

Pharmacological and Brain Stimulation Treatment of Anxiety Disorders:
Current Treatments and Future Directions

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Abstract

Modern pharmacological treatments for anxiety disorders are safer and more tolerable than they were 30 years ago. Unfortunately, treatment efficacy and duration have not improved in most cases despite a greater understanding of the pathophysiology of anxiety. Moreover, innovative treatments have not reached the market despite billions of research dollars invested in drug development. In reviewing the literature on current treatments, we argue that evidence-based practice would benefit from better research on the causes of incomplete treatment response as well as the comparative efficacy of drug combinations and sequencing. We also survey three approaches to the development of innovative anxiety treatments: the continued development of drugs based on specific neuroreceptors; the pharmacological manipulation of fear-related memory; and the electrical or electromagnetic stimulation of specific brain areas. We highlight directions for future research, as none of these approaches is ready for clinical use.

Keywords: pharmacotherapy; anxiety disorders; antidepressants; memory consolidation; psychedelics; transcranial magnetic stimulation

1. Introduction

Pharmacological treatments for anxiety disorders have become more tolerable, available, and numerous over the past half century. At the same time, research has yielded a vastly improved understanding of the neurobiological and physiological mechanisms involved in chronic anxiety and stress responses, suggesting new approaches to the treatment of anxiety disorders. Despite these impressive changes, however, between one third and one half of patients on a modern antidepressant do not achieve sustained remission from anxiety (Pollack, Otto, et al., 2008).

Why does this efficacy gap exist, and what should be the next step in treatment for these patients? Unfortunately, although patients often use antidepressant medications for years, high-quality data on the drugs' long-term efficacy are limited. The problem is compounded by the growing number of different drug classes, which has prompted clinicians to combine drugs and change dosing regimens without good data on optimal treatment combinations. Billions of research dollars later, have we hit a wall in the development and application of pharmacological treatments for anxiety? What hope might there be for a genuine breakthrough treatment for treatment-refractory anxiety?

To evaluate these questions, we first review evidence for the safety, tolerability, and efficacy of first- and second-line drugs in the anxiety disorders. We discuss the strength of evidence for drug-drug and drug-psychotherapy combinations used as adjunctive or augmenting treatment approaches to treatment-refractory anxiety. In the remainder of this review, we evaluate potential innovations in the treatment of anxiety disorders, including novel molecular targets, memory-modulating drugs, psychedelic and narcotic drugs, and brain stimulation treatments. The results have largely been disappointing so far; in many cases, however, we

identify concrete questions for future research, many of which can best be addressed through innovative research methods.

2. Pharmacotherapy for Anxiety Disorders: Current Status

2.1. Antidepressant Medications

2.1.1. Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

The widely studied SSRIs, and to a growing degree, the SNRIs (and for obsessive-compulsive disorder [OCD] the mixed noradrenergic and serotonergic reuptake inhibitor tricyclic clomipramine), are considered the first-line pharmacological treatments for anxiety disorders (see Ravindran & Stein, 2010, for a review). Specific phobia is the exception. In specific phobia, these medications have rarely been studied or used clinically because exposure therapy is considered the first-line treatment for specific phobia. The few studies comparing SNRIs to SSRIs show similar responses in the anxiety disorders that have been studied. SSRIs and SNRIs work by blocking the reuptake of serotonin or norepinephrine, respectively, which increases synaptic levels of 5-HT (i.e., serotonin) in the synapse. This starts a cascade of downstream effects on other neurotransmitters, second messengers, and immediate early genes, ultimately producing long-term neurochemical changes in the brain (Krishnan & Nestler, 2008).

SSRIs are efficacious for a wide range of psychiatric disorders (e.g., major depression, premenstrual symptoms, eating disorders), have few side effects, and have low potential for abuse; they are also equally effective, safer in overdose, and more tolerable than the older tricyclic antidepressants (TCAs; Ravindran & Stein, 2010).

Nonetheless, SSRIs have some drawbacks. Approximately 30% to 50% of patients experience more mild and transient side effects, most commonly nausea, diarrhea, headache,

insomnia, jitteriness, or restlessness. It is thought that anxious patients are more sensitive to jitteriness with these agents, though this has not been conclusively studied. These effects can be minimized by starting at a low dose and increasing the dose gradually over two to four weeks. Sexual side effects such as diminished sexual interest, performance, or satisfaction are also common, occurring in one third to half of patients on an SSRI. Erectile dysfunction and anorgasmia can often be improved with various medications, but reduced sexual interest is more difficult to treat and often is more effectively treated with dose reductions or drug holidays. Finally, SSRIs can metabolically interact with and change the blood levels of other drugs, and are associated (especially short half life drugs) with a withdrawal syndrome that can mimic anxiety when suddenly stopped. In addition, SSRIs have been associated with increased suicidal ideation, prompting the US Food and Drug Administration's (FDA) "black box" warning for individuals 24 years old or younger. Notably, the evidence behind this warning has been widely criticized (e.g., Kaizar, Greenhouse, Seltman, & Kelleher, 2006), and many experts consider it appropriate to prescribe SSRIs to children with severe functional impairment when followed by careful monitoring (Ravindran & Stein, 2010).

SSRIs and SNRIs usually take between two to six weeks to produce an initial response, which is typically defined as at least 25% improvement in symptom severity from baseline (i.e., beyond random noise or natural symptom fluctuations). Full benefit may not be seen for another four to six weeks, or even longer (e.g., Montgomery, Sheehan, Meoni, Haudiquet, & Hackett, 2002). Across most studies, lower dosages are often as effective as higher dosages (e.g., Marshall, Beebe, Oldham, & Zaninelli, 2001). However, in OCD, higher dosages are associated with better response (Bloch, McGuire, Landeros-Weisenberger, Leckman, & Pittenger, 2009). Venlafaxine, an SNRI, has shown a linear dose–response curve in most studies with depression

and some evidence consistent with this in some anxiety disorders (Pollack et al., 2007; Rudolph et al., 1998). In addition to SSRI-like side effects, venlafaxine is associated with elevations in blood pressure, making this a safety issue with older adults and those with cardiovascular issues.

Nevertheless, nonresponse can occur for many reasons, including insufficient dose or duration of treatment, poor adherence, or true treatment resistance. This complicates clinical management because different causes of nonresponse generally indicate different management strategies. Data from patients with depression, and some uncontrolled data with anxiety, suggest that about 20% of patients may need 10 to 12 weeks or longer before responding (Tedeschini, Fava, & Papakostas, 2011). Thus, increasing the dose to the highest level tolerated is always recommended for any patient with an incomplete response. Nonadherence to and beliefs about medication may be factors in nonresponse as well. Only half of patients refill their first prescription (Mullins, Shaya, Meng, Wang, & Bron, 2006), and many patients discontinue their medications within the first six months of treatment (Grilo et al., 1998; Warden et al., 2009). Psychological factors, including negative beliefs about perceived harmful effects, stigma, and lack of "buy in" of the treatment rationale, are negatively related to adherence and outcome (e.g., Aikens, Nease, Nau, Klinkman, & Schwenk, 2005; Warden et al., 2009). These issues can be addressed through careful psychoeducation and monitoring. Clearly, treatment nonresponse is both important and highly idiographic.

There are serious questions about how much, and for whom, the placebo effect contributes to antidepressant response. In a recent meta-analysis, Fournier and colleagues (2010) found that for patients with mild or moderate depression symptoms, drug response (compared with placebo), may be minimal or nonexistent; however, for patients with very severe depression, the benefit of antidepressants over placebo is substantial. This robust finding in

depression should be systematically examined in the anxiety disorders as well.

