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Advances in Psychopharmacology for Anxiety Disorders

Abstract: Anxiety disorders are among the most prevalent psychiatric disorders, but compared with mood and psychotic disorders, are understudied in terms of newer pharmacotherapeutic approaches. Certain anxiety disorders, such as generalized anxiety disorder, and related conditions such as posttraumatic stress disorder (PTSD), may be refractory to the approved first-line treatments, like selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). Here we will review the most recent pharmacological treatment modalities under investigation for anxiety disorders and related conditions such as PTSD. The review includes a discussion of neurotransmitter and peptide pathways. We will present novel treatment options from medication classes that are widely studied in anxiety, such as the serotonin and gamma-aminobutyric acid (GABA) system, and also more novel mechanisms like glutamate modulators (e.g., ketamine, riluzole and D-cycloserine), corticotropin releasing factor and vasopressin receptor antagonists, neuropeptides such as neuropeptide Y and oxytocin, anticonvulsants such as pregabalin and gabapentin, mifepristone, and adrenergic agents such as propranolol and prazosin. Our review of the literature suggests that while there are some agents under investigation that may appear promising in the future, most of them are relatively early in development and there are very few new medications that carry immediate promise for the treatment of anxiety disorders. We hope this review encourages further investigation of novel therapeutics for anxiety, focusing primarily on new drug development of nonmonoamine and peptide systems.

Introduction

Anxiety disorders are the most common class of psychiatric disorders (1). They are commonly associated with functional impairment (2) and are, along with depression, among the leading causes of disability and work absences (3). The cost burden of anxiety disorders may also be greater than any other psychiatric disorders, even mood disorders, due to their high prevalence and the increased costs of medical and psychiatric treatment (4, 5). In spite of this, compared with mood, schizophrenia spectrum, and autism spectrum disorders, there has been less research for novel therapeutics for the anxiety disorders in the last two decades. The most recent Food and Drug Administration (FDA)-approved treatments for anxiety disorders have been repurposed antidepressant treatments. Currently, the mainstays of pharmacological treatment for anxiety disorders are selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and benzodiazepines. Anxiety is responsive to several

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forms of psychotherapy including cognitive behavioral therapy (CBT), but medication treatments will be the focus of this review.

Anxiety disorders, as described in the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV-TR), consisted of the following diagnoses (if one were to exclude Not Otherwise Specified and Anxiety Disorders due to Substances or Medical Conditions): generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder (PD) with or without agoraphobia, posttraumatic stress disorder (PTSD), social phobia, and specific phobia (6). The DSM-5 includes a total of nine distinct anxiety disorders (see Table 1). It classifies OCD under its own class of disorders, called obsessive-compulsive and related disorders, while PTSD is listed under trauma- and stressor-related disorders (7). For the purpose of this review, we will not discuss OCD, a distinct disorder in terms of pathophysiology and treatment, while PTSD will be included as newer therapeutics for PTSD overlap with other anxiety disorders. Additionally, anxiety due to a substance or medical disorder will not be discussed as the treatment often involves management of the underlying cause.

The current treatments for anxiety disorders are summarized in Table 2. It is notable that, with the exception of specific phobia, the first line treatment for all anxiety disorders are SSRIs and SNRIs. Previously, tricyclic antidepressants (TCAs) were the favored choice for PD and OCD but have been relegated to second-line treatment due to concerns about side effects, including anticholinergic effects, weight gain, sedation, cardiac effects, and the danger of death in overdose. Monoamine oxidase inhibitors (MAOIs) have proven efficacy in anxiety disorders but their use is limited by dietary restrictions, drug interactions, and side effects. Benzodiazepines, a medication class dating back to the 1950s, were considered a first-line treatment for PD and generalized anxiety as well, but due to concerns about tolerance and dependence, it is recommended that they be used judiciously, especially in patients with a past substance abuse history and in special populations (children/adolescents, elderly, and medically ill persons). Finally, alternative treatments that are currently not approved by the FDA include anticonvulsants, including gabapentin and pregabalin, and antipsychotics including quetiapine. Although there is limited evidence to support their use, they may be appropriate in cases of refractory anxiety, with the caveat that tolerability and safety may be a concern in the case of antipsychotics.

