HHS Public Access

Author manuscript

Expert Opin Emerg Drugs. Author manuscript; available in PMC 2016 September 01.

Published in final edited form as:

Expert Opin Emerg Drugs. 2015 September ; 20(3): 393–406. doi:10.1517/14728214.2015.1049996.

Emerging Drugs for the Treatment of Anxiety

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Abstract

Introduction—Anxiety disorders are among the most prevalent and disabling psychiatric disorders in the United States and worldwide. Basic research has provided critical insights into the mechanism regulating fear behavior in animals and a host of animal models have been developed in order to screen compounds for anxiolytic properties. Despite this progress, no mechanistically novel agents for the treatment of anxiety have come to market in more than two decades.

Areas covered—The current review will provide a critical summary of current pharmacological approaches to the treatment of anxiety and will examine the pharmacotherapeutic pipeline for treatments in development. Anxiety and related disorders considered herein include panic disorder, social anxiety disorder, generalized anxiety disorder and posttraumatic stress disorder. The glutamate, neuropeptide and endocannabinoid systems show particular promise as future targets for novel drug development.

Expert opinion—In the face of an ever-growing understanding of fear related behavior, the field awaits the translation of this research into mechanistically novel treatments. Obstacles will be overcome through close collaboration between basic and clinical researchers with the goal of aligning valid endophenotypes of human anxiety disorders with improved animal models. Novel approaches are needed to move basic discoveries into new, more effective treatments for our patients.

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Financial and competing interests disclosure:

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Keywords

anxiety; anxiolytic; clinical trial; endocannabinoid; glutamate; neuropeptide; panic disorder; posttraumatic stress disorder

1. Background

Anxiety disorders are among the most prevalent and disabling psychiatric disorders in the United States (1, 2). Approximately one in four adults will suffer from an anxiety disorder at some point in their lives. Patients with anxiety disorders experience substantial physical and emotional discomfort and have elevated rates of substance use and medical illnesses. Co-occurring anxiety disorders in the context of other psychiatric disorders, for example major depressive disorder (MDD) or bipolar disorder, are associated with a more chronic and treatment refectory course and these patients are at an elevated risk for suicide (3, 4). The combination of high prevalence and high functional disability associated with anxiety disorders leads to a particularly high economic and social cost.

The core feature of anxiety disorders is excessive fear and anxiety and related behavioral disturbances. The diagnostic schema for anxiety disorders in the United States was revised with the publication of the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-V) (5). The DSM-V recognizes the following anxiety disorders: separation anxiety disorder, selective mutism, specific phobia (SP), social anxiety disorder (SAD), panic disorder, agoraphobia, generalized anxiety disorder (GAD), substance/medication-induced anxiety disorder and anxiety disorder due to another medication condition. There are two residual categories for presentations that do not fit any of the preceding categories: other specific anxiety disorder and unspecified anxiety disorder. Separation anxiety disorder and selective mutism are expressed primarily in childhood and will not be discussed here further. In DSM-V, agoraphobia has been added as a new diagnosis and posttraumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD) have been moved elsewhere in the diagnostic schema. PTSD is a disorder of excessive fear and anxiety and is appropriately retained in considerations of the biology and treatment of anxiety disorders. OCD may be distinctive compared to the anxiety disorders and PTSD in terms of clinical presentation, biology and treatment.

The current review will provide a critical summary of current pharmacological approaches to the treatment of anxiety and will examine the pharmacotherapeutic pipeline for anxiety treatments in development. The current review focuses on therapeutic agents that are in early or late phase human testing for anxiety disorders at the time of this writing. For an in-depth review of anxiolytic development from a preclinical perspective, the reader is directed to several recent reviews (6, 7)

2. Medical need

Substantial progress has been made in neurobiological research aimed at uncovering the molecular and neurocircuit alterations that lead to anxiety. Basic research has provided critical insights into the mechanism regulating fear behavior in animals and a host of animal

models have been developed in order to screen compounds for anxiolytic properties. Despite this progress, no mechanistically novel agents for the treatment of anxiety have come to market in more than two decades. The validity of current animal models of human anxiety disorders is limited, thereby imposing a major challenge to drug discovery in this area. For a thorough discussion of animal models of anxiety and their utility, please see (7).

There is an urgent need for mechanistically novel, more effective treatments for anxiety. As touched on above, anxiety disorders are associated with substantial functional impairment (8) and patient and family burden (9). These disorders are associated with increased utilization of health care services (10) and reduced work productivity (11). Current treatments fall short of what is needed to meet this large public health burden. For example, recent large meta-analyses were unable to support the efficacy of benzodiazepines (12) or azapirones (e.g., buspirone) for panic disorder (13). PTSD, GAD and SAD likewise are only partially responsive to currently available treatments, including serotonin selective reuptake inhibitors (SSRIs) (14, 15). Troublingly, a report from the Institute of Medicine concluded that the available evidence was inadequate to support the efficacy of SSRIs or other pharmacotherapy in PTSD (16). Clearly, the discovery of novel pharmacotherapeutic treatments for anxiety represents a large unmet medical need.

