

General Psychiatry **Pharmacotherapy of anxiety disorders in the 21st century: A call for novel approaches**

Eric Bui,^{1,2} Franklin King,^{1,2} Andrew Melaragno^{1,2}

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ABSTRACT

While limited advances have occurred in the past 30 years in the pharmacological management of anxiety and stress-related disorders, novel molecular pathways both within and without the monoamine systems are currently under investigation and offer promising new avenues for more effective future treatments. Enhancing psychotherapy approaches with pharmacological compounds offers the potential to not only transform the standard of care of these conditions, but more broadly would introduce a paradigm shift in the way medications and their role in psychiatric care are conceptualised. Although further human trials and more translational research are sorely needed, continuing to pursue innovative mechanisms and treatments is hoped to yield substantial results in the coming decades and a departure from the reliance on chemical agents of the 20th century.

PHARMACOLOGICAL TREATMENT OF ANXIETY DISORDERS IN THE PAST 30 YEARS

Over 30 years after the introduction of fluoxetine in 1986, the first-line pharmacotherapy of anxiety disorders still relies on selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants, two closely related classes of drugs derived from fluoxetine.¹ Admittedly, these SSRI and SNRI drugs, along with serotonin 5-hydroxytryptamine 1A (5-HT_{1A}) receptor agonists such as buspirone, also introduced in 1986, have significantly improved the pharmacological treatment of anxiety by offering options that were significantly more tolerable to patients and vastly safer in overdose than prior treatments. Nevertheless, if we consider SSRIs/SNRIs as belonging to a broader class of medications that modulate levels of central nervous system monoamine neurotransmitters (principally serotonin and norepinephrine, but also dopamine), then no major innovation in terms of therapeutic targets has occurred since the introduction of monoamine oxidase inhibitors and tricyclic antidepressants in the 1950s. Benzodiazepines, the other major class of Food and Drug Administration

(FDA)-approved antianxiety medications, also date back to the 1950s, and target the gamma-aminobutyric acid (GABA) receptor in a similar fashion to their more toxic predecessors, meprobamate and the barbiturates, whose use dates back to the beginning of the 20th century. Moreover, the use of benzodiazepines is now more limited due to concerns of abuse, dependence and mortality in polypharmacy with concomitantly prescribed (or abused) opioids.² Clearly, since the advent of fluoxetine, no major breakthrough has been achieved in the pharmacological treatment of anxiety disorders in the past three decades, with advances being mostly incremental.

The factors contributing to this lack of major advances are many, but at least three interconnected ones should be highlighted. First, research efforts and the majority of FDA-approved medications for anxiety have long revolved around the monoamine and the GABA systems, restricting the range of possible innovation to incremental steps within a narrow framework. Second, the development of drugs has developed somewhat serendipitously in parallel with the rigorous accumulation of basic science supporting a more comprehensive understanding of the molecular and cellular pathophysiology and brain circuit dysfunction involved in anxiety disorders. A gap in translational research has created a situation where the leaps gained from the former are not effectively used to inform the latter. For example, most FDA-approved treatments for anxiety were initially developed or tested for another condition, usually depression. Furthermore, development efforts usually focus on identifying drugs based on their affinity to brain receptors but do not account for the complex interaction between different circuits, nor for the upregulation and downregulation that can occur when a new drug is introduced. Third, the conceptualisation of how drugs work for anxiety disorders largely follows a



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¹Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts, USA

²Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, United States

Correspondence to

Dr Eric Bui;

tebui@mg.harvard.edu

medical model³—that is to say, chronic administration of a drug to compensate for a chronic deficit, much like the lifelong administration of insulin to a patient with type 1 diabetes. This frame is partially at odds with the efficacy of psychotherapeutic approaches, which in many cases have actually been demonstrated to be curative in nature,⁴ reversing underlying biological abnormalities evidenced by neuroimaging findings.⁵ In fact, there is no satisfactory explanatory model for how both antidepressants and psychotherapy could be efficacious in anxiety disorders.

We therefore propose that future research in anxiety disorders should focus on novel neurotransmitter pathways, building on a better understanding of the molecular and cellular pathophysiology of (pathological) anxiety, with an aim to fully and definitively restore functions altered.

NOVEL PROMISING PHARMACOLOGICAL PATHWAYS

The oxytocin system that is implicated in reproductive and prosocial behaviours⁶ has also been found to play a role in stress-related^{7,8} and anxiety disorders.⁹ Empirical evidence suggests that targeting the oxytocin system may reduce avoidance,¹⁰ anxiety and stress.¹¹ Oxytocin administration has thus been proposed as a potential treatment target for stress-related and anxiety disorders;^{12,13} however, to date no efficacy data from prospective clinical trials are available.