Although anxiety disorder may respond to appropriate first- and second-line pharmacologic treatments with or without psychotherapy, there is reasonable concern about the dearth of options for the large number of patients who are nonresponsive to current treatment options. Most of the current pharmacotherapies for anxiety disorders act via the monoamine system (e.g., SSRIs, SNRIs, TCAs, and MAOIs) or as agonists of gamma-aminobutyric acid (GABA-A) receptors (the benzodiazepines). There is a clear need for more efficacious treatments with novel mechanisms. We will therefore focus on the promising next-generation antianxiety treatments, which are currently in development, discussing them in the context of their putative mechanisms of action.

Table 1. Anxiety Disorders

Agoraphobia	Now a distinct disorder in DSM-5
Generalized Anxiety Disorder	
Panic Disorder	
Selective Mutism	Newly classified in DSM-5
Separation Anxiety Disorder	Newly classified in DSM-5
Social Anxiety Disorder (Social Phobia)	
Specific Phobia	
Anxiety Disorder Due to Another Medical Condition	
Substance/Medication-Induced Anxiety Disorder	Diagnoses merged in DSM-5
Other Specified Anxiety Disorder	Split from "Not Otherwise Specified" from DSM-IV-TR
Unspecified Anxiety Disorder	Split from "Not Otherwise Specified" from DSM-IV-TR

Novel treatments

While the previous focus of pharmacological research in anxiety disorders was on the role of the serotonin system, there has been a shift in experimental therapeutics in the last 20 years toward other novel pathways such as cannabinoid, glutamate, and neuropeptide systems (8). These agents have been tested in preclinical studies using animal models of anxiety such as classical fear conditioning and elevated plus-maze; a few of them are undergoing testing in early human studies. We will present these compounds and the current state of their development; for agents currently undergoing testing in the United States we will include the National Clinical Trial (NCT) numbers from clinicaltrials.gov.

Serotonin

The serotonin system has been reported to be a primary mediator in the etiology of anxiety and its

Table 2. Current Treatments for Anxiety Disorders

Disorder	FDA-Approved Medications	Off-Label Medications	Psychotherapy	Recommendations
Generalized Anxiety	SSRI: escitalopram; paroxetine SNRI: duloxetine; venlafaxine (XR)	SSRI: fluoxetine; sertraline; citalopram TCAs MAOIs Mirtazapine Pregabalin Gabapentin Hydroxyzine Antipsychotics: quetiapine	CBT	First-Line: SSRI or SNRI Second-Line: benzodiazepines; buspirone; TCAs; pregabalin CBT
Panic Disorder	SSRI: fluoxetine; paroxetine; sertraline SNRI: venlafaxine (XR) Benzodiazepines: clonazepam; alprazolam TCAs: clomipramine; imipramine	SSRI: escitalopram SNRI: duloxetine; desvenlafaxine TCAs MAOIs Phenelzine Pregabalin Gabapentin Benzodiazepines: lorazepam	CBT Psychodynamic	First-Line: CBT or SSRI, SNRI or Combination
Social Anxiety Ddisorder	SSRI: paroxetine; sertraline; fluvoxamine SNRI: venlafaxine (XR)	SSRI: fluoxetine MAOIs Pregabalin Gabapentin Benzodiazepines D-cycloserine Propranolol	Exposure therapy CBT	First-Line: SSRI or SNRI Exposure therapy Second-Line: MAOIs
Specific Phobias	None	D-cycloserine	Exposure therapy	First-Line: exposure therapy
Posttraumatic Stress Disorder	SSRI: paroxetine; sertraline	SSRI: fluoxetine SNRI: venlafaxine (XR); duloxetine; desvenlafaxine TCAs MAOIs Mirtazapine Prazosin Antipsychotics: risperidone Anticonvulsants: lamotrigine; topiramate; oxcarbazepine	Prolonged exposure therapy	First-Line: SSRI and/or exposure therapy Second-Line: antipsychotics
Anxiety	Benzodiazepines: clonazepam; alprazolam; chlordiazepoxide; oxazepam Antipsychotics: trifluoperazine Buspirone Hydroxyzine	Mirtazapine TCAs Antipsychotics: olanzapine; quetiapine Pregabalin Gabapentin Tiagabine		