However, most data on the causes of treatment nonresponse, response, and relapse are correlational; even classic randomized controlled trials (RCTs) do not reveal what caused these classes of effects at the level of individual patients. Such individual-level information would be extraordinarily helpful to clinicians who must decide how to proceed in each case. Specialized multi-stage clinical trials have been developed that allow investigators to estimate true drug response from placebo response at the individual level (Marks, Thanaseelan, & Pae, 2009; Oetting, Levy, Weiss, & Murphy, 2011).

Clinicians need better data to inform clinical decision making when patients do not respond to initial treatment. Meta-analyses can provide some guidance through estimates of individual versus combined treatment effects. In many cases, however, these studies collapse across trials differing in dose, duration, treatment algorithms, and other methods. Once subsets of studies are identified that more closely match the clinical question, there may be too few studies to make a precise estimate. Accordingly, methodologists have developed a new type of clinical trial, the Sequential Multiple Assignment Randomized Trial (SMART), that allows investigators to compare the efficacy of entire pre-specified treatment sequences (Oetting et al., 2011). This novel approach should be used to examine the optimal treatment sequence for partial or nonresponders to initial anxiety treatments.

2.1.2. Other Antidepressants

Extensive studies of TCAs show similar efficacy to SSRIs for panic disorder (PD; e.g., Mavissakalian, 2003) and generalized anxiety disorder (GAD; e.g., Schmitt et al., 2005), but not social anxiety disorder (SAD). Only one tricyclic, the highly serotonergic clomipramine, works in OCD (e.g., Katz, DeVeaugh-Geiss, & Landau, 1990). TCAs are lethal in overdose, and,

compared to SSRIs, have a markedly broader, more problematic, and less tolerable side effect profile: dry mouth, blurred vision, constipation, urinary retention, cardiac arrhythmia, tachycardia, sedation, postural hypotension, dizziness, and headache. Nonetheless, TCAs may well work when first-line agents do not.

Monoamine oxidase inhibitors (MAOIs) are effective for both PD and SAD and are thought by some experts to be excellent options for severe treatment-resistant anxiety disorders (e.g., Bakish et al., 1995). However, they have the worst side effect profile and greatest safety burden of all antidepressants. Patients on an MAOI can experience dangerous hypertensive reactions if they consume tyramine-containing foods (e.g., cheese, beer, and wine) or use certain drugs (e.g., meperidine, decongestants, or energy drinks containing ephedrine or phenylpropylamine). They may also gain weight, lose sleep, and feel sedated during the day while taking MAOIs. Thus, clinicians do not routinely prescribe MAOIs to their patients with anxiety disorders, although they are probably not considered frequently enough in treatment resistant patients.

Few double-blind, placebo-controlled RCTs have examined the efficacy of other antidepressants for anxiety disorders. Mirtazapine may be efficacious in SAD (e.g., Muehlbacher et al., 2005; Schutters, Van Megan, Van Veen, Denys, & Westenberg, 2010) and posttraumatic stress disorder (PTSD; e.g., Davidson et al., 2003); nefazodone, in PTSD but not GAD (Van Ameringen et al., 2007); and trazodone, in GAD (Rickels, Downing, Schweizer, & Hassman, 1993). Finally, bupropion has not demonstrated efficacy in PTSD and PD (Becker et al., 2007; Hertzberg, Moore, Feldman, & Beckham, 2001), though it is often used as an adjunctive antidepressant across the anxiety disorders. There are also problematic adverse side effects with mirtazapine (e.g., weight gain, sleepiness, lipid abnormalities, and leukopenia),

nefazodone (rare liver toxicity; Aranda-Michel et al., 1999), and bupropion (e.g., seizure risk).

2.2. Benzodiazepines

Benzodiazepines bind to a specific receptor site on the gamma-aminobutyric acid–A receptor (GABA–A) complex and facilitate GABA inhibitory effects via effects on a chloride ion channel (Davidson, 1989). They were initially considered a first-line treatment for anxiety because of their tolerability and equal efficacy to TCAs; however, they became second-line options when it became clear that SSRIs were both more tolerable and efficacious. Currently, benzodiazepines are primarily used for individuals who have had suboptimal responses to antidepressants (e.g., Simon et al., 2009).

Benzodiazepines are also used for their short-term, time-limited effects (e.g., flying on airplane) or to help reduce anxiety during the initial weeks of an antidepressant when anxiolytic effects have yet to occur (Goddard et al., 2001). These uses are appealing to the patient but not always desirable, as they can reinforce pill taking, serve as a safety signal that undermines self-efficacy, and become incorporated into the conditioned fear response. These concerns are exacerbated when benzodiazepines are taken on an as-needed basis. As-needed use links pill taking to rapid reduction in anxiety, powerfully reinforcing avoidance in anxiety-provoking situations and encouraging longer-term reliance on the drug. This may be one reason why benzodiazepines have been associated with reduced response to cognitive behavioral therapy (e.g., Watanabe, Churchill, & Furukawa, 2007).

Chronic benzodiazepine use is associated with physiological dependence, short-term cognitive and psychomotor impairment, and rebound anxiety upon discontinuation. Patients with a history of substance abuse are at increased risk of abusing benzodiazepines. Where clinically indicated, benzodiazepines can be gradually tapered and eventually discontinued over a

period of several months while starting another medication or CBT (Otto et al., 2010).

2.3. Alpha-delta Calcium Channel Anticonvulsants

The alpha-delta calcium channel class of anticonvulsants, including both gabapentin and the newer agent pregabalin, widely reduce neuronal excitability and resemble the benzodiazepines in their ability to alter the balance between inhibitory and excitatory neuronal activity. Also similar to benzodiazepines, these drugs have a rapid onset of action and are superior to placebo in GAD (Feltner et al., 2008) and SAD (Feltner, Liu-Dumaw, Schweizer, & Bielski, 2011); meta-analytic evidence suggests that pregabalin may even reduce depressive symptoms that co-occur with GAD (D. J. Stein, Baldwin, Baldinetti, & Mandel, 2008). These drugs have fewer problems with abuse, tolerance, and withdrawal than benzodiazepines and in fact have been used as treatments for both alcohol (Furieri & Nakamura-Palacios, 2007) and stimulant (Urschel, Hanselka, & Baron, 2011) dependence.

2.4. Beta Blockers and Azapirones

Beta blockers and azapirones have even fewer uses. Beta blockers have been prescribed as single-dose agents for performance-related anxiety (e.g., musician at a critical audition; James, Burgoyne, & Savage, 1983) because they can reduce the peripheral physical symptoms (e.g. palpitations, hands trembling) of anxiety within 30 to 60 minutes; however, they do not affect the cognitive and emotional symptoms of anxiety. Azapirones bind to the 5-HT_{1A} receptor and are thought to alter control of the firing rate of serotonin neurons. They typically take two to four weeks to take effect, are generally well tolerated, and lack the dependence issues of the benzodiazepines. However, GAD is the only anxiety disorder in which the azapirones have consistently demonstrated efficacy (Davidson, DuPont, Hedges, & Haskins, 1999); since GAD often includes a depression component, antidepressant medications are the more logical

treatment choice (Ravindran & Stein, 2010).

