Searching for Active Ingredients to combat youth anxiety and depression

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Standfirst: At Wellcome we are committed to finding the next generation of approaches for youth anxiety and depression. Since 2020 we have been learning 'what works, for whom, and why?', by commissioning reviews into the 'active ingredients' of successful interventions. Here we share four key 'calls to action' that we hope the mental health science community can take forward.

Anxiety and depression are mental health problems that affect millions globally each year, with considerable social and economic impact[1]. Median (peak) age of onset for these conditions is around 17 (5.5) and 31 (20.5) years respectively[2], with adolescence a window of both vulnerability and opportunity for prevention and intervention. At the Wellcome Trust, we are developing a programme to fund mental health research that will help inform new interventions to create a world where 'no-one is held back by mental health problems'. As a foundational project we commissioned over 50 research teams to review the evidence on what we have termed the 'active ingredients' for anxiety and depression in 14-24-year olds, i.e. those aspects of an intervention that drive clinical impact, are conceptually well-defined, and link to specific hypothesised mechanisms of action (Table 1). Wellcome selected these teams based on their expertise, the quality of their proposals, and to ensure a diverse range of potential active ingredients were considered. With this commissioned work, our aim is to provide the field with an overview, bringing together insights across a large and cross-disciplinary literature, and for the commission to signpost the way to future research priorities. To accompany this Collection of reviews from the commission we share below four key 'calls to action' that we hope the mental health science community can take forward.

Make better use of existing evidence across discipline boundaries

Commissioning reviews that could be completed within the first year of our programme has allowed us to take a birds' eye view on the state of the science and share findings with the research community. Looking across the whole commission, we did not see the emergence of clear 'best bets'. Perhaps unsurprisingly given heterogeneity in the field, the overall impression has been one of many ingredients of small effect. On the other hand, given the dominance put on psychotherapy (e.g., CBT) and pharmacotherapy (e.g., SSRIs), we might have expected to see considerably stronger evidence for these relative to other active ingredients. Instead, findings highlight a role for a much broader variety of potential approaches, both within and outside the healthcare setting.

Taking a secondary research approach has also been helpful in highlighting limitations and gaps in existing data. While depression and anxiety so often onset in youth, teams reported that the majority of studies relevant to their active ingredient focused on adults, and that it may not always be appropriate to extrapolate findings to adolescence. An additional common experience was that it was difficult to address the questions of 'for whom?' and 'why?' in the brief we gave teams of 'what works for whom and why?'. Work on personalised intervention is still in its infancy; most studies lack the power or were not designed to compare subgroups; little research has taken place outside a high-income country context, and the mechanisms of action for many of the active ingredients are still poorly understood. Discovering and highlighting these gaps has been an invaluable part of the learning process.

Mental health science is inherently interdisciplinary, and while exciting this raises several challenges. It is impossible for individual scientists to hold expertise in more than two or three areas at most, meaning a team science approach is required. However, experts across disciplines often 'speak different languages', with existing academic structures serving to reinforce discipline boundaries. Our commission aimed to provide a means to bring researchers together who may not have been familiar with each others' work, with monthly meetings and an online forum to encourage dialogue. We also explicitly asked teams to bring perspectives from multiple disciplines to their reviews. While a given active ingredient may target mechanisms at a specific level, its effects will ripple both backwards and forwards across biological, cognitive, interpersonal, and societal levels of explanation.

Seek conceptual clarity

A feature across the papers included in this Collection is a careful definition of the concept under review. In recent years researchers have called for a tighter focus in evaluating behavioural and psychological therapies, to look at not just whether it is effective, but also at the specific sub-components driving the change. The term 'active ingredients' was influenced by the 'evidence-based kernels' framework[3], which argues that therapies must be evaluated at the level of core components, such that 'deleting any component of a kernel would render it inert'. Relatedly, an important research question in intervention science asks whether therapeutic efficacy is driven by theoretically mediated factors (e.g., bias modification in CBT), or to 'common factors' across therapies such as empathy and social connection[4,5]. The active ingredients approach applies and extends these ideas beyond psychological therapies to any intervention that may prevent or reduce symptoms of anxiety and depression, from the biological to the societal. For example, while some of the papers in this Collection address putative active ingredients of existing psychological therapies (e.g., emotion regulation[6], social relationships[7], problem solving[8], decentering[9], helpful thinking patterns[10]), others use this same approach but apply it to the neurobiological domain (e.g., psychobiotics[11]) or look at how individuals use an active ingredient in everyday life (e.g., emotional awareness via ecological momentary assessment[12]). Our focus on conceptual clarity in defining active ingredients complements our commitment to bring conceptual clarity, and where possible some core measures, to how we consider impact in terms of outcomes[13].

Focus on what works for whom and why

By asking teams to evaluate 'what works, for whom and why?', we made evaluating the efficacy of their chosen ingredient a starting point. The dominant funding model to date in mental health science is one of forward translation, in which investment into basic causal mechanisms is assumed the best route to discovering effective interventions[14]. However, mental health conditions such as anxiety and depression are highly heterogeneous, both in terms of aetiology and treatment outcomes[15]. Such complex causal pathways mean that the above forward translation model alone is unlikely to yield a complete understanding of what works and why for all individuals, and indeed progress via this approach has stalled in recent decades. At the same time, there are treatments that we know are effective, but we don't know why. By focusing on the active ingredients of what works for different people, our research teams have been able to highlight effective approaches for which underlying mechanisms may still be poorly understood, signposting the way to future research.