disorders. As noted in the Introduction and in Table 2, the majority of treatments for anxiety, including SSRIs, SNRIs, and azapirones like buspirone, are serotonergic. Thus, there is interest in therapeutics to develop agents that target specific serotonin receptors for an anxiolytic effect. For example, buspirone, a 5-HT_{1A} agonist, is being investigated for depressive symptoms and neuroprotection in GAD (NCT01546896). Given the documented efficacy of buspirone for GAD, and preclinical research, there have been other nonazapirone 5-HT_{1A} agonists under development for anxiety treatment (9), but the results so far have been disappointing. Gepirone (BMY-13,805, ORG-13,011), a selective 5-HT_{1A} receptor partial agonist, has undergone clinical development as an anxiolytic and antidepressant agent. Early studies suggested efficacy for anxiety symptoms in MDD subjects (10). However, it failed to receive FDA approval for the treatment of either anxiety or depression. PRX-00023, a selective 5-HT_{1A} partial agonist, did not show superior efficacy on anxiety measures compared with placebo in an RCT, although modest efficacy on some depressive measures was noted (11). Additionally,

there is a phase 2 trial of another selective 5-HT_{1A} partial agonist, TGFK08AA, in phase 2 development for GAD (12).

There are also medications that act on multiple serotonin receptors that are being studied for anxiety. The SSRI vilazodone, which is approved by the FDA for MDD, is also a 5-HT_{1A} receptor agonist and is under study in a RCT for social anxiety disorder (NCT01712321). Vilazodone is also in phase 3 trials for GAD (NCT01844115, NCT01766401, NCT01629966) and in a phase 4 trial for treatment of PTSD with comorbid depression (NCT01715519). Vortioxetine (Lu AA21004) is also a 5-HT_{1A} agonist and a 5-HT_3 antagonist, and was recently studied for MDD and GAD on the basis of preclinical studies supporting its antidepressant and anxiolytic effects (13). Vortioxetine was recently FDA-approved for MDD, but its efficacy for anxiety is not yet demonstrated. While one RCT reported efficacy of vortioxetine in reducing anxiety in GAD (14) and another reported efficacy in preventing relapse in GAD (15), three subsequent randomized, double-blind reports indicated that vortioxetine did not separate from placebo in GAD on primary or secondary outcome measures (16–18).

5-HT_6 receptor antagonists have been reported to have anxiolytic properties in animal studies (19). There are no known published trials of these compounds in humans although there are two novel drugs under development, AVN-101 and AVN-397, which are being studied for the treatment of anxiety (8).

Finally, agomelatine is a melatonin-1/melatonin-2 agonist and 5-HT_{2C} receptor antagonist that has been studied in depression but also may have anxiolytic properties (20). Agomelatine was reported to be efficacious for GAD compared with placebo (21), and in a randomized, double-blind discontinuation study was reported, to have a lower rate of relapse compared with placebo in GAD (22). There are no other known ongoing studies of agomelatine in anxiety disorders.

GLUTAMATE MODULATORS

Glutamate, which is a precursor for GABA, is the primary excitatory neurotransmitter of the central nervous system. Glutamate is comprised of ionotropic and metabotropic receptors (mGluR), with the latter being a target of pharmacological treatments for mood, psychotic, and anxiety disorders. Several animal studies have reported anxiolytic effects of mGluR modulators, in particular mGluR1, mGluR2, mGlu3, and mGluR5 (23). However, results in human studies have been more disappointing. For example, LY354740, an mGluR 2–3 agonist, did not show a difference from placebo in a randomized controlled comparison study with paroxetine (24) in patients with PD. After studies with LY354740 were halted due to concerns about bioavailability, LY544344, a pro-drug of LY354740, was studied for GAD in an 8-week randomized placebo-controlled trial and found to be efficacious, but the study was halted due to concerns about convulsive activity in preclinical trials (25). Currently there are studies underway for two mGluR modulators: ADX-71149, an mGluR2 positive allosteric modulator (NCT01582815), in phase 2, tested for major depressive disorder with anxiety symptoms; and, RGH-618, an mGluR1/5 antagonist with promising preclinical data, currently undergoing phase 1 studies and potential future development for (unspecified) anxiety disorders (8).