3. Existing treatment

3.1 First line treatments

Agents with current U.S. Food and Drug Administration (FDA) approval for the treatment of anxiety disorders are summarized in Table 1. Multiple randomized controlled trials (RCTs) support the efficacy of SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) as first line treatments for GAD, SAD, panic disorder and PTSD (17–20). An analysis of 12 RCTs in panic disorder found a mean effect size for SSRIs relative to placebo of 0.55 (21). In the case of GAD, Response rates for SSRIs of between 60 and 75% are generally reported in RCTs, compared to response rates of between 40–60% for placebo (22). Data suggest that PTSD may be less amenable to current pharmacotherapy compared to other anxiety disorders. A Cochrane review of pharmacotherapy for PTSD including 35 RCTs and 4597 participants did support the use of SSRIs as first-line medication treatment (20).

3.2 Second line and other treatments for anxiety disorder

Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) have reasonable efficacy data in anxiety disorders but are usually reserved for second-line treatment due to safety and tolerability issues. The benzodiazepines play an important role in the treatment of some anxiety disorders, however these agents too are usually reserved for second-line or adjunctive use due to tolerability and abuse liability issues. These agents have the advantage of a rapid onset of action, inviting their use early in the course of treatment prior to the onset of efficacy of a co-administered SSRI/SNRI. Data supporting the longer-term efficacy of benzodiazepines is more limited. For example, Goddard et al showed that co-administration of clonazepam with sertraline in the treatment of panic disorder resulted in a significantly greater proportion of responders in the sertraline/clonazepam group at the end of one week, but not at study end (23). Anticonvulsants, including gabapentin and

pregabalin, have mixed data to support efficacy in certain anxiety disorders. The data for second generation antipsychotics (SGAs) in anxiety disorders is likewise mixed, and will be reviewed in greater detail below.

4. Current research goals

As a group, anxiety disorders represent a heterogeneous group of illnesses that have excessive fear and anxiety as their core phenomenology. Psychiatry has struggled to determine the appropriate nosological classification of these disorders and the newest version of the DSM presents yet another configuration, as noted above. The changing diagnostic landscape and uncertain boundaries between anxiety disorders create challenges for drug development, compounding other hurdles noted above. In response to these challenges, some major pharmaceutical companies have either substantially reduced their investment in CNS research or else eliminated their CNS programs altogether. This concerning development compels changes in the approach to anxiety drug development by academia and industry.

Most recently, investigators and government agencies have advocated for a dimensional approach to the study and treatment of anxiety (24). This approach relies on braking down disorders into phenotypic dimensions that cut across traditional diagnostic boundaries and then mapping these phenotypes onto discrete perturbations at the neurocircuit and molecular level. For example, factor analytic studies suggest that PTSD is best represented by the 5 symptom clusters of re-experiencing, avoidance, numbing, dysphoric arousal, and anxious arousal (25) and recent neuroimaging findings have linked amygdala volume specifically to the dimension of anxious arousal (26). Current research goals, therefore, including developing novel pharmacological agents that may target specific dimensions of the anxious phenotype based on a refined understanding of underlying neurobiology.

5. Scientific rationale

The rational development of therapeutics for anxiety disorders is based on a solid understanding of underlying pathophysiology and on the development and application of valid animal models. As noted above, there are currently important limitations regarding both of these fundamental points. The gamma-aminobutyric acid (GABA) system has historically been the primary focus of anxiolytic drug discovery. More recently, the SSRIs and SNRIs – first developed for the treatment of depression – have become the mainstay of anxiolytic treatment. The incomplete effectiveness of current treatment and the burdening neuroscience of fear related behavior, however, compel the search for novel, more effective treatments. In the section below, we provide a critical review of the current landscape of drug development for anxiety disorders. Organized by neurochemistry, we begin by reviewing agents that act on the serotonin, melatonin, norepinephrine and dopamine systems. We then review progress in the clinical development of agents the target the glutamate and GABA systems, neuropeptide systems and the endocannabinoid system. The glutamate, neuropeptide and endocannabinoid systems may show particular promise as target for novel drug development.

6. Competitive environment

See Table 2 for a summary of investigational and emerging treatments for anxiety disorders.

6.1. Serotonin

6.1.1. Vortioxetine—Vortioxetine is a serotonergic compound developed by Lundbeck and is approved by the U.S. FDA and European Medicines Agency (EMA) for treatment of MDD (27). Vortioxetine is a serotonin transporter (SERT) inhibitor with additional effects as a 5-HT1A receptor (full) agonist, a 5-HT1B receptor (partial) agonist, and a 5-HT1D, 5-HT3, and 5-HT7 receptor antagonist. Vortioxetine increases extracellular levels of serotonin, dopamine, noradrenaline, acetylcholine and histamine within ventral hippocampus and prefrontal cortex (PFC) and modulates GABA and glutamate neurotransmission in preclinical studies (28).

To date, 3 separate randomized controlled trials (RCTs) of vortioxetine have been conducted in patients with GAD and have produced equivocal results (29–31). In one study, patients with GAD were randomized to 8 weeks of vortioxetine 5 mg per day (n=150) versus placebo (n=151); total HAM-A score was lower in the vortioxetine group (-14.30 vs −10.49, $P<0.001$) (29). The results of two other RCTs in GAD, however, were negative (30, 31). Most common side effects reported in the vortioxetine groups were nausea, headache, dizziness, and dry mouth (29–32). Taken together, the clinical trial data to date is suggestive of a benefit of vortioxetine in GAD but additional studies may be required to confirm these findings.