2.5. Approach to Initial Non-Response

Many patients with anxiety disorders do not respond completely to initial treatment. At this point, prescribers often combine an antidepressant with an effective anxiolytic drug that has a different mechanism of action, such as a benzodiazepine or other type of antidepressant (so called “combination” treatment). Typically, they will switch to a new agent if the symptoms do not decrease by 25% within six weeks and will add a different agent if symptoms do not fully remit within twelve weeks. Another approach, known as “augmentation,” refers to adding a treatment that is not necessarily known to be effective by itself, but which enhances response to the other drug (i.e. addition of an atypical antipsychotic medication such as risperidone, olanzapine or quetiapine).

Very few studies have empirically evaluated the use of these combination or augmentation strategies in the anxiety disorders. These studies require large sample sizes. In depression, the STAR*D trial (Rush, 2007) systematically examined various add-on strategies following citalopram (SSRI) nonresponse. The addition of cognitive therapy or medication, using either another antidepressant, sustained-release bupropion, or extended-release venlafaxine strategies, was generally effective for initial nonresponse (Thase et al., 2007). A study of similar scale has not been conducted in the anxiety disorders. Augmentation strategies using thyroid hormone and lithium were effective at later stages in treatment, but these agents have never been used for refractory anxiety disorders.

For severe treatment-resistant cases of anxiety, augmentation of the antidepressant with an atypical antipsychotic (e.g., risperidone, quetiapine) has been shown to be effective. This strategy appears to be effective for OCD (Ipser et al., 2006; Komossa, Depping, Meyer, Kissling,

& Leucht, 2010). There are several small studies of augmentation in GAD, but no controlled evidence for PD or SAD. Recently, small studies supporting this use for PTSD have been called into question by a large RCT showing that augmentation with risperidone conferred no additional advantage (Krystal et al., 2011).

Some antipsychotics have been used as a monotherapy for anxiety disorders. A recent Cochrane review supports the unique efficacy of quetiapine as monotherapy in GAD (Depping, Komossa, Kissling, & Leucht, 2010). However, quetiapine was recently denied FDA approval for GAD, presumably because of its risky side effect profile (e.g., lipid abnormalities, weight gain, and glucose intolerance) and concerns that it would be widely used in primary care without careful consideration of alternative anxiolytic strategies. Similar concerns also exist for other antipsychotics, which can produce severe side effects and often require careful monitoring. These risks likely outweigh the modest benefits in efficacy, though antipsychotic monotherapy may be useful and effective for some patients.

2.6. Pharmacotherapy in Combination with Psychotherapy

Patients with anxiety disorders prefer psychotherapy over psychotropic medications (Barlow, 2004) but are more likely to receive psychotropic medications first (Wang et al., 2005). There has been some interest in adding cognitive behavioral interventions to existing treatment with antidepressants or benzodiazepines; but, with the possible exception of PD (Bandelow, Seidler-Brandler, Becker, Wedekind, & R  ther, 2007; Otto, Smits, & Reese, 2006), this approach has not yielded strong additive effects. These results have led some investigators to conclude that combined treatment should not be considered a first-line approach (Otto et al., 2006) and should be reserved for patients with severe anxiety who require medication (Zwanzger, Diemer, & Jabs, 2008). However, limited data has failed to show efficacy for adding

medication to CBT (Simon et al., 2008) or CBT to medication (Simon et al., 2009) in patients with refractory anxiety disorders.

2.7. Summary

As reviewed in Table 1, SSRIs, and possibly SNRIs, are the frontline treatments for most anxiety disorders. However, patients often show partial or nonresponse, prompting a change in the current medication or the addition of a new medication. Unfortunately, the empirical literature for these augmentation strategies is still in its infancy. Clinical care in these cases is guided more by trial and error, using broad empirically-derived principles. Innovations in the design of clinical trials should allow future research to examine the efficacy of multiple strategies for the treatment of nonresponse.

3. Future Directions in Pharmacological Targets

While much drug development is concerned with improving the efficacy and tolerability of existing anxiety medications (Nemeroff, 2003), considerable resources have been invested to identify novel molecular targets over the past decade (Miller, 2010). Recent research in this area has largely focused on drugs that act more selectively on specific subtypes of serotonergic receptors.

3.1. Refinement of Existing Pharmacological Targets

Preclinical studies in mice have shown that inactivated brain 5-HT_{1A} receptors result in anxious behaviors that are insensitive to SSRIs (Gross et al., 2002), suggesting that postsynaptic 5-HT_{1A} receptors in the forebrain and hippocampus should be targeted. However, azapirones, partial or full 5-HT_{1A} agonists, as reviewed above, have not proven to be incrementally more effective than SSRIs.

Similarly, GABA-A subunits (e.g., α_2), which mediate the anxiolytic effect of benzodiazepines (L w et al., 2000), have been targeted. However, the development of some α_2 agents were terminated due to adverse effects (M hler, 2012), and none has come to market despite a decade of research. Eszopiclone, marketed as a hypnotic, also reduces anxiety through α_2 and α_3 GABA-A receptors. In double-blind trials for both GAD and PTSD, eszopiclone produced greater specific anxiolytic effects compared to placebo when added to a SSRI (Pollack et al., 2011; Pollack et al., 2008). This effect is especially provocative in PTSD, for which traditional benzodiazepines are not helpful and possibly harmful (Ravindran & Stein, 2009).

3.2. Novel Pharmacological Targets

Given the limitations of our current medications targeting monoamine or GABA neurotransmitter systems, investigators are also pursuing altogether novel treatment approaches and molecular targets (Holmes, Heilig, Rupniak, Steckler, & Griebel, 2003), including modulatory agents such as neuropeptides.

Neuropeptides are short-chain amino acid neurotransmitters and neuromodulators implicated in anxiety, pain, and stress regulation (Belzung, Yalcin, Griebel, Surget, & Leman, 2006). Their activity is more discretely localized than antidepressants, suggesting a more favorable side effect profile (Madaan & Wilson, 2009). However, few neuropeptides have been successfully translated from animal models to human anxiety disorders, possibly because they cannot easily cross the blood-brain barrier (Roesler & Schr der, 2011).

Substance P, a member of the tachykinin family of neuropeptides, acts on brain tachykinin (NK₁) receptors involved in anxiety and stress responses (Holmes et al., 2003). Clinical trials of NK₁ antagonists suggest they reduce both anxiety and depression and have less sexual side effects and nausea compared to traditional antidepressants (Madaan & Wilson, 2009).

However, subsequent clinical trials have failed to show consistent evidence of efficacy and safety (e.g., Mathew et al., 2011).

Corticotropin-releasing factor (CRF), a neuropeptide found in both amygdala and other key anxiety-related areas, acts on the CRF₁ and CRF₂ receptors to produce stress- and anxiety-related behavior in animals (Heinrichs, De Souza, Schulteis, Lapsansky, & Grigoriadis, 2002). CRF regulates activity in the hypothalamic-pituitary-adrenal (HPA) axis, which mediates behavioral, immune, and autonomic aspects of the stress response. Much research suggests that hypersecretion of CRF is critical to the development of affective and anxiety disorders (for a review, see Arborelius, Owens, Plotsky, & Nemeroff, 1999). Accordingly, various CRF antagonists have been developed to block its effects in the nervous system. Here as well, a decade of research failed to show consistent evidence for efficacy and safety (Gutman, Owens, Skelton, Thirvikraman, & Nemeroff, 2003; Zobel et al., 2000).

