishes data on service performance from all of its area services, which in turn has led to improved performance.[7] Evaluation of current systems is needed. For example, it is unclear whether the Better Access framework within Australia has led to significant impact on anxiety disorders. Alternate models may need to be evaluated. Further effectiveness research is also needed. At present, the vast majority of clinical trials for anxiety are conducted in university or highly specialised services. Testing of these effects in real-world services is needed, along with evaluation of barriers and methods to mitigate these.

References

[1] Baxter AJ, Scott KM, Vos T, Whiteford H (2013) Global prevalence of anxiety disorders: a systematic review and meta-regression. Psychological Medicine 43:897-910

[2] Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA (2015) Annual Research Review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. Journal of Child Psychology & Psychiatry 56 (3):345-365. doi:10.1111/jcpp.12381

[3] Rachman S, Hodgson R (1974) Synchrony and desynchrony in fear and avoidance. Behaviour Research and Therapy 12:311-318

[4] Andrews G, Bell C, Boyce P, Gale C, Lampe L, Marwat O, Rapee R, Wilkins G (2018) Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. Australian & New Zealand Journal of Psychiatry 52 (12):1109-1172. doi:10.1177/0004867418799453

[5] Productivity Commission (2019) Mental Health, Draft report - Overview & Recommendations. Canberra

[6] van Straten A, Hill J, Richards DA, Cuijpers P (2015) Stepped care treatment delivery for depression: A systematic review and meta-analysis. Psychological Medicine 45:231-246

[7] Clark DM (2018) Realizing the Mass Public Benefit of Evidence-Based Psychological Therapies: The IAPT Program. Annual Review of Clinical Psychology 14 (1):159-183. doi:10.1146/annurev-clinpsy-050817-084833