Ketamine is a glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist used in anesthesia and pain, and also used as a substance of abuse with hallucinogenic and psychotomimetic properties. Over the past 10 years several studies have reported rapid antidepressant effects after a single administration of IV ketamine in treatment-resistant major depressive disorder (TRD) (26, 27). Multiple trials are ongoing using intravenous and intranasal ketamine for MDD and bipolar depression (28, 29), but ketamine is also currently being developed as a treatment for anxiety (including clinical trials in PTSD and OCD). Preclinical studies have reported the anxiolytic effects of ketamine in several animal models of anxiety, including the elevated-plus maze (30). A recently completed study (NCT00749203) in 40 subjects with PTSD involved administration of IV ketamine 0.5 mg/kg and midazolam in a crossover design. Compared with IV midazolam, IV ketamine was associated with superior efficacy in reducing PTSD symptoms at 24 hours (as measured with the self-report impact of event scale) (31). Additionally, there are open-label studies of oral ketamine for the treatment of comorbid depression and anxiety (32, 33).

Riluzole is a glutamate modulator approved for the treatment of amyotrophic lateral sclerosis (ALS), which has also been studied as an adjunctive agent in TRD (34–36), with trials currently ongoing for MDD, OCD, and multiple neurological conditions, given riluzole's neuroprotective properties. Animal studies supported the efficacy of riluzole in models of anxiety (37, 38). We only found a single clinical therapeutic trial with riluzole in the literature: Mathew and coworkers enrolled 18 subjects with GAD in an 8-week study with open-label riluzole 100 mg/day (39). Twelve of the 15 patients (80%) who completed the trial responded [experiencing ≥50% improvement in Hamilton Anxiety Rating Scale (HAM-A) anxiety scores] and eight of 15 patients (53%) experienced remission of anxiety (39). The study was, however, limited by open design and

a low number of subjects. Subsequent functional imaging studies reported that patients with GAD who were openly treated with riluzole experienced changes in hippocampal volumes and *N*-acetylaspartate (NAA) concentrations which correlated with improvement on anxiety scales, when compared with a treatment group of healthy volunteers (40, 41). A phase 2 randomized, double-blind, placebo-controlled study of riluzole in PTSD is currently beginning at Yale University (NCT02019940).

AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors are ionotropic glutamate receptors. There are several animal studies of AMPA modulators, including PEPA, primarily in fear extinction models of anxiety, showing positive anxiolytic effects (42). One AMPA modulator, Org 26576, has been studied for MDD (43). To date, however, there are no known studies in the pipeline for AMPA modulators for anxiety disorders.

Among glutamatergic drugs, one of the best studied in anxiety disorders is D-cycloserine (DCS), an NMDA partial agonist, previously used as a treatment for tuberculosis and studied in schizophrenia. In animal and human studies DCS has been shown to facilitate fear extinction (44). Although it is not known to be efficacious as a monotherapy for anxiety (45), DCS has been successfully used in the augmentation of exposure or cognitive behavioral therapy, as discussed below. DCS has been reported to reduce anxiety in persons performing cognitive tasks (46), facilitate declarative learning (47), and to reduce reactivity to phobic stimuli in persons with a specific phobia on a functional MRI (48).

DCS has been studied for augmentation of psychotherapy in PD, social anxiety disorder, OCD, PTSD, and specific phobias. In PD, Otto and others reported that patients receiving DCS instead of placebo for augmentation of CBT had statistically significant improvement in clinical measures (49). Another study in PD, a randomized controlled trial (RCT), found no difference between DCS or placebo when added to CBT+flooding, but did note that DCS may speed up clinical improvement (50). We found one study actively recruiting for DCS augmentation of CBT in PD (NCT01680107), while another active study is investigating the effects of DCS enhancement, versus placebo, on CBT in PD (NCT00790868).