Other neuropeptide targets under investigation include neuropeptide Y (NPY) and vasopressin (V1B). Evidence suggests that NPY is involved in an endogenous alarm system that may modulate behavioral responsiveness to chronic stress (for a review, see Heilig, 2004). NPY receptor agonists can reduce anxiety in a dose-response manner (Heilig et al., 1993), and V1B antagonists appear to reduce both anxiety and depression under extremely stressful test situations in rodents (Griebel et al., 2002). Once more, however, costly drug development has failed to yield fruit in human trials.

Other molecular targets, including agents that block the effects of glutamate or that promote compensatory neurogenesis are being actively pursued (Snyder, Soumier, Brewer, Pickel, & Cameron, 2011). Glutamate is a major excitatory synaptic neurotransmitter with a reported role in neuronal plasticity. For example, blocking glutamate activity and stimulating N-

methyl-d-aspartate (NMDA) receptors may reduce stress and anxiety, possibly by restoring neurogenesis (Mathew, Keegan, & Smith, 2005). Riluzole, an NMDA receptor antagonist with a relatively safe side effect profile, may reduce anxiety in patients with anxiety disorders (e.g., Coric et al., 2005; Mathew et al., 2011; Pittenger et al., 2008). Ketamine, another NMDA antagonist, has been preliminarily associated with symptom reduction in patients with treatment-resistant depression (e.g., Zarate et al., 2006) and anxiety (e.g., Rodriguez, Kegeles, Flood, & Simpson, 2011).

Pharmaceutical drug development represents a high-risk gamble for the industry, requiring substantial investments of time and capital for an historically low yield. Given the repeated failure of translational drug development to bear fruit, it is not surprising that the pharmaceutical industry has decreased its investment in such areas in recent years (Miller, 2010). Unfortunately, promising new directions, such as the promotion of neurogenesis to improve anxiety regulation, are unlikely to reach the market anytime soon.

4. Pharmacological Modulation of Learning and Memory

While the search for new drugs based on novel molecular targets has been faltering in recent years, preliminary human research into the use of memory-modulating drugs has been flourishing. The goal of this research is to develop drugs that enhance or disrupt specific learning or memory processes to improve outcome. The approach departs substantially from traditional psychopharmacology, which has primarily evaluated drugs that have more direct effects on anxiety and depression. Adjunctive memory modulation requires more than taking a pill: To be effective, the pill must be paired with specific memory or learning experiences. If the approach is successful, patients may one day take a drug to help consolidate what they learned in psychotherapy, or take a different drug to weaken the memory of a recent traumatic event. Far

from being science fiction, this approach leverages our improved understanding of the neurobiology underlying the formation and disruption of both normal and pathological memories.

4.1. Enhancing Extinction Learning in Exposure Therapy

Exposure therapy is an empirically supported intervention in the anxiety disorders (Kramer et al., 1998) wherein patients undergo repeated, sustained exposure to previously avoided memories, people, objects, or situations that have produced marked fear. Exposure therapy reduces fear primarily through fear extinction (Rothbaum & Davis, 2003), a form of inhibitory learning in which previously fear-producing stimuli are associated with safety. Exposure procedures are thought to make these safety associations more retrievable than the aversive associations that previously triggered fear (Craske et al., 2008). Nonetheless, extinguished fear can return upon subsequent stress (Bouton, 2002), suggesting that there is ample room for improvement in this treatment modality. Indeed, research has begun to suggest that the pharmacological augmentation of extinction learning may improve outcome acutely. When used to augment exposure therapy, drugs that promote extinction learning may yield greater, faster, or longer-lasting fear reduction.

The most studied of these putative memory-enhancing drugs for human anxiety disorders is D-cycloserine (DCS). Long known as an antibiotic and antituberculosis drug, DCS may strengthen the consolidation of new extinction learning by increasing activity in amygdalar NMDA receptors, which are central to the neural circuitry of extinction (e.g., Gabriele & Packard, 2007). DCS was first shown to successfully augment virtual reality exposure therapy in specific phobia (Ressler et al., 2004), and has since been associated with moderate-to-large effect sizes in augmenting exposure therapy at post-treatment, relative to placebo plus exposure, in

simple phobia, social phobia, panic disorder, and OCD (see Norberg, Krystal, & Tolin, 2008, for a meta-analysis). These effect sizes were observed across fewer sessions of exposure therapy than patients typically receive in the exposure therapy literature, suggesting that DCS augmentation may accelerate improvement. However, DCS may be less effective at augmenting exposure therapy as the number of sessions increases (Norberg et al., 2008). This is consistent with recent animal data suggesting that the extinction enhancement effects of DCS drop off after the first extinction session (Langton & Richardson, 2008). Thus, the approach may be most effective for patients who have not responded to previous CBT (Guastella et al., 2008; Hofmann et al., 2006) or who have severe symptoms (Siegmund et al., 2011). Future research should extend the number of therapy sessions to allow benchmarking against the RCT literature on exposure therapy as well as examine the safety, tolerability, and efficacy of longer-term use.

Few side effects or safety concerns have been reported for 50 mg oral DCS, the most common dosing used in augmentation studies (Hofmann, Smits, Asnaani, Gutner, & Otto, 2011). However, some NMDA receptor modulators (e.g., DCS) increase tolerance to alcohol (e.g., Krystal, Petrakis, Mason, Trevisan, & D'Souza, 2003), suggesting that DCS might exacerbate preexisting alcohol abuse or dependence symptoms. This remains to be evaluated in future clinical trials.

Yohimbine, an α -2-adrenoreceptor antagonist, was previously used to treat erectile dysfunction (Tam, Worcel, & Wyllie, 2001) and to provoke panic attacks in experimental studies of panic disorder (e.g., Charney, Heninger, & Breier, 1984). It increases extracellular levels of norepinephrine in limbic and prefrontal brain areas associated with fear and fear extinction (for a review, see Holmes & Quirk, 2010). In a small RCT of patients with claustrophobia (Powers, Smits, Otto, Sanders, & Emmelkamp, 2009), yohimbine augmented exposure therapy in

comparison to placebo at one-week follow-up but not at immediate post-treatment. This may be consistent with research showing that memory consolidation effects peak six hours after the extinction event (Monfils, Cowansage, Klann, & LeDoux, 2009). The side effect profile of yohimbine includes increased anxiety (one of the effects it is intended to prevent), blood pressure, frequency of urination (Tam et al., 2001). Optimal dosing studies of yohimbine are needed to balance the benefit of potential extinction consolidation effects against its panic-inducing properties.

Methylene blue (MB), an antimalarial agent, textile dye, and laboratory stain, may enhance memory in low doses (e.g., Gonzalez-Lima & Bruchey, 2004). Unlike DCS and yohimbine, which act on specific types of receptors, MB accumulates and enhances metabolism wherever energy needs are the greatest, showing particular affinity for neurons in the brain. Its activity-dependent mechanism of action is fundamentally distinct from traditional pharmacological approaches that seek to modulate activity at specific neural receptors. Further, MB has a short half-life (for a review, see Rojas, Bruchey, & Gonzalez-Lima, 2012), suggesting its peak levels might be more precisely synchronized with post-session memory consolidation windows than drugs with longer half-lives, such as DCS. Although low-dose, oral MB has mild side effects, including blue urine and some urinary discomfort, high-dose intravenous MB administered to patients on a serotonergic medication (e.g., SSRIs) has been associated with serotonin syndrome (Food and Drug Administration, 2011). Initial human trials of low-dose MB for augmentation of exposure-based therapy are under way.