6.1.2 Vilazodone—Vilazodone was developed by Merck and was approved by the U.S. FDA for the treatment of MDD in 2011 (33). In addition to functioning as an SSRI, vilazodone acts as a 5-HT1A receptor partial agonist, similar to buspirone. Preclinical studies show that activation of presynaptic 5-HT1A autoreceptors function to delay the anti-anxiety and antidepressant effects of SSRIs (34). Through simultaneous blockade of the SERT and activation of the 5-HT1A receptor, vilazodone may overcome this delay. This dual mechanism of action can potentially shorten the delay of anti-depressive action, decrease side-effects related to serotonin reuptake inhibition in SSRI, and alleviate anxiety symptoms (35). The true clinical implications of this pharmacodynamics profile, however, remains unclear.

To date, there are no published RTCs examining vilazodone in patients with anxiety disorders. A post-hoc analysis of two phase III RCTs involving patient with MDD suggested vilazodone could be beneficial in treatment of MDD with anxious features (36). Following 8 weeks of treatment, patients in the active arm showed significant improvement in somatic and psychic symptoms of anxiety compared to placebo. Some data suggest a lower sexual dysfunction with vilazodone compared to SSRIs. However, more studies needed to be done to clarify this (36, 37). Overall, more studies are required in order to fully evaluate the potential of vilazodone for patients with anxiety disorders.

6.2. Melatonin

6.2.1. Agomelatine—Agomelatine is a mechanistically unique melatonin receptor (MT1, MT2) agonist and a 5-HT2C receptor antagonist (38). The agent is approved for the treatment of MDD in Europe but has no indications in the U.S. Molecular and cellular studies show that agomelatine's synergistic effects on the melatonin and serotonin systems can enhance neuroplasticity, including enhancing neurogenesis in the adult hippocampus (39). Preclinical studies also show that agomelatine reduces stress-induced increases in glutamate release within the PFC and synchronizes circadian rhythm by stimulating melatonergic and serotonergic receptors in suprachiasmatic nucleus (SCN) of the hypothalamus (38). There is some overlap between the neural effects of agomelatine and conventional antidepressants and it is currently unclear to what extent the unique molecular effects of agomelatine contribute to its mechanism of action.

Two RCTs of agomelatine have been completed in patients with GAD (40, 41) . In a phase III, 12-week, 3-arm RCT including escitalopram as an active comparator, agomelatine showed significant reduction in HAM-A scores over placebo (41). Escitalopram and agomelatine had similar efficacy. The results of a second RCT, which included a 42 week open label period (25–50 mg/d) followed by a 6 months double-blind period, showed a significantly lower relapse rate in agomelatine vs placebo group (19.5% vs 30.7%; p=0.045) (42). A meta-analysis that included six RCTs in patients with MDD with anxieties features provides support for the efficacy of agomelatine for the treatment of anxiety symptoms (43). A few case reports and open label trials have shown the efficacy of agomelatine augmentation in treatment of OCD (44). The result of recent phase II trial investigating the efficacy of agomelatine in OCD has not yet been published (NCT01108393).

6.3. Norepinephrine and Dopamine

Noradrenergic hyperactivity has been established as a critical component of the stress response and abnormal noradrenergic signaling has been consistently implicated in anxiety related behavior (45–47). Elevated catecholamine activity during the stress, which can impair PFC function, has been linked to PTSD and other anxiety disorders in both clinical and preclinical studies (48). Cerebrospinal fluid (CSF) levels of norepinephrine have been found to be significantly higher in patients with PTSD compared to healthy volunteers (49). Translational research in particular supports inhibition of the alpha-1 receptor and/or stimulation of the alpha-2 receptor as pharmacological strategies in PTSD or other anxiety disorders (50).

6.3.1 Guanfacine—Guanfacine is a noradrenergic alpha-2 receptor agonist that is approved in an extended release form for Attention Deficit Hyperactivity Disorder (ADHD) (51). Agonist activity at alpha-2 presynaptic auto-receptors reduces aberrant noradrenergic signaling, which is hypothesized to lead to attenuation of anxiety and trauma-related symptoms (50). To date, two small double-blind RCTs have not provided clear evidence of guanfacine's efficacy to ameliorate PTSD symptoms in adults (52, 53). There is open label evidence showing the efficacy of this agent in treatment of PTSD symptoms and PTSD-related nightmares in a child and adolescent population (54) . There are currently no RCTs of guanfacine in other anxiety disorders. Although the clinical trial data to date does not

support the efficacy of guanfacine in PTSD, studies are ongoing in other anxiety disorders, including GAD, SP and SAD (NCT01470469).

6.3.2. Nepicastat—Nepicast is a selective dopamine beta-hydroxylase (DBH) inhibitor, currently under investigation as a treatment for PTSD (NCT00659230, NCT00641511). Inhibition of beta-hydroxylase reduces the conversion of dopamine to norepinephrine, thereby reducing noradrenergic synaptic signaling. Interestingly, this agent has been shown to be effective in attenuating cocaine and alcohol related behaviors in animal studies. (55) Much more research will be required to determine if this interesting class of drugs has potential efficacy in PTSD or other anxiety disorders.

6.4. Second Generation Antipsychotics

Numerous RCTs have been conducted to evaluate the efficacy of second-generation antipsychotics (SGAs) for the treatment of anxiety disorders, including risperidone, ziprasidone, olanzapine, aripiprazole and quetiapine. The potential efficacy of SGAs in GAD and PTSD has received the most attention.