Several studies of DCS have been published in social anxiety disorder. Two earlier investigations reported a positive response of 50 mg DCS on the augmentation of exposure therapy in social phobia (51, 52). More recently, one study found that DCS did not augment the effect of CBT on sleep quality compared with placebo (53). Smits and coworkers reported the DCS was efficacious in the augmentation to CBT only in subjects with low conscientiousness and high agreeableness (54) or in those who reported successful reduction in fear after treatment (55). In another study, the same group of researchers found no separation between DCS and placebo in the remission or response rates, but did report a more rapid response in the DCS group (56). Given these negative results, it is not surprising that there are no known ongoing studies of DCS augmentation of social anxiety disorder.

D-cycloserine has also been studied extensively for specific phobias. While one study reported the efficacy of DCS in augmenting exposure therapy for acrophobia (57), a subsequent study did not find DCS to separate from placebo in postexposure treatment of height phobia (58). Two studies of spider phobia reported no difference between DCS and placebo but Gutner and colleagues reported a reduction in disgust in the DCS group to subliminal fear cues (59, 60). There is a trial currently recruiting to test DCS for augmentation of one-session exposure therapy for acrophobia (NCT01037101).

In an RCT with 25 subjects, DCS has been reported to be superior to placebo in improving PTSD symptoms when administered as augmentation to virtual reality exposure therapy (61). Previously, another group studying DCS augmentation for exposure therapy for PTSD found that DCS separated from placebo in participants with high conscientiousness and low extraversion, while both groups with lower education had worse outcomes (62). The same group reported DCS did not differentiate from placebo in its overall treatment effect but reported a greater response to DCS compared with placebo in patients with more severe PTSD at baseline and those that required longer treatment (63). Interestingly, one group reported worse outcomes for persons receiving DCS versus placebo for augmentation of exposure therapy (64). Additionally, there are currently several on-going studies of DCS in PTSD: a VA study comparing hydrocortisone, D-cycloserine, and placebo on fear extinction in veterans with PTSD (NCT00674570), a trial investigating DCS and mifepristone for blocking memory consolidation in PTSD (NCT01490697), and two studies of DCS in PTSD in youth and adolescents (NCT01157416, NCT01157429).

On balance, DCS is the most widely studied of the glutamatergic strategies and the literature thus far supports a modest benefit for the augmentation of psychotherapy. However, several studies do not detect this efficacy.

Memantine is an NMDA receptor antagonist approved for the treatment of moderate to severe Alzheimer dementia. It has been tested previously in animal studies as monotherapy and augmentation

for depression and OCD (65). To date, it has only been studied openly in small trials. One study reported minimal improvement in seven patients with GAD, while 10 OCD subjects experienced a modest benefit (66). In another case series of 15 patients with GAD with or without comorbid social anxiety disorder, Schwartz et al. reported a reduction in anxiety from baseline (67). Another small open-label study reported an improvement in memory and hyperarousal in four patients with PTSD (68). There are no known active studies of memantine for anxiety disorders other than OCD.

ANTICONVULSANTS

A previous review of anticonvulsants for anxiety disorders (69) reported strong evidence for use of certain medications in anxiety. The strongest evidence is for the use of pregabalin in GAD with positive separation from placebo in multiple placebo-controlled randomized trials (70, 71). Pregabalin is thought to act on the alpha-2 delta subunit of calcium channels to reduce neurotransmitter release, and thus has antiepileptic effects. Pregabalin has FDA approvals for neuropathic pain, postherpetic neuralgia, fibromyalgia, and as an adjunct treatment for partial seizures. It is also approved for use in GAD in Europe, but after the FDA did not approve its use in 2009, Pfizer withdrew its application in 2010. In one study, pregabalin was shown to have efficacy versus placebo in generalized social anxiety disorder, at 450 mg/day (72), while another study found pregabalin at 600 mg/day (but not at 450 mg/day or 300 mg/day) to be superior to placebo in a randomized, double-blind study (73).