4.2. Disrupting the Consolidation and Reconsolidation of Fear Memories

If it is possible to strengthen extinction memories pharmacologically, might it also be possible to weaken pathological memories, or even to prevent them from forming? Animal, and some human, research has begun to address this controversial question.

4.2.1. Disrupting Memory Consolidation

Although memory consolidation is typically an adaptive mechanism that allows us to remember important information, it has been proposed that excessive consolidation may occur during emotionally arousing experiences (McGaugh, 2000). In this hypothesis, stress hormones such as epinephrine act on β -adrenergic receptors to enhance memory for emotional events (Cahill & McGaugh, 1995). Thus, blocking β -adrenergic receptors during the consolidation window might weaken the memory and prevent the onset of an anxiety disorder (e.g., Pitman et al., 2002). Unfortunately, studies that have examined the effects of the beta blocker propranolol in recently traumatized individuals have been largely negative both at post-treatment (Vaiva et al., 2003) and follow-up (e.g., Pitman et al., 2002). In addition, many of these studies had small sample sizes and did not allocate patients randomly to treatment (e.g., Vaiva et al., 2003). Furthermore, although direct conditioning has been implicated in some cases of panic disorder, specific phobia, and social phobia (Rachman, 1990), not all anxiety disorders arise through specific conditioning experiences that might be targeted within this approach.

4.2.2. Disrupting Posttraumatic Memory Reconsolidation

Research has also explored the use of drugs to disrupt memory reconsolidation, a hypothetical process in which remembering a memory makes the memory temporarily susceptible to new information (Przybylski, Roulet, & Sara, 1999). Beta blockers and glucocorticoid receptor antagonists may disrupt the reconsolidation of potentially pathological fear memories (Sara, 2000). In the idealized approach, patients would retrieve the targeted

memory and take a drug that weakens the reconsolidation of that memory. Thus, treatment could target demonstrably pathological memories as opposed to trying to weaken the initial consolidation of memories that might one day become pathological.

Unfortunately, evidence for the efficacy and safety of disrupting reconsolidation is sparse and equivocal. Animal research suggests that propranolol may interfere with reconsolidation of newly formed memories (Debiec, Bush, & LeDoux, 2011; Muravieva & Alberini, 2010) but less so with older memories (e.g., Milekic & Alberini, 2002). Clinically, this may be problematic given that an average of 8 years pass before patients with an anxiety disorder receive treatment (Christiana et al., 2000). Moreover, propranolol increases variability in blood pressure and may not be appropriate for people with a high risk of stroke (Webb, Fischer, & Rothwell, 2011). For individuals at risk for PTSD who are receiving emergency treatment for physical injuries, its blood pressure effects are particularly problematic. It is also unclear whether glucocorticoids such as cortisol, which is released during emotionally arousing experiences, disrupt or promote memory consolidation (McGaugh & Roozendaal, 2009). Whereas human studies suggest that low doses of cortisol may disrupt reconsolidation (e.g., de Quervain & Margraf, 2008; Schelling, Roozendaal, & De Quervain, 2004), animal studies suggest that *blocking* glucocorticoid receptors may have the same effect (de Quervain et al., 2009, 2011). The observed relationships among glucocorticoids, hormones, and memory appear to be highly sensitive to experimental characteristics.

4.3. Discussion

It would be a tremendous feat of translational science if the pharmacological modulation of learning and memory could be established as a safe, reliable, and specific treatment approach. That possibility remains hypothetical for now, as many conceptual, empirical, practical, and

ethical issues need to be addressed with more targeted research. First, memory consolidation is a well established phenomenon, whereas reconsolidation is not. Side effects, delayed consolidation, and extinction need to be ruled out as alternative explanations for apparent reconsolidation effects in many studies (McGaugh & Roozendaal, 2009). Second, drugs that promote long-term consolidation may affect other aspects of memory, such as nonemotional memory and memory for information occurring before or after the target event. Studies of DCS in healthy individuals have yielded equivocal, mostly null, findings thus far concerning nonemotional memory (Kuriyama, Honma, Koyama, & Kim, 2011; Otto et al., 2009). MB, however, appears to have broad memory-enhancing and neuroprotective properties and is being investigated in patients with cognitive impairments (Rojas et al., 2012). Moreover, double-blind human research suggests that propranolol can both impair recall of emotional information and improve recall of neutral information (e.g., Strange, 2003). Third, some memory-modulating drugs may exhibit a U-shaped dose-response relationship, promoting memory consolidation at low doses but inhibiting it at high doses; this appears to be true for MB (Rojas et al., 2012) and some glucocorticoids (McGaugh & Roozendaal, 2009). Fourth, temporal parameters, such as the duration of exposures and the half-life of the drug (relative to the consolidation window), may determine whether unintended impairment of extinction or strengthening of reconsolidation occurs (Quirk & Mueller, 2007). For example, some animal research has shown that DCS coupled with short-duration exposure (Lee, Milton, & Everitt, 2006), and propranolol with long-duration exposure (Cain, Blouin, & Barad, 2004), leads to strengthened fear memories—the opposite of what should have been observed if DCS were to strengthen extinction and propranolol were to impair reconsolidation (Quirk & Mueller, 2007). Fifth, long-term data on outcome are absent for

all of the memory modulation approaches, suggesting a clear need for longer-term follow-up assessments in future research.

Finally, the ethics of memory modulation must be carefully considered vis a vis emerging data on the safety, specificity, and efficacy of these drugs (Henry, Fishman, & Youngner, 2007; President's Council on Bioethics, 2003). For example, should memory-enhancing medications such as DCS be withheld if a patient experiences an adverse event (e.g., a panic attack that terminates exposure) during the therapy session? What, if anything, should be done if the adverse event happens soon after the patient leaves the session, when he or she cannot be directly monitored? Under what circumstances might it be appropriate to administer a memory-weakening drug? The answers to these important questions cannot be answered with available data, and thus must be informed by future data on the risks and benefits to patients.

5. 3,4-methylenedioxymethamphetamine (MDMA) and Cannabidiol

Although most psychedelic drugs have been illegal or heavily regulated in the U.S. and abroad for the past several decades, some researchers (e.g., Bouso, Doblin, Farré, Alcázar, & Gómez-Jarabo, 2008; Doblin, 2002) have argued that psychedelic and other drugs may be able to augment exposure-based treatments for anxiety disorders (Bouso et al., 2008; Doblin, 2002). Indeed, correlational evidence links psychedelic substances to increased activation in the ventromedial prefrontal cortex (vmPFC) and decreased amygdala activation (Bergamaschi et al., 2011; Vollenweider & Kometer, 2010; Vollenweider, Liechti, Gamma, Greer, & Geyer, 2002). Moreover, these substances may increase access to internal emotional states and reduce avoidance of fearful or anxiety-provoking triggers (Johansen & Krebs, 2009). But are they safe and effective?

Among the psychedelic drugs, 3,4-methylenedioxymethamphetamine (MDMA; “ecstasy”) is thought to be the best candidate for exposure augmentation (Doblin, 2002). Traditional psychedelics, such as lysergic acid diethylamide (LSD; “acid”) and psilocybin (“mushrooms”), can impair cognitive functioning, visual perception, and emotional control, whereas MDMA does not (Cami et al., 2000; Harris, Baggott, Mendelson, Mendelson, & Jones, 2002; Tancer & Johanson, 2003). When given in small doses (1.5 to 1.7 mg/kg), MDMA produces a short-term release of serotonin, dopamine, and norepinephrine, the same neurotransmitters that SSRIs and SNRIs act on over longer-term courses of administration. Based on these observations and several case studies, Doblin (2002) speculated that MDMA might provide a critical window during which adjunctive MDMA could improve the learning and habit change that might occur during psychotherapy, and that this benefit might be realized in as few as 1 to 3 drug sessions. These hypotheses are premature given the available data and ignore the risks associated with MDMA.