6.4.1. Aripiprazole—Aripiprazole is approved by the FDA for schizophrenia, bipolar disorder, MDD (adjunct), autistic disorder and Tourette's syndrome. Aripiprazole has a unique pharmacodynamic profile as a partial agonist at the D2 receptor, along with antagonist activity at the 5-HT1A and 5-HT2A receptors. Two small RCTs of aripiprazole have been conducted in OCD with promising preliminary results (56, 57). In addition, open label trials of aripiprazole have been conducted in GAD, panic disorder (58), MDD with anxious features (59) and PTSD (60) with initial encouraging results. Additional randomized controlled data are required to further characterize the efficacy of aripirazole in anxiety disorders.

6.4.2. Other SGAs—Several large RCTs support the efficacy of quetiapine in GAD (61, 62). There is mixed evidence for the efficacy of risperidone in GAD (63, 64) and there is comparatively less support for olanzapine and ziprasidone. A large multi-site RCT of risperidone as augmentation in PTSD in a Veteran Affairs population was negative (65). Since SGAs are associated with significant adverse effects in some cases (e.g., metabolic syndrome and motor disturbances), the clinician must weigh the risks and benefits of SGAs in the treatment of anxiety. Given the limited data supporting efficacy, these agents may be reserved for third or fourth line treatments in certain cases.

6.4.3. Brexpiprazole—Brexpiprazole is a D2/D3 receptor partial agonist currently under investigation as an adjunctive treatment in PTSD and in MDD with anxious features (NCT02013531,NCT02196506).

6.5. Glutamate and GABA

6.5.1. Pregabalin—Pregabalin, 3-isobutyl-GABA, was initially developed by Pfizer for the treatment of epilepsy and neuropathic pain and was approved by the European Medicines Agency for treatment of GAD in 2006 (66). There is no FDA approval for this compound for anxiety in the US. Pregabalin is a chemical analogue of GABA, though with

no activity on GABA receptors. The drug binds to the alpha-2-beta subunit of presynaptic voltage dependent calcium channels, resulting in reduced Ca^{2+} influx and reduced release of glutamate and norepinephrine into the synaptic cleft (66). The inhibitory effect of pregabalin on excitatory neuronal pathways, hypothesized to be overactive in anxiety disorders, may contribute to its anxiolytic effect (28).

Pregabalin has demonstrated efficacy in several RCTs in GAD (67, 68), although the FDA ultimately determined that there was insufficient evidence of efficacy to grant approval. A meta-analysis in patient with GAD showed equal efficacy between pregabalin and the other comparators studied: duloxetine, ecitalopram, paroxetine, and venlafaxine (69). Pregabaline was also similarly effective in GAD compared to alprazolam and lorazepam (70, 71). There is limited evidence showing the efficacy of pregabalin augmentation with SSRI in OCD or PTSD (72, 73). Of note, pregabalin is recommended as a first line of treatment in comorbid GAD and epilepsy (74).

6.5.2. Ketamine—Ketamine is a noncompetitive glutamate N-methyl-D-aspartate (NMDA) receptor antagonist currently FDA approved as an anesthetic agent (75). Over the last decade, several small RCTs have provided evidence that ketamine results in a rapid antidepressant effect (e.g., within one day), even in patients with treatment resistant depression (TRD) (76–79). In the largest study of ketamine conducted to date in patients with TRD (n=73), ketamine was associated with a higher antidepressant response rate compared to midazolam (used as a psychoactive control condition) at the 24-hour primary outcome time point (64% and 28%, respectively; odds ratio: 2.18) (80). Most recently, ketamine has been examined for potential efficacy in PTSD (81) and OCD.

A recently published RCT is the first study to examine the efficacy of ketamine in PTSD (81). In this study, ketamine was administered as a single intravenous (IV) infusion in a double blind, randomized crossover study in 41 patients with chronic PTSD and symptom change at 24 hours post treatment was the primary outcome measure. Ketamine was associated with a significant reduction in symptom severity measured using the Impact of Event Scale, compared to midazolam (mean difference score: 12.7, P = .02). The treatment was generally well tolerated. Future studies examining the safety and efficacy of repeated treatments of ketamine in PTSD will be required in order to more completely evaluate the potential for this therapy in chronic or treatment-refractory PTSD.

Two small clinical trials of ketamine have been conducted in patients with OCD, yielding mixed results (82, 83). In the first study, ketamine administered IV in an open label fashion was not associated with symptom improvement in 10 patients with treatment refractory OCD (82). In a second small RCT involving 15 patients with OCD, ketamine was associated with significant symptom improvement, with 50% of the sample meeting response criteria following ketamine compared to 0% following placebo (83). Clearly, more data is needed to evaluation the potential efficacy of ketamine in OCD.

6.5.3 Glutamate Metabotropic Receptor Modulators—Preclinical studies have demonstrated a key role for glutamate in the regulation of fear and anxiety, in addition to depressive behaviors (84). Metabotropic glutamate receptor (mGluR) modulators,

particularly mGluR1, mGluR2/3 and mGluR5 have been shown to modulate anxiety and fear in preclinical studies (85, 86). A small RCT investigating the effects of the mGluR2/3 agonist LY354740/LY544344 in patients with GAD was halted due to concerns regarding the potential for convulsions (87). A separate mGluR2/3 agonist failed to demonstrate benefit in panic disorder within the context of an RCT (88). An ongoing study is being conducted to evaluate the safety and efficacy of another mGluR2/3 receptor agonist, pomaglumetad methionil, in treatment of PTSD (NCT02234687).

Other glutamate metabotropic receptor modulator including, mGluR1 and mGluR5 antagonist, have shown positive results in animal model of anxiety (84). Although there have been some initial setbacks, mGluR modulators yet represent a promising area for future treatment development for anxiety.