Gabapentin has a mechanism of action similar to pregabalin. It is also approved for neuropathic pain, postherpetic neuralgia, and partial seizures, but has been widely used off-label for various indications, including anxiety. It was found to be efficacious in a small (N=69), randomized, double-blind, placebo-controlled study in social anxiety disorder (74). Another RCT found a treatment difference between gabapentin and placebo only in patients with severe panic symptoms (75). There are currently no known ongoing trials of gabapentin for anxiety disorders.

Tiagabine is an anticonvulsant that is thought to inhibit GABA uptake thereby increasing GABA activity. It is approved for partial seizures and there is preclinical evidence for its anxiolytic effects (76). While open-label studies for PD, GAD, and PTSD are suggestive of efficacy (69), several RCTs, however, do not support the efficacy of tiagabine in GAD (77) or PD (78). A small, randomized, double-blind crossover study with gabapentin and tiagabine in social anxiety disorder reported that both drugs could be effective in reducing the anxiety score (79).

Lamotrigine is an anticonvulsant thought to inhibit voltage-dependent sodium channels resulting in decreased glutamate release. It is FDA-approved for treatment of bipolar disorder and for seizures. In animal studies, lamotrigine has been shown to have anxiolytic properties (80). There are, however, very few studies of lamotrigine in anxiety disorders. One small case series reported improvement in symptoms in PD with agoraphobia (81). One small (N=15) randomized, double-blind, placebo-controlled trial of lamotrigine in PTSD, reported an improvement in symptoms, suggesting the need for further large-scale study (82). To date, however, no studies of lamotrigine for anxiety disorders are underway, with the exception of a phase 3 trial comparing topiramate and lamotrigine in persons with PTSD and alcohol dependence (NCT00571246).

NEUROPEPTIDES

Neuropeptides are small proteins playing the role of neuronal signaling molecules; they are involved in a variety of brain functions, including analgesia, reward, social behaviors, learning, and memory. Specific neuropeptides also play significant roles in modulating fear and anxiety.

Oxytocin is a neuropeptide with a significant role in attachment and prosocial behaviors in both animals and humans. It has been studied in autism and schizophrenia, given the severe dysfunction in interpersonal relationships in these disorders. There is evidence in healthy adults that oxytocin has positive effects on emotional modulation (83); in high-stress individuals it can reduce negative cognitive appraisals elicited by high-stress tasks (84). In subjects with generalized social anxiety disorder, oxytocin reportedly reduced amygdalar reactivity to fearful faces as measured with functional MRI (85).

Oxytocin has to be administered either sublingually or intranasally due to its poor absorption in the digestive tract. It is well-tolerated with no known serious side effects. A randomized, double-blind study comparing intranasal oxytocin to placebo as an augmentation to exposure therapy in social anxiety disorder did not report a difference in treatment outcomes between groups, but subjects receiving oxytocin did report more positive evaluations and opinions of their own performance compared with the control group (86). Currently, there is one known ongoing clinical trial of oxytocin nasal spray and its effects on social behavior in social anxiety disorder (NCT 01856530).

Substance P, also known as neurokinin-1 (NK-1), a neuropeptide widely found in the central nervous

system, has also been associated with anxiety in preclinical studies. NK-1 receptor antagonists therefore have been studied for anxiety disorders. In a randomized, double blind trial, comparing it to paroxetine and placebo for social anxiety disorder, the NK-1 antagonist LY686017 did not separate from placebo on outcome measures (87). The selective NK-1 receptor antagonist GR205171 showed promise as a potential anxiolytic in an investigation of cerebral blood flow in patients with social anxiety disorder, with efficacy superior to placebo and comparable to citalopram (88). This same compound, however, did not separate from placebo in an 8-week RCT with 39 subjects with chronic PTSD (89). Another NK-1 receptor antagonist, L-759274, was reported to not be efficacious in the treatment of GAD in a proof-of-concept RCT (90). Currently, GW823296 (Orvepitant) is undergoing a phase 2 randomized, double-blind, placebo controlled fixed-dose study of for PTSD (NCT01000493).