Even under well controlled and monitored administration, people taking MDMA have been reported to experience acute mild depersonalization, derealization, symptoms of thought disorder, loss of body control, altered impressions of sensory information, a distorted sense of space and time, and a post-administration syndrome involving decreased energy, appetite, and affect (Vollenweider, Gamma, Liechti, & Huber, 1998). More deleterious risks include possible neurotoxic effects when MDMA is used in environments with ambient temperatures higher than 78 degrees F (Malberg & Seiden, 1998), depletion of serotonin levels associated with chronic use (Colado, Williams, & Green, 1995; McCann, Szabo, Scheffel, Dannals, & Ricaurte, 1998), and persistent changes in memory following high-dose or frequent use (e.g., Hatzidimitriou, McCann, & Ricaurte, 1999; Reneman et al., 2001; Zakzanis & Young, 2001). In addition to

raising doubt that MDMA would be well-tolerable, acceptable, and safe, many of these side effects are highly salient, suggesting that both patients and clinicians could not be blinded to treatment status in a placebo-controlled RCT of MDMA.

Cannabidiol (CBD), one of many cannabinoids found in marijuana, also has some limited preliminary evidence supporting its use in the treatment of anxiety. CBD acts directly on limbic and paralimbic brain areas (Crippa et al., 2004; Fusar-Poli et al., 2009), decreasing anxiety without the consciousness-altering effects of tetrahydrocannabinol, a primary psychoactive compound in marijuana (Mechoulam, Parker, & Gallily, 2002; Zuardi, 2008). Existing studies of CBD for anxiety are few and largely uncontrolled. In two recent studies, low-dose CBD was associated with decreased subjective anxiety (Crippa et al., 2011; Crippa, Zuardi, & Hallak, 2010), suggesting that it may help anxious patients confront anxiety-provoking situations (Bergamaschi et al., 2011). In a small placebo-controlled, double-blind study of CBD in patients with social phobia, patients who received CBD immediately before completing a simulated public speaking task reported reduced anxiety, cognitive impairment, and negative self-evaluations during the task compared to patients who received placebo (Bergamaschi et al., 2011). However, no robust association between CBD blood plasma levels and performance on the task emerged. Notably, CBD can produce anxiogenic reactions, at high doses, including symptoms of panic (Crippa et al., 2004)—another example of an agent producing the symptoms it is being used to treat.

Claims about the efficacy of psychedelic drugs have not been rigorously evaluated, which is unlikely to happen unless the regulatory and sociopolitical climate becomes more favorable. If it does, then we will be able evaluate, for the first time, research complying with minimal standards of high-quality evidence, including controls, blinding, random assignment to treatment

conditions, and sample sizes sufficiently large to detect broad treatment effects. Research would also need to address the risks associated with misuse.

6. Novel Brain Stimulation Treatments

In the past decade, technological advances, combined with improved understanding of neural circuits involved in psychiatric disorders, have allowed for the development of treatments based on electrical or electromagnetic modulation of brain activity. In these brain stimulation treatments, the provider stimulates specific brain regions associated with psychiatric dysfunction, which theoretically either boosts or reduces activity in the targeted region, depending on the stimulation parameters. Unfortunately, despite considerable advances in our understanding of the neural circuitry of anxiety, few studies have examined the effects of brain stimulation treatments in patients with anxiety disorders. This gap may be easier to close for less invasive treatments, such as repetitive transcranial magnetic stimulation (rTMS).

rTMS uses an alternating magnetic field applied outside the skull to stimulate electrical activity near the surface of the cerebral cortex. The operator sets the parameters of the magnetic field, such as its intensity and frequency, and activates the rTMS device near the part of the head closest to the targeted brain region. The resulting stimulation of the cerebral cortex may modulate the activity of monoamine neurotransmitters in regions such as right limbic, paralimbic, and frontal cortical structures (Ben-Shachar, Belmaker, Grisaru, & Klein, 1997). rTMS poses minimal risk of convulsions or cognitive impairment (Belmaker & Fleischmann, 1995) and may have antidepressant-like effects (Levkovitz, Grisaru, & Segal, 2001; Post & Keck, 2001). Symptom improvement is transient, however, suggesting that rTMS may have to be repeated to sustain treatment gains (Levkovitz et al., 2001; Post & Keck, 2001).

Clinicians must make several critical decisions when using rTMS, such as how frequently the magnetic field should alternate and where to apply the field. Evidence supports the use of both high- (10-20 Hz, likely to increase neural activity) and low-frequency (1 Hz, likely to reduce activity) stimulation applied to different brain areas (Cohen et al., 2004). High-frequency rTMS applied to the right dorsolateral prefrontal cortex (dlPFC) has been associated with significantly reduced subjective ratings of anxiety, PTSD symptoms (Cohen et al., 2004), and compulsive urges in OCD patients, while also improving mood (Wassermann & Lisanby, 2001). Low-frequency rTMS applied to the right PFC has been related to reductions both in hyperarousal symptoms and a neural biomarker related to hyperarousal in PTSD (Karl, Malta, & Maercker, 2006; Osuch et al., 2009). However, neither high- nor low-frequency stimulation of the left lateral prefrontal and mid-occipital areas has been associated with similar effects (e.g., Karl et al., 2006). Thus, the literature is inconclusive on the major parameters of rTMS treatment for anxiety disorders. One possibility to be examined further is that the optimal stimulatory frequency may be different across brain regions and hemispheres.

Deep brain stimulation (DBS) involves the surgical placement of electrodes into specific brain areas, providing electrical pulses that modulate regional neural activity (Kleiner-Fisman et al., 2006). It has long been used to treat movement and pain disorders (Gildenberg, 2005; Kringelbach et al., 2007). Preliminary evidence suggests that DBS may effectively treat affective and anxiety disorders when applied to the nucleus accumbens, subgenual anterior cingulate, or ventral internal capsule (Bewernick et al., 2010). The best evidence of efficacy thus far is in treatment-refractory OCD (e.g., Greenberg et al., 2010; Koning, Figee, Munckhof, Schuurman, & Denys, 2011). One systematic review (Lakhan & Callaway, 2010) estimates that half of patients with OCD who are treated with DBS report large symptom improvement.

Rigorously controlled empirical data and systematic reviews are lacking for other anxiety disorders. Major drawbacks of DBS include its invasiveness and the risk of medical complications associated with neurosurgery (e.g., infection, swelling, intracranial hemorrhage). Interestingly, DBS used to treat individuals with movement disorders has also been associated with side-effects of depression, hypomania, hallucinations, compulsive gambling, hypersexuality, and cognitive dysfunction (Burn & Tröster, 2004). These complications appear to be highly dependent on electrode placement, which is an area that requires further investigation.

Vagal nerve stimulation (VNS) has been the least studied brain stimulation treatment for anxiety. The vagus nerve is a major parasympathetic component of the autonomic nervous system that transmits signals of autonomic arousal from the body to the brain, which interprets and uses the signals to inform an individual's emotional state (Groves & Brown, 2005). VNS is based on the hypothesis that stimulating this important parasympathetic nerve will improve the regulation of autonomic arousal, thereby reducing symptoms of anxiety. In VNS, a neurosurgeon implants an electrical stimulator and tethers its leads to the vagus nerve. The clinician can then use an external device to control stimulator.