6.5.4 D-Cycloserine and drug-augmentation of psychotherapy—There has been growing interest in designing rational combinations of medication with psychotherapy – based on mechanisms of fear learning and extinction – as a novel approach to the treatment of anxiety disorders (see (89) for a recent review). Among the strategies studied, the combination of the NMDA receptor modulator d-cycloserine (DCS) with specific forms of cognitive behavioral therapy (CBT) has received the most attention. DCS is a partial agonist at the glycine site on the NMDA receptor, and was originally used as an antimicrobial agent. Systemic infusion of DCS enhances fear extinction in animal models (90) and multiple clinical trials in human populations now support the hypothesis that DCS can enhance the efficacy of CBT for anxiety disorders (91–93). In an early proof of concept study, patients with specific phobia (e.g., acrophobia) were randomized to receive behavioral exposure therapy plus placebo or behavioral exposure therapy plus DCS (94). Patients randomized to therapy plus DCS had significantly reduced symptoms at both one week and 3 months following treatment. To date, positive trials have been reported in PTSD, specific phobia, SAD, panic disorder and OCD. Negative studies have also been reported (95).

6.6. Neuropeptides

6.6.1 Corticotrophin-Releasing Factor—Corticotrophin-releasing factor (CRF) or hormone (CRH) is a 41 amino-acid neuropeptide first isolated in the 1980's. A large body of literature indicates that stress-related anxiety is associated with chronically elevated activity of central nervous system (CNS) circuits that utilize CRF. CRF is involved in mediating the neuroendocrine, immune, autonomic, and behavioral responses to stress (96). The identification of CRF was followed by the discovery of three CRF paralogs (urocortins 1, 2, and 3) and two CRF/urocortin receptors CRF1 and CRF2 (97).

Acute and chronic centrally administered CRF produces anxiety-like responses such as sleep disturbances, loss of appetite and anhedonia in numerous animal models of anxiety disorders (98). CRF1 antagonist demonstrate anxiolytic activity in multiple animal models (99, 100). Preclinical studies have specifically implicated CRF1 receptor located within the amygdala as mediating the fear-related behaviors in the context of stress (101). Clinical studies show increased CSF concentrations of CRF in PTSD (102, 103). Given this confluence of data,

CNS-penetrant CRF1 receptor antagonists have been developed and have undergone extensive testing by the pharmaceutical industry (104)

Unfortunately, no CRF1 receptor antagonist to date has successfully demonstrated safety and efficacy in phase III clinical testing for a stress related psychiatric disorder. In one case, a large multicenter RCT in GAD failed to show superiority of the selective CRF-1 receptor antagonist pexacerfont, compared with placebo (105). Clinical trials involving the CRF-1 receptor antagonists verucerfont and emicerfont in SAD have been completed with undisclosed results (106). A large NIH-supported multi-site study involving the CRFR1 antagonist GSK561679 (GlaxoSmithKline) in PTSD has been recently completed and results are likewise pending (107).

Despite a large amount of preclinical and mechanistic data implicating the CRF system in fear related behaviors and anxiety disorders, the field still awaits positive results from clinical trials.

6.6.2 Neuropeptide Y—Neuropeptide Y (NPY) is a 36 amino acid peptide, belonging to the pancreatic polypeptide family and is co-localized and released with neurons containing norepinephrine. In addition to being the most abundant peptide known, most mammals have identical NPY sequences, making NPY one of the most evolutionary conserved peptides. NPY was first isolated and sequenced in 1982 and since its discovery several functions were discovered, linking NPY to the regulation of energy balance, stress responses (108), sleep and food intake. High expression levels of NPY are found in brain regions implicated in the control of anxiety such as the amygdala, hippocampus, brainstem, nucleus accumbens, locus coeruleus, and the hypothalamus, where the highest concentrations are present (109). NPY exerts its action by binding to the G-protein coupled NPY receptors, consisting of Y1-Y5. The Y1 and Y2 receptors in particular have been shown to mediate anti-anxiety and antidepressant actions of NPY (110, 111). Recently, researchers have identified NPY related mechanisms that may underlie the development of early life anxiety using a nonhuman primate model of anxious temperament (112). Their findings suggest higher levels of Y1 and Y5 receptors in the amygdala are associated with reduced anxiety. Genetic manipulation of the NPY system provides additional evidence implicating Y1 and Y5 receptors in reducing anxiety and increasing stress resilience.

Preclinical research supports the potent anxiolytic actions of NPY in a wide range of animal model, including fear-potentiated startle, social interaction, conflict paradigms and the elevated plus maze (113). In a recent preclinical study, rats were infused with intranasal NPY or placebo before exposure to a single prolonged stress (a model of PTSD) and compared to untreated controls. The findings revealed that intranasal NPY infusion attenuates development of PTSD-like symptoms in rats and even seven days later rats displayed lower depressive like behavior and reduced anxiety (114).

The role of NPY in behavioral effects of stress has also been clinically demonstrated in human studies. Plasma NPY responses to yohimbine, an alpha-2 receptor antagonist, and placebo were measured in a group of combat veterans with PTSD compared to healthy control subjects. The authors found the PTSD patients had lower baseline plasma NPY and

blunted yohimbine-stimulated increases in plasma NPY (115). Higher plasma NPY levels were also observed in combat-exposed veterans without PTSD compared with veterans presently reporting PTSD, implying the role of NPY in resilience and coping (116). Of note, it is unclear the extent to which peripheral NPY levels correlate with central functioning. Cerebrospinal fluid (CSF) levels of NPY are also significantly lower in combat related PTSD compared with healthy, non-combat exposed controls (117, 118). Clearly, the NPY system is a promising target for novel anxiety therapeutics. Pharmacotherapeutic strategies focusing on increasing NPY signaling in the CNS may represent a promising avenue for future research.