Ketamine, an N-methyl-D-aspartate receptor (NMDA) receptor antagonist, has been recently shown to rapidly reduce the severity of depression symptoms.¹⁴ Preliminary data also suggest a potential efficacy in post-traumatic stress disorder (PTSD),¹⁵ obsessive-compulsive disorder,¹⁶ and social and generalised anxiety disorders.¹⁷

Research has demonstrated the involvement of the endocannabinoid system in the regulation of various physiological operations including pain, inflammation, gastrointestinal, metabolic and cardiovascular function, and has been recently proposed as a potential therapeutic target in psychiatry and for anxiety disorders.¹⁸ In particular, preclinical studies reported that inhibition of the fatty acid amide hydrolase and monoacylglycerol lipase leads to increased signalling in the endocannabinoid system and was associated with reductions in anxiety-like behaviours in rodents.¹⁹ However, other agents to regulate the endocannabinoid system have also been proposed.²⁰ For example, cannabidiol, a compound found in *Cannabis sativa*, has been the focus of recent attention.²¹

Anxiety disorders, particularly fear-based disorders, are hypothesised to arise from a deficit in fear processing and/or extinction learning.²² Thus, systems implicated in the consolidation of fear memories have been investigated as potential treatment targets.

First, the oestradiol and progesterone system has been implicated in the consolidation of fear. For example, a review of 17 studies found that higher estradiol levels were associated with enhanced fear extinction recall, suggesting a potential role of oestrogen for the treatment

of PTSD.²³ Second, the renin–angiotensin system has become the focus of attention of recent translational research.²⁴ Preclinical data suggest that blocking the angiotensin 1 receptor may enhance the extinction of fear memory in rodents.²⁵ In another recent animal study, the administration of the angiotensin II receptor antagonist losartan mitigated artificially induced deficits in extinction in female rodents.²⁶ A clinical trial in humans of daily administration of losartan for PTSD is currently under way (NCT02709018).

More importantly, while the large majority of pharmacological treatments for anxiety disorders available to date have relied on the traditional model of chronic drug administration to treat putatively chronic, lifelong disorders, these recent advances in our understanding of fear learning have been the stepping-stone for new approaches aiming to pharmacologically manipulate fear consolidation and extinction learning. Data have suggested that stored memories are rendered labile during retrieval, and that these memories undergo a reconsolidation process after being retrieved. This has led to efforts to block memory reconsolidation using the beta-blocker propranolol for PTSD.²⁷ Recently, in a randomised controlled trial of six sessions of propranolol (vs placebo) administration 90 min before a brief memory retrieval were found efficacious for PTSD.²⁸ This may be relevant to other anxiety disorders, although findings have not been extended to other conditions to date. Both recent animal and human studies report that propranolol may enhance extinction,^{29,30} suggesting that propranolol administration might act as a fear extinction learning enhancer rather than a postretrieval amnesia inducer, and future studies should test whether propranolol could enhance fear extinction learning during exposure-based therapies.

In fact, several other strategies focused on enhancing fear extinction learning through the administration of pharmacological compounds during sessions of exposure have also been examined for fear-based disorders.^{31,32} The NMDA partial agonist D-cycloserine has been the most studied potential pharmacological enhancer of exposure-based therapies. Results from a recent meta-analysis suggest that D-cycloserine has a small augmentation effect on exposure-based therapies for specific phobia, social anxiety, panic disorder, obsessive-compulsive disorder and PTSD.³³ Other compounds have also been studied or are being studied as potential enhancers of exposure therapies, including methylene blue^{34,35} or estradiol.³⁶ Others yet are to be studied based on their potential role on fear extinction, including for example the angiotensin II receptor antagonist losartan, as described above.²⁶

PHARMACOLOGICALLY ASSISTED PSYCHOSOCIAL INTERVENTIONS

While recent advances in our understanding of memory processes have led to novel strategies to combine pharmacotherapy and psychotherapeutic approaches—the

emergence of brief and targeted administration of drugs as a way to pharmacologically manipulate memory processes—these approaches fall into broader efforts in the field of anxiety disorders (and psychiatric disorders in general) to use pharmacotherapy to assist or enhance psychosocial interventions.

Although widely known as the active ingredient in the recreational drug ecstasy, 3,4-methylenedioxymethamphetamine (MDMA) was historically used as an adjunct to psychotherapy in the late 1970s,³⁷ prior to its designation as a Schedule I drug by the US Drug Enforcement Administration in 1985. MDMA's proposed mechanism of action is both complex and unclear, but appears to primarily involve inducing the release of norepinephrine and serotonin as well as concomitantly inhibiting their reuptake.³⁸ Due to its enhancement of feelings of inner awareness and social bonding, it was suggested to be particularly well suited to psychiatric states characterised by emotional numbing, fear state or social disconnection, such as PTSD.³⁹ MDMA has recently been the focus of much attention with regard to its use to facilitate the processing of trauma memories during therapy.⁴⁰ MDMA-assisted psychotherapy is currently undergoing clinical trials for treatment of PTSD, with a phase II randomised, double-blind study of first responders with severe treatment-resistant PTSD showing promising efficacy results maintained at 12-month follow-up.⁴⁰