Originally a treatment for epilepsy, VNS may also reduce anxiety. In one study (Rush et al., 2000), all of the patients receiving VNS reported some improvement in anxiety, including agitation (73%), psychic anxiety (50%), and somatic anxiety (36%). Moreover, George et al. (2003) reported improvement in clinician- and patient-rated anxiety across 10 weeks of VNS for anxiety disorders. As well-controlled studies of VNS for the anxiety disorders are not available for anxiety disorders, it cannot be recommended for clinical use. Future research may be facilitated by less invasive versions of VNS now in development, including an external method of stimulation that does not require surgery.

Brain stimulation techniques may one day allow practitioners to have greater control over the timing and neural targets of treatment and may one day improve remission rates among patients with otherwise treatment-resistant anxiety. However, research must first identify specific brain regions where inactivity causes or maintains the pathognomonic features of the disorder. Research must also establish that stimulation of one brain area does not adversely affect other areas. Such evidence needs to be robust, and the disorder highly treatment-refractory, before clinicians should recommend costly, surgically invasive brain stimulation treatments to their patients. Still, for some patients, DBS and VNS may be the only options short of more radical neurosurgery. On the other hand, it should be much easier for noninvasive treatments such as rTMS to move forward. Future research on rTMS should continue to evaluate the relative efficacy of high- versus low-frequency stimulation, and it should investigate whether symptom reduction can be maintained through repeated treatment over the longer term. If shown to be effective and safe, rTMS may someday provide a noninvasive option that could be used to augment psychotherapy or anxiety medications by reducing hyperarousal-related factors that otherwise could impede treatment progress.

7. Discussion

Today, patients with anxiety disorders benefit from decades of psychopharmacological research that has yielded safer, more tolerable side-effect profiles than before—but without improved efficacy. As we have reviewed above, first-line antidepressants, such as the SSRIs and possibly the SNRIs, do a reasonable job of reducing anxiety, but they act slowly and often do not lead to sustained remission. Faced with incomplete response, clinicians and patients must decide how treatment should proceed. What they need, but often do not have, is the answer to Gordon Paul's (1969) famous question: "What treatment, by whom, is most effective for this individual

with that specific problem, under which set of circumstances, and how does it come about?” (p. 44). Despite billions of dollars spent in pharmaceutical research and development, this complex question cannot be answered adequately for common clinical scenarios. The information gap forces clinicians to generalize (often grossly) from studies designed to answer narrow parts of the question—usually “is drug X effective for disorder Y?” Research on anxiety disorders needs to more frequently use designs that allow sequences of treatments to be evaluated and compared (Oetting et al., 2011), and that provide more direct information about the action of drugs on the specific pathophysiology of anxiety disorders (Klein, 2011). Indeed, such approaches may do as much to close the information gap as to illuminate individual differences in the pathophysiology of anxiety disorders (Klein, 2011)—a goal congruent with initiatives recently advanced by the National Institute of Mental Health (Insel et al., 2010). We need to understand how clinicians can better use and combine the drugs on which so much money has already been spent while we wait for the more slowly moving innovative developments in drug development to occur.

New treatments for anxiety are being developed along three broad paths: continued drug development focused on highly specific neuroreceptor targets; the pharmacological manipulation of memory to enhance adaptive processes and block maladaptive processes; and the electrical or electromagnetic stimulation of the brain. Unfortunately, none of these treatment approaches is ready for everyday clinical use. The reasons for this are different in each case. Translational research, for example, has identified drugs that act on highly specific, molecular targets, but the efficacy and safety these drugs have demonstrated in animals often have not translated to humans. It may not be cost-effective for drug companies to continue investing so heavily in this area, even if there are promising leads, because other medical illness applications may provide better return on investment.

Pharmacological manipulation of memory and learning is a relatively new and highly innovative field. Research has shown it is not only theoretically plausible but empirically possible. Whether it is ethical and safe, however, and whether consolidation or reconsolidation (rather than the modulation of fear expression) is the primary mechanism of action, remain to be seen. Augmentation of exposure therapy (e.g., with DCS) has yet to be tested where it may be most effective: as a treatment for incomplete responders to prior SSRI or CBT. Much basic research is needed on the generality of these drug's effects on nontarget memory processes, as well as on the long-term efficacy of augmentation. Substantial conceptual, practical, and ethical uncertainty still surrounds blocking the consolidation or reconsolidation of fear-related memories. Finally, the small literature on alternative augmentation approaches involving psychedelic substances is thin, unlikely to get past regulatory barriers without significant change, and difficult to justify given the drugs' often nontrivial side effects.

Research on brain stimulation treatments is relatively new in anxiety disorders. DBS and VNS, which involve neurosurgery, are probably best reserved for the most treatment-resistant and functionally-impairing anxiety disorders, such as OCD. Research on these highly invasive interventions will necessarily move slowly but should be pursued vigorously so long as they are safe. rTMS, however, can be studied most readily because it is noninvasive and has a more modest side effect profile; somewhat surprisingly, however, rTMS has rarely been studied in anxiety disorders. As research on rTMS continues, it will be interesting to see if the hypothesized frequency-dependent modulation of neural activity associated with rTMS is replicated, as it may suggest new hypotheses about the role of neural metabolism in anxiety, which may carry over to other treatments.

How can future research improve progress in the development and application of pharmacological treatments for anxiety disorders? The most critical questions on the application side concern the parameters and sequencing of existing treatments and to better understand the determinants of treatment response and nonresponse at the individual level. These issues are far from resolved, even for first-line treatments such as SSRIs. Other burgeoning research areas, such the investigation of treatment response as a function of genetic markers, may one day allow clinicians to prescribe optimal initial treatments based on the patient's unique genetic profile. On the novel treatment development side, basic questions concerning the safety, tolerability, specificity, mechanisms of action, and ethics need to be addressed. Ideally, research on the application of existing treatments and the development of new treatments will inform each other as this decade advances.

References

- Aikens, J. E., Nease, D. E., Nau, D. P., Klinkman, M. S., & Schwenk, T. L. (2005). Adherence to maintenance-phase antidepressant medication as a function of patient beliefs about medication. *Annals of Family Medicine, 3*, 23-30.
- Aranda-Michel, J., Koehler, A., Bejarano, P. A., Poulos, J. E., Luxon, B. A., Mobin Khan, C., Ee, L. C., et al. (1999). Nefazodone-induced liver failure: Report of three cases. *Annals of Internal Medicine, 130*, 285-288.
- Arborelius, L., Owens, M. J., Plotsky, P. M., & Nemeroff, C. B. (1999). The role of corticotropin-releasing factor in depression and anxiety disorders. *The Journal of Endocrinology, 160*, 1-12.
- Bakish, D., Hooper, C. L., West, D. L., Miller, C., Blanchard, A., & Bashir, F. (1995). Moclobemide and specific serotonin reuptake inhibitor combination treatment of resistant anxiety and depressive disorders. *Human Psychopharmacology: Clinical and Experimental, 10*, 105-109.
- Bandelow, B., Seidler-Brandler, U., Becker, A., Wedekind, D., & Rüther, E. (2007). Meta-analysis of randomized controlled comparisons of psychopharmacological and psychological treatments for anxiety disorders. *World Journal of Biological Psychiatry, 8*, 175-187.
- Barlow, D. H. (2004). Psychological treatments. *American Psychologist, 59*, 869-878.
- Becker, M. E., Hertzberg, M. A., Moore, S. D., Dennis, M. F., Bukenya, D. S., & Beckham, J. C. (2007). A placebo-controlled trial of bupropion SR in the treatment of chronic posttraumatic stress disorder. *Journal of Clinical Psychopharmacology, 27*, 193-197.