6.6.3 The Substance P / Neurokinin System—The substance P/neurokinin system has been extensively studied in mood and anxiety disorder research since it's discovery in the 1930s. Basic research in neuropeptides sparked following a positive clinical trial for aprepitant (MK-869), a synthetic neurokinin receptor antagonist, in a placebo controlled trial in patients with MDD (119). Substance P is an 11 amino acid peptide, belonging to a group of proteins called tachykinins, mediating its biological actions through G-protein coupled tachykinin receptors including neurokinin 1 receptor (NK1). Substance P and NK1 are broadly distributed in brain regions implicated in stress including the hypothalamus basolateral amygdala, hippocampus, nucleus accumbens, and frontal cortex (120, 121).

Although preclinical testing has demonstrated robust antidepressant effects, inconsistent results have been demonstrated in the anxiolytic profiles of NK1 antagonists in a number of animal models (122, 123). Significantly elevated substance P concentrations in CSF are observed in PTSD (124), providing translational evidence for the role of substance P and NK1 receptor in stress related behaviors and anxiety disorders.

A 12-week, multicenter RCT was conducted to assess the efficacy and safety of the NK1 antagonist orvepitant (60 mg/day) compared to placebo in subjects with PTSD. This Phase IIb trial had to be terminated before completion owing to the occurrence of isolated events of seizures (125). A Phase IIa, proof-of-concept randomized, double blind, placebo-controlled trial was conducted to evaluate the NK1 antagonist GR205171 in patients with chronic PTSD (126). Although, there was significant improvement in the mean CAPS total score across all patients over time, no significant difference was found between GR205171 and placebo. Interestingly, an exploratory analysis showed that GR205171 treatment was associated with significant improvement compared to placebo on the CAPS hyperarousal symptom cluster.

Several trials with inconsistent results have been conducted to test the efficacy of NK1 receptor antagonist in SAD. In an initial proof-of-concept study in SAD of AV608, an NK1 receptor antagonist developed by Avera Pharmaceuticals, results were suggestive of efficacy; however these findings were not replicated in subsequent RCTs (127). A phase IIa RCT of LY68601, an NK1 receptor antagonist developed by also failed to demonstrate efficacy in SAD (128).

Given the negative data to date, the potential for neurokinin modulators as novel anti-anxiety drugs remains uncertain.

6.6.4 Cholecystokinin—Cholecystokinin (CCK) is a 115 amino acid pre-hormone originally described in the gastrointestinal (GI) tract and subsequently observed to be abundant throughout the CNS. The two primary CCK receptors – CCK-A and CCK-B – are G-protein coupled receptors and are localized to both the CNS and the GI system, with CCK-B being predominant in the brain. CCK tends to potentiate anxiety in animal models, for example in the context of the elevated plus maze and the open field test (129). Building on these studies, it was observed that infusion of CCK caused anxiety in healthy adults and panic attacks in patients with panic disorder (130). Interestingly, recent work has shown a close relationship between CCK and the endocannabinoid system in extinction learning and fear-potentiated startle (131). These results encouraged significant interest in the CCK system for treatment development and several non-peptide selective CCK receptor antagonists have been developed. Clinical trials of CCK receptor antagonists in GAD and panic disorder have yielded negative results and future treatment development focused on the CCK system is uncertain (132).

6.6.5 The Endocannabinoid System—A growing body of preclinical work demonstrates an important role for the endocannabinoid system in anxiety and fear-related behavior (85). Endocannabinoid signaling modulates multiple behavioral processes, including sleeping, appetite, pain, and emotional memory. (133). The system consists of polyunsaturated fatty acid endogenous ligands [anandamide (AEA) and 2-arachidonoylglycerol (2-AG)] and two G protein-coupled receptors, cannabinoid receptors 1 (CB1) and 2 (CB2) (134). The CB1 receptor is widely distributed in the CNS, including the frontal cortex, amygdala, basal ganglia, hippocampus, and periaqueductal gray. CB2 receptor are likewise widely distributed (135). A recent positron emission tomography (PET) study utilizing the CB1-selective radioligand [(11)C]OMAR found abnormally elevated binding of CB1 in individuals with PTSD compared to healthy volunteers (136).

To date, there is paucity of data examining the effects of agents that target the endocannabinoid system in anxiety disorder populations. A recent small open study of oral delta-9-THC (a primary active ingredient in cannabis) showed encouraging results in PTSD (137). A second study found evidence for a beneficial effect of cannabidiol for public speaking in SAD (138). Of note, concerns regarding side effects of direct CB1 agonist or antagonist compounds – including depression, anxiety and psychotic symptoms – may serve to limit the utility of direct CB receptor modulators (139, 140). In contrast, agents acting to inhibit one of the primary enzymes, fatty acid amide hydrolase (FAAH), have yielded positive results in preclinical models of fear and anxiety (141). A recent study utilized a genetic knock-in mouse model of a common variant in the human FAAH as well as human neuroimaging to show that reduced FAAH signaling is associated with enhanced PFC-amygdala connectivity and fear extinction (142). A clinical trial utilizing a FAAH inhibitor (PF-04457845) is currently being conducted in the context of fear conditioning in humans (NCT01665573).