For example, Bennett et al.[9] show that decentering (psychological distancing) is effective for reducing negative emotional states; however, the causal pathway to efficacy at neural and cognitive levels has not yet been fully elucidated. Conversely, Cohen Kadosh et al.[11] have argued that there is currently little evidence to support targeting the gut microbiome as an effective approach in preventing or treating youth anxiety, despite strong mechanism-driven hypotheses. The commission has shown that active ingredients are at different stages in the research process: for some, efficacy is well-established, and the

focus should now be on understanding mechanisms with a view to refining targets and populations, whereas for others the focus is on establishing efficacy in youth using well-powered, high-quality trials.

Involve underrepresented groups and promote new voices

While mental health science is diverse in terms of contributing disciplines, it does not fully represent the global community, either in terms of researchers or research participants. Most of our research teams reported that only a minority of the reviewed literature was conducted in low- and middle-income (LMIC) countries. Very little research considered cultural and linguistic differences, which are often treated as noise rather than signal that could drive more targeted and culturally appropriate interventions. While acknowledging considerable room for improvement, we endeavoured to include underrepresented groups in two key ways. First, in 2020 we commissioned five teams with Leads based in LMICs (representing 17% of all projects), and for our 2021 commission we instigated a target to commission at least 25% of projects with Leads based in LMICs (a target we exceeded with 33%). Second, we are committed to ensuring that the voice of those with lived experience is heard and incorporated into our work. We mandated that each research team should seek input from young people with lived experience, use their insights in the review process, and include these in their published output. These insights are evident throughout this Collection; for example, Filia et al.[7] explicitly discuss the role youth advisers played in developing search strategies and consulting on findings, and point out where youth opinion deviates from the focus in the published literature. Our view is that including these voices has strengthened the science, for example by helping to refine research protocols and offer new perspectives.

Conclusions

Progress on understanding what works for whom and why in youth anxiety and depression is hampered by challenges applicable across mental health science. Diagnostic categories and measurement are imperfect, aetiology is complex and heterogeneous, and we lack biomarkers or other means of predicting who will respond to particular interventions. Our active ingredients programme is designed with this complexity in mind, starting with a focus on 'what works' and encouraging back-translation to gain an understanding of 'why' and 'for whom'. Progress will only be made by acknowledging existing limitations in the field and working together to resolve them. Our 'calls to action' emphasise approaches that we have found fruitful for our active ingredients commission, but we are sure there are many more. We are keen to 'learn in public' alongside and as part of the mental health science community to stop young people being held back by mental health problems.

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Competing interests
The authors declare no competing interests.

Table 1: Active Ingredients to prevent or treat youth anxiety and depression reviewed by Wellcome-funded teams (2020-21)

Behaviours and activities	**Beliefs and knowledge**	**Brain/Body functions**
• **Behavioural activation:** increasing engagement with positive activities • **Collaborative goal setting and tracking** • **Engagement with the arts** • **Exposure:** facing one's fears in a planned manner • **Physical activity:** more bodily movement • **Problem solving** • **Relaxation techniques:** better stress response via relaxation • **Remote measurement technologies:** use of remote technologies to monitor changes in biology, behaviour, and environment relevant to the problems • **Self-disclosure:** sharing information with others about personal experiences and characteristics	• **Agency:** developing a sense of agency through social action • **Cultural connection:** connection with one's own culture • **Mental health literacy** • **Sense of mattering** • **Sense of purpose** • **Self-evaluation:** improved view of self • **Spiritual and religious beliefs**	• **Circadian rhythms:** better sleep-wake cycles • **Gut microbiome:** improving gut microbiome function • **Hippocampal neurogenesis:** growth of new neurons in the hippocampal region of the brain • **Omega-3 supplements** • **Reduced levels of inflammation in the body** • **Selective serotonin reuptake inhibitors:** use of antidepressants
Cognitive and attentional skills	**Human connections**	**Socioeconomic factors**
• **Affective awareness:** knowing how one feels • **Decentering:** better able to shift perspective • **Emotional controllability:** beliefs about the extent to which emotions are controllable • **Emotional granularity:** improved ability to characterise emotional experiences • **Emotion regulation:** improved management of emotions • **Grief reduction:** use of strategies to target feelings of grief • **Helpful attentional and interpretational thinking patterns** • **Hopefulness:** learning to be more hopeful • **Mental imagery:** helpful use of emotional mental imagery • **Perfectionism reduction** • **Repetitive negative thinking reduction** • **Self-compassion**	• **Communication in families** • **Digital quality social connection** • **Family support** • **Loneliness reduction** • **Neighbourhood cohesion:** increased neighbourhood social connection • **Peer support:** support from a peer who has experienced anxiety and/or depression • **School connectedness:** sense of connection to school life • **Social inclusion:** improved inclusion for those who are minoritized on the basis of their identity (e.g., sexual and gender) • **Social relationships:** facilitating improvements in social relationships **Working alliance:** a functional and collaborative relationship with a helper	• **Economic transfers:** increased financial resources via cash transfers • **Urban access to green space**

Note: This is not a comprehensive list of all possible active ingredients. Wellcome selected these based on the quality of the submitted proposals, the teams' expertise, and to ensure a diverse range of ingredients were considered. Categories used are imperfect and merely for ease of navigation.