Neuropeptide Y (NPY) is one of the most abundant neuropeptides in the brain. It has been shown in preclinical trials to be related to stress and anxiety responses, and treatment in animal studies have been shown to have anxiolytic effects (91). In humans, NPY has been closely linked to trauma, with multiple studies showing reduced plasma and cerebrospinal fluid levels of NPY in persons with PTSD as compared with healthy adults (92). There are two published studies of intranasal NPY, one as a tolerability study in healthy volunteers (93) and another in overweight subjects to test the effects on appetite and body weight regulation (94). Currently, our group at Icahn School of Medicine at Mount Sinai is conducting a phase 1, randomized, double-blind, dose escalation study of intranasal NPY in PTSD (NCT01533519).

Arginine vasopressin (AVP) has been shown in animal models to be related to anxiety responses, and vasopressin V_{1A} and V_{1B} receptor antagonists may have anxiolytic properties (95, 96). Only one published human study of V_1 antagonists has been published. Griebel and coworkers compared a vasopressin V_{1B} antagonist, SSR149415, in a randomized, double-blind study to escitalopram, paroxetine, and placebo in MDD and GAD, and found that SSR149415 did not separate from placebo in outcome measures for GAD (97). Currently under study is a novel V_{1A} receptor antagonist, SRX246, which is being studied in healthy volunteers. In a functional MRI study it attenuated the effects of vasopressin on amygdala reactivity to angry faces (98). SRX246 is currently being investigated in a phase 1 trial for PTSD (8).

Cholecystokinin (CCK) is a peptide which helps regulate gastric secretions and motility and biliary function in the gastrointestinal system; in the nervous system it is involved in memory and in anxiety and fear processing. Preclinical research has supported the findings of the role of CCK-2 in anxiety and the potential use of CCK-2 antagonists as anxiolytics. Subsequent studies of these agents, however, failed to yield positive results (8). There are currently no CCK antagonists being studied for anxiety disorders.

In summary, neuropeptides represent a promising avenue in the treatment of anxiety disorders but no clear winner has yet emerged.

Corticotrophin-releasing factor (CRF) receptor antagonists have been reported to have anxiolytic effects in animal models (99). Their role is related to modulating the chronic hypercortisolemia associated with chronic stress; CRF dysfunction has been described across the entire spectrum of anxiety disorders (100). To date, however, there are few published investigations of CRF antagonists in anxiety. One randomized, double-blinded study of the CRF-1 antagonist Pexacerfont (BMS-562086), which compares it to escitalopram and placebo in GAD, reported that Pexacerfont did not separate from placebo on primary outcome measures (101). Currently ongoing, a multicenter phase 2 RCT of another CRF-1 antagonist, Verucerfont (GSK561679) is being studied in women with PTSD (NCT01018992). There are also completed but not published studies for social anxiety disorder comparing GSK561679 and the CRF-1 antagonist Emicerfont (GW876008) to alprazolam and placebo (NCT00555139), and a phase 2 trial comparing GW876008 to paroxetine and placebo (NCT00397722).

GABA AGONISTS

The efficacy of benzodiazepines, GABA-A agonists, in anxiety disorder is well documented but, as noted above, long-term risks make it important to develop newer GABAergic medications. To date, however, several GABA-A receptor subtype agonists have either failed to reach the market due to lack of efficacy or poor tolerability (8). AZD7325, a GABA-A alpha-2-3 modulator, failed to separate from placebo in a phase 2 comparative trial with placebo and alprazolam for GAD (NCT00808249). The novel GABA modulator IW-2143 (formerly BNC-210) is in phase 1 studies for anxiety (Bionomics).

MIFEPRISTONE

Mifepristone, also known as RU-486, is a progesterone inhibitor used for early pregnancy termination (hence the nickname "the morning-after

pill"). Mifepristone has been studied for psychotic depression, and for improving cognition in bipolar disorder and schizophrenia. There is extensive literature on hypothalamic-pituitary-adrenal axis dysfunction in PTSD. Preclinical studies support the use of mifepristone for preventing fear reconsolidation (102), and the same group is studying this effect in humans with PTSD in a phase 4 trial (NCT01490697). There is one small (N=8) randomized, double-blind, placebo-controlled study of mifepristone in combat PTSD, which reported a reduction in scores in rating scales (103). Currently, there is a multicenter randomized, double-blind, placebo-controlled trial of mifepristone in combat-related PTSD (NCT01946685). One group is studying mifepristone for cognitive impairment in late-life anxiety disorders (NCT01333098).