7. Potential development issues

Key development issues already alluded to in this review are (1) the changing landscape of anxiety disorder definitions, (2) uncertainty regarding the fundamental pathophysiology of

anxiety disorders and (3) the less-than-optimal validity of current models for anxiety disorders. Please see Griebel and Holmes for a recent discussion of these development issues (7). One approach to address these issues involves identifying reliable intermediate phenotypes for anxiety disorders that may facilitate translational research between preclinical and clinical studies. Human *in vivo* neuroimaging applied to anxiety disorder populations has revealed relatively consistent abnormalities within brain systems that detect and regulate fear, including the amygdala, hippocampus and medial PFC. For example, patients with PTSD evidence exaggerated neural response to threat within the amygdala and a parallel reduction in responses within the PFC (143). Similarly, abnormal fear learning or fear extinction has been demonstrated in PTSD and may facilitate translational drug discovery since these behaviors can be studies with high fidelity in animals (144). It is hoped that the continued refinement of the clinical nosology of anxiety disorders in close tandem with an evolving knowledge base of the mechanisms of fear regulation and the optimization of animal models of anxiety will converge on accelerated and more efficient treatment development.

8. Conclusions

Anxiety disorders are common and are associated with significant levels of subjective suffering, functional impairment and poor treatment outcome. Currently available first-line treatments for anxiety disorders include SSRI and SNRI medication, with benzodiazepines best suited for short-term and adjunctive anxiolytic treatment. TCAs and MAOIs are effective but tolerability issues limit their use. Other available treatments with comparatively less data may be indicated in certain cases and include anticonvulsants and SGAs. Compounds currently in clinical development for anxiety disorders include new monoaminergic agents and SGAs. Encouragingly, mechanistically novel compounds targeting glutamate, neuropeptide and endocannabinoid systems are also in development. Beyond the compounds covered in the current review, other potentially promising areas for future research include neurotrophic signaling systems, the renin-angiotensin system, the acetylcholine system and even components of the opioid system (145). Combining target selective agents with psychotherapy based on a growing appreciation of the mechanisms of fear regulation is another promising avenue. The clear medical need for new, more effective treatments compels a continued vigorous drug discovery effort for anxiety disorders.

9. Expert opinion

Anxiolytic drug discovery may be at a tipping point. Thanks to an explosion of research in the past 10 years, our understanding of fear related behavior is among the most developed knowledge area in behavioral neuroscience. On the other hand, these discoveries have yet to lead to mechanistically novel, more effective treatments for disorders of fear and anxiety in humans. As noted above, important obstacles in the drug development process for anxiety include continued gaps in our understanding of the pathophysiology of anxiety disorders and limitations in current animal models of anxiety. The shifting diagnostic boundaries of anxiety disorders and an absence of valid, reliable human biomarkers has further hindered the drug development process.

A close collaboration between basic and clinical researchers will be required to move the field closer towards its treatment discovery goals. Valid endophenotypes for human anxiety disorders must be identified and mapped onto preclinical models. These endophenotypes have the potential to increase the fidelity and efficiency of early phase clinical research by providing biological targets as surrogate endpoints for novel compounds. For example, candidate compounds could be screened quickly for their capacity to modulate human amygdala responses to threat using functional MRI in an early phase clinical trial. The time is ripe to use translational approaches to move basic discoveries into new, more effective treatments for our patients.

Acknowledgments

In the past 3 years, J Murrough has served on advisory boards for Janssen Research and Development and Genentech, has provided consultation services for ProPhase, LLC and Impel Neuropharma and has received research support from Janssen and Avanir Pharmaceuticals; he is named on a patent pending for neuropeptide Y as a treatment for mood and anxiety disorders; he is named on a patent pending for lithium as a method to maintain the antidepressant response to ketamine. D Charney (Dean of Icahn School of Medicine at Mount Sinai), and Icahn School of Medicine at Mount Sinai has been named on a use patent on ketamine for the treatment of depression. The Icahn School of Medicine has entered into a licensing agreement for the use of ketamine as therapy for treatment-resistant depression. D Charney and Icahn School of Medicine at Mount Sinai could potentially benefit if ketamine were to gain approval for the treatment of depression. D Charney is named on a patent pending for ketamine as a treatment for PTSD and for neuropeptide Y as a treatment for mood and anxiety disorders; he has received funding from the U.S. Department of Defense, NIH, NIH/NIMH, NARSAD, USAMRAA; he has severed on the scientific advisory board for the Institute of Medicine Committee on DHS Workforce Resilience and on the editorial board of CNS Spectrums. J Murrough is supported by NIH grant K23MH094707 and by the Doris Duke Charitable Foundation.