While psychedelic agents were initially the focus of intensive research to treat psychiatric disorders, societal views shifted dramatically towards the end of the 1960s in the face of widespread recreational use and highly publicised media accounts of adverse events.⁴¹ These agents appear to exert their primary effect via agonist activity at the 5-HT_{2A} receptor, although the 5-HT_{1A} receptor has also been implicated.⁴² Similarly to recent efforts focused on MDMA, others have recently revisited the potential use of these compounds during therapy sessions. While much of both the scientific literature as well as media attention have remained focused on the use of psychedelics in the treatment of major depressive disorder,⁴³ an increasing body of evidence suggests that psychedelics may exert significant effects on anxiety disorders. The efficacy of psychedelic compounds has been in every case studied when administered under some degree of psychological support, often with non-directive psychotherapy and instrumental evocative music, leading to the use of the term 'psychedelic-assisted psychotherapy' to describe these treatment modalities.⁴⁴

Ayahuasca is a brewed beverage derived from two Amazonian plant species, *Psychotria viridis* containing the active psychedelic ingredient, dimethyltryptamine (DMT), and *Banisteriopsis caapi* which contains its precursor.⁴⁵ Long used by indigenous populations in South America for mystical and therapeutic purposes, the use of ayahuasca has spread throughout the Western world, where it is employed for a variety of purposes, including self-exploration and healing of mental health conditions.⁴⁶ Observational studies of ceremonially administered

ayahuasca have reported lasting effects of serenity, relaxation and inner peace 1–2 weeks following a single session,⁴⁷ with sustained reductions in a scale measuring minor psychopathological symptoms, including anxiety, as well as reductions in the personality trait of harm avoidance, found in one of two subgroups at 6 months.⁴⁸ Increases in scores in the non-judging subscale of the Five Facet Mindfulness Questionnaire (a construct that measures acceptance and a non-evaluative stance towards thoughts and emotions⁴⁹), for which higher scores have previously been linked to a reduced level of anxiety and depression,⁵⁰ have also been reported following ayahuasca administration,⁵¹ including in a group of subjects with borderline personality disorder traits.⁵² An open-label trial conducted on an inpatient psychiatric unit reported a decrease in the anxious depression subscale of the Brief Psychiatric Rating Scale following a single dose of ayahuasca,⁵³ and a randomised, double-blind study comparing ayahuasca with placebo found significant decreases in baseline panic-like symptoms (although not in state or trait anxiety), during the actual drug experience.⁵⁴ When administered parenterally, DMT results in a significantly shorter peak effect than other psychedelics, with the most acute effects lasting only several minutes.⁵⁵ While a paucity of recent studies have examined DMT in controlled environments, limited data have reported patients experiencing both anxiety and euphoria, often alternating or existing simultaneously.^{56 57}

Other compounds that might be used in conjunction with psychotherapy sessions are the naturally occurring fungal alkaloid, psilocybin and the synthetic compound related to the ergot-derived lysergic acid, lysergic acid diethylamide (LSD). Psilocybin is currently the most commonly studied agent, likely due to its large therapeutic index and its short half-life relative to LSD.^{58–60} Research using psilocybin for anxiety disorders was first renewed in a double-blind label trial of varying doses of psilocybin, which found rapid, acute reductions in symptoms of obsessive-compulsive disorder.⁶¹ Building on prior studies from the 1960s and 1970s that found significant reductions in end-of-life anxiety associated with terminal cancer following LSD-assisted psychotherapy,⁶² a pilot study in 2011 found rapid decreases in anxiety associated with end of life.⁶³ Two subsequent randomised, double-blind trials with patients with terminal cancer achieved similar results; however, perhaps of greater interest than the acute effects was the finding in both studies that at 6-month follow-up at least 80% of subjects continued to experience an enduring reduction in anxiety symptoms, after only a single treatment session.^{64 65} A study using LSD-assisted psychotherapy in patients with life-threatening disease found significant reductions in state anxiety at 2-month follow-up, with a similarly enduring effect on anxiety reduction sustained at 12-month follow-up.⁶⁶ At present, several clinical trials examining the use of psilocybin-assisted therapy are currently recruiting, including subjects with anxiety associated with serious illness as well as obsessive-compulsive disorder.

While limited advances have occurred in the past 30 years in the pharmacological management of anxiety and stress-related disorders, novel molecular pathways both within and without the monoamine systems are currently under investigation and offer promising new avenues for more effective future treatments. Furthermore, enhancing psychotherapy approaches with pharmacological compounds offers the potential to not only transform the standard of care of these conditions, but more broadly would introduce a paradigm shift in the way medications and their role in psychiatric care are conceptualised. Although further human trials and more translational research are sorely needed, continuing to pursue innovative mechanisms and treatments is hoped to yield substantial results in the coming decades and a departure from the reliance on chemical agents of the 20th century.

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Dr. Bui Eric is an assistant professor of psychiatry at Harvard Medical School and the Center for Anxiety and Traumatic Stress Disorders and Complicated Grief Program at the Massachusetts General Hospital. He received his M.D. from the University Paul Sabatier, Toulouse, France, where he also completed a Ph.D. in Neurosciences. He currently serves on the Board of Directors of the International Society for Traumatic Stress Studies, and as an associate editor of the European Journal of Psychotraumatology. To date, he has published over 120 scientific articles and book chapters in the field of anxiety disorders, posttraumatic stress disorder, complicated grief and related disorders. His research focuses specifically on understanding the mechanism and improving the treatment of anxiety and stress-related conditions.