ALPHA- AND BETA-ADRENERGIC AGENTS

Guanfacine is an alpha−2 receptor agonist approved for the treatment of hypertension, which was later found to have potential effects on attention and was approved for ADHD. However, it did not separate from placebo in two RCTs for PTSD (104, 105). An open-label trial of guanfacine in children and adolescents reported potential improvement in symptoms (106). To date, there are no known active studies of guanfacine in anxiety disorders.

Propranolol is a beta-blocker approved for multiple indications including hypertension, arrhythmias, migraine prophylaxis, and tremor. It has been widely used in the treatment of performance anxiety and social anxiety disorder but with limited evidence for its efficacy. There is also limited evidence for its effects in PD or other anxiety disorders. Propranolol gained interest as a treatment in PTSD after Pitman and colleagues published a study on the potential effect of preventing the development of PTSD when administering propranolol shortly after a traumatic event (107). Subsequent larger-scale studies did not support the initial findings of efficacy (108) and propranolol became a controversial topic due to concerns that it would "block" memories (109). Animal studies, however, have suggested that propranolol, due to its central activity, can prevent reconsolidation of traumatic memories through its effects on protein synthesis. Several studies have reported the potential efficacy of propranolol enhancement in PTSD (110). There is an ongoing phase 2 study of propranolol for the reduction of traumatic memories in PTSD (NCT01713556) and a study of the effects of propranolol on fear responses in anxiety and PTSD (NCT01631682).

NATURAL REMEDIES

Although an extensive literature exists on potential anxiolytic efficacy of more than 20 herbal compounds, for most of them the evidence base is still inconclusive. To date, the only compound with efficacy data supported by multiple quality RCT studies is kava, a plant from the South Pacific whose active ingredients are lipophilic resinous compounds named kavalactones. A Cochrane meta-analysis of six RCTs using kava in anxiety disorders revealed a statistically significant mean reduction of five points on the HAM-A over placebo (111). Another recent pooled analysis supports the use of kava in the treatment of anxiety, with a significant result occurring in four out of six RCTs reviewed (mean Cohen's coefficient d=1.1) (112). However, kava can be associated with liver toxicity, including some cases of severe liver toxicity. The data for other compounds (e.g., galphimia, echinacea, chamomile, ginkgo, passionflower, roseroot, ashwagandha, Iranian borage, lemon balm, and milk thistle) are still insufficient to support their efficacy.

DISCUSSION

Based on our review of novel therapeutics for anxiety disorders across multiple neurotransmitter and peptide pathways, it is evident that there still remains a paucity of efficacious treatment options for anxiety disorders. Despite the potential promise of several newer compounds, such as certain metabotropic glutamate receptor modulators, CFR antagonists, and vasopressin antagonists, in phase 2 studies these drugs have not yet yielded positive results in larger-scale trials. Interestingly, the compounds that show greater promise are those that are already in use for other indications and have been repurposed for anxiety, such as mifepristone, pregabalin, and DCS. There is also evidence for using prazosin in PTSD nightmares and possibly even for treating daytime symptoms. In contrast to the well-replicated data for the efficacy of ketamine in depression, the efficacy for PTSD is very preliminary; it remains to be seen whether the effects of ketamine can be replicated in a larger PTSD population.

Overall, the tendency to "look backward" at drug compounds that are already in use is only going to yield so much success. While prazosin, ketamine, D-cycloserine, and pregabalin may find a wide use for disorders like PTSD and GAD, there needs to be a stronger impetus to continue exploring other pathways, such as GABA, glutamate, neuropeptide, and serotonin systems, for newer pharmacotherapeutics. There are several promising agents under development, but recent history has not been

encouraging. Given the high prevalence and morbidity of anxiety disorders among the general population and the high unmet need for effective treatments for these conditions, it is crucial that our field place a renewed emphasis on the discovery of novel, more effective pharmacological treatments.

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