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Table 1

Current FDA-Approved Treatments for Anxiety Disorders

Pharmacologic Class	Examples	Molecular Target(s)	FDA-Approved Indications	Dose Range	Common Adverse Effects	Pregnancy Category
SSRI	Escitalopram	SERT	GAD	10–20 mg daily	Nausea, Diarrhea, Headache, Insomnia, Somnolence, Sexual dysfunction	C
	Fluoxetine	SERT	OCD, PD	20–60 mg daily	As above	C
	Fluvoxamine	SERT	OCD, SAD	100–300 mg daily	As above	C
	Paroxetine	SERT	GAD, OCD, PD, PTSD, SAD	20–50 mg daily	As above	D
	Sertraline	SERT	OCD, PD, PTSD, SAD	50–200 mg daily	As above	C
SNRI	Duloxetine	SERT, NET	GAD	60–120 mg daily	As above, plus Hypertension	C
	Venlafaxine	SERT, NET	GAD, PD, SAD	75–225 mg daily	As above	C
BZD	Alprazolam	GABA-AR	Anxiety (non-specific), PD	1–4 mg daily	Somnolence, Cognitive problems, Appetite change, Fatigue (Class Effects)	D
	Chlordiazepoxide	GABA-AR	Anxiety (non-specific),	15–40 mg daily	As above	C
	Clonazepam	GABA-AR	PD	1–4 mg daily	As above	D
	Diazepam	GABA-AR	Anxiety (non-specific)	2–10 mg daily	As above	D

Pharmacologic Class	Examples	Molecular Target(s)	FDA-Approved Indications	Dose Range	Common Adverse Effects	Pregnancy Category
	Lorazepam	GABA-AR	Anxiety (non-specific)	1–6 mg daily	As above	D
	Oxazepam	GABA-AR	Anxiety (non-specific)	30–120 mg daily	As above	C
TCA	Clomipramine	SERT, NET, mACh, A1R, H1R	OCD, PD	25–250 mg daily	Dry mouth, Constipation, Urinary retention, Somnolence, Dizziness, Weight gain, Sexual dysfunction, Orthostasis (Class Effects)	C
	Doxepine	SERT, NET, mAChR, A1R, H1R	Anxiety (non-specific)	75–300 mg daily	As above	C
	Imipramine	SERT, NET, mAChR, A1R, H1R	PD	100–200 mg daily	As above	C
MAOI	Phenelzine	MAO	PD	45–90 mg daily	Dry mouth, Constipation, Orthostasis, Weight gain, Sexual dysfunction, Somnolence, Dizziness, Headache	?
Antihistamine	Hydroxyzine	H1R	Anxiety (non-specific)	200–400 mg daily	Sedation, Dry mouth, Dizziness, Headache	C
Other	Buspirone	5-HT1AR	Anxiety (non-specific)	20–60 mg daily	Nausea, Dizziness, Headache	B

A1R, Alpha-adrenergic 1 receptor; BZD, Benzodiazepines; GABA, Gamma-aminobutyric acid; GABA-AR, GABA A receptor GAD, Generalized Anxiety Disorder; H1R, Histamine 1 receptor; MAO, Monoamine oxidase; MAOI, MAO inhibitor; mAChR, Muscarinic acetylcholine receptor; NET, Norepinephrine Transporter; OCD, Obsessive-Compulsive Disorder; PD, Panic Disorder; SERT, Serotonin

Transporter; SAD, Social Anxiety Disorder; SNRI, Serotonin Norepinephrine Reuptake Inhibitor; SSRI, Selective Serotonin Reuptake Inhibitor; TCA, Tricyclic Antidepressant; 5-HT, 5-hydroxytryptamine; 5HT1AR, 5-HT 1A receptor

Table 2

Investigational and Emerging Treatments for Anxiety Disorders

Mechanistic Class	Compound	Molecular Target / Pharmacodynamics	Disorder	Manufacturer	Phase of Development
5-HT	Vortioxetine	SERT; 5-HT1AR (full) agonist; 5-HT1BR (partial) agonist; 5-HT1DR, 5-HT3R and 5-HT7R antagonist	GAD	Lundbeck	Phase III
	Vilazodone	SERT; 5-HT1AR partial agonist	GAD	Merck	Phase III
	PRX-03140	5-HT4R partial agonist	PTSD	EPIX	Phase II
Melatonin	Agomelatine	M1 and M2 agonist, 5-HT2CR antagonist	GAD, OCD	Servier	Phase III Phase II
NE / Dopamine	Guanfacine	A2R agonist	GAD, SAD	Shire	Phase II
	Nepicastat	DBH inhibitor	PTSD	Roche	Phase II
SGA	Aripiprazole	D2R partial agonist; 5-HT2AR antagonist	PTSD	Otsuka	Phase II
	Brexpiprazole	D2/D3R partial agonist	PTSD	Otsuka	Phase III
Glutamate / GABA	Pregabalin	VDCC	SAD	Pfizer	Phase III
	Ketamine	NMDAR antagonist	PTSD	Generic	N/A
	Ganaxolone	GABA-AR PAM	PTSD	Purdue Pharma	Phase II
Neuropeptide	Itriglumide	CCK-BR antagonist	GAD, PD	Rottapharma Madaus	Phase II
	Verucerfont	CRF-1 antagonist	PTSD	Neurocrine Biosciences	Phase II

A1R, alpha-adrenergic 1 receptor; CCK, cholecystokinin; CRF, corticotrophin releasing factor (CRF); DBH, dopamine beta-hydroxylase; GABA, gamma-aminobutyric acid; GAD, generalized anxiety disorder; M, melatonin; NET, norepinephrine transporter; NMDA, N-methyl-D-aspartate; mGlu, metabotropic glutamate receptor; OCD, obsessive compulsive disorder; PAM, positive allosteric modulator; PD, panic disorder; PTSD, posttraumatic stress disorder; R, receptor; SAD, social anxiety disorder; SERT, serotonin transporter; SGA, second generation antipsychotic; VDCC, voltage-dependent calcium; 5-HT, 5-hydroxy-tryptamine