- Belmaker, R. H., & Fleischmann, A. (1995). Transcranial magnetic stimulation: A potential new frontier in psychiatry. *Biological Psychiatry*, *38*, 419-421.
- Belzung, C., Yalcin, I., Griebel, G., Surget, A., & Leman, S. (2006). Neuropeptides in psychiatric diseases: An overview with a particular focus on depression and anxiety disorders. *CNS and Neurological Disorders Drug Targets*, *5*, 135-145.
- Ben-Shachar, D., Belmaker, R. H., Grisaru, N., & Klein, E. (1997). Transcranial magnetic stimulation induces alterations in brain monoamines. *Journal of Neural Transmission*, *104*, 191-197.
- Bergamaschi, M. M., Queiroz, R. H. C., Chagas, M. H. N., de Oliveira, D. C. G., De Martinis, B. S., Kapczinski, F., Quevedo, J., et al. (2011). Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology*, *36*, 1219-1226.
- Bewernick, B. H., Hurlmann, R., Matusch, A., Kayser, S., Grubert, C., Hadrysiewicz, B., Axmacher, N., et al. (2010). Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biological Psychiatry*, *67*, 110-116.
- Bloch, M. H., McGuire, J., Landeros-Weisenberger, A., Leckman, J. F., & Pittenger, C. (2009). Meta-analysis of the dose-response relationship of SSRI in obsessive-compulsive disorder. *Molecular Psychiatry*, *15*, 850-855.
- Bouso, J. C., Doblin, R., Farré, M., Alcázar, M. A., & Gómez-Jarabo, G. (2008). MDMA-assisted psychotherapy using low doses in a small sample of women with chronic posttraumatic stress disorder. *Journal of Psychoactive Drugs*, *40*, 225-236.

- Bouton, M. E. (2002). Context, ambiguity, and unlearning: Sources of relapse after behavioral extinction. *Biological Psychiatry*, 2002, 976-986.
- Burn, D. J., & Tröster, A. I. (2004). Neuropsychiatric complications of medical and surgical therapies for Parkinson's disease. *Journal of Geriatric Psychiatry and Neurology*, 17, 172-180.
- Cahill, L., & McGaugh, J. L. (1995). A novel demonstration of enhanced memory associated with emotional arousal. *Consciousness and Cognition*, 4, 410-421.
- Cain, C. K., Blouin, A. M., & Barad, M. (2004). Adrenergic transmission facilitates extinction of conditional fear in mice. *Learning and Memory*, 11, 179-187.
- Cami, J., Farré, M., Mas, M., Roset, P. N., Poudevida, S., Mas, A., San, L., et al. (2000). Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): Psychomotor performance and subjective effects. *Journal of Clinical Psychopharmacology*, 20, 455-466.
- Charney, D. S., Heninger, G. R., & Breier, A. (1984). Noradrenergic function in panic anxiety: Effects of yohimbine in healthy subjects and patients with agoraphobia and panic disorder. *Arch Gen Psychiatry*, 41, 751-763.
- Christiana, J., Gilman, S., Guardino, M., Mickelson, K., Morselli, P., Olfson, M., & Kessler, R. (2000). Duration between onset and time of obtaining initial treatment among people with anxiety and mood disorders: An international survey of members of mental health patient advocate groups. *Psychological Medicine*, 30, 693-703.
- Cohen, H., Kaplan, Z., Kotler, M., Kouperman, I., Moisa, R., & Grisaru, N. (2004). Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in

- posttraumatic stress disorder: A double-blind, placebo-controlled study. *American Journal of Psychiatry*, *161*, 515-524.
- Colado, M. I., Williams, J. L., & Green, A. R. (1995). The hyperthermic and neurotoxic effects of "Ecstasy" (MDMA) and 3,4 methylenedioxyamphetamine (MDA) in the Dark Agouti (DA) rat, a model of the CYP2D6 poor metabolizer phenotype. *British Journal of Pharmacology*, *115*, 1281-1289.
- Coric, V., Taskiran, S., Pittenger, C., Wasyluk, S., Mathalon, D. H., Valentine, G., Saksa, J., et al. (2005). Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: An open-label trial. *Biological Psychiatry*, *58*, 424-428.
- Craske, M. G., Kircanski, K., Zelikowsky, M., Mystkowski, J., Chowdhury, N., & Baker, A. (2008). Optimizing inhibitory learning during exposure therapy. *Behaviour Research and Therapy*, *46*, 5-27.
- Crippa, J. A. de S., Derenusson, G. N., Ferrari, T. B., Wichert-Ana, L., Duran, F. L., Martin-Santos, R., Simões, M. V., et al. (2011). Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: A preliminary report. *Journal of Psychopharmacology*, *25*, 121-130.
- Crippa, J. A. de S., Zuardi, A. W., Garrido, G. E. J., Wichert-Ana, L., Guarnieri, R., Ferrari, L., Azevedo-Marques, P. M., et al. (2004). Effects of cannabidiol (CBD) on regional cerebral blood flow. *Neuropsychopharmacology*, *29*, 417-426.
- Crippa, J. A. de S., Zuardi, A. W., & Hallak, J. E. C. (2010). Uso terapêutico dos canabinoides em psiquiatria. *Revista Brasileira de Psiquiatria*, *32*, 556-566.
- Davidson, J. R. T. (1989). Seizures and bupropion: A review. *Journal of Clinical Psychiatry*, *50*, 256-261.

- Davidson, J. R. T., DuPont, R. L., Hedges, D., & Haskins, J. T. (1999). Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. *Journal of Clinical Psychiatry, 60*, 528-535.
- Davidson, J. R. T., Weisler, R. H., Butterfield, M. I., Casat, C. D., Connor, K. M., Barnett, S., & van Meter, S. (2003). Mirtazapine vs. placebo in posttraumatic stress disorder: A pilot trial. *Biological Psychiatry, 53*, 188–191.
- de Quervain, D. J.-F., Aerni, A., Schelling, G., & Roozendaal, B. (2009). Glucocorticoids and the regulation of memory in health and disease. *Frontiers in Neuroendocrinology, 30*, 358-370.
- de Quervain, D. J.-F., Bentz, D., Michael, T., Bolt, O. C., Wiederhold, B. K., Margraf, J., & Wilhelm, F. H. (2011). Glucocorticoids enhance extinction-based psychotherapy. *Proceedings of the National Academy of Sciences, 108*, 6621-6625.
- de Quervain, D. J.-F., & Margraf, J. (2008). Glucocorticoids for the treatment of post-traumatic stress disorder and phobias: A novel therapeutic approach. *European Journal of Pharmacology, 583*, 365-371.
- Debiec, J., Bush, D. E. A., & LeDoux, J. E. (2011). Noradrenergic enhancement of reconsolidation in the amygdala impairs extinction of conditioned fear in rats--a possible mechanism for the persistence of traumatic memories in PTSD. *Depression and Anxiety, 28*, 186-193.
- Depping, A. M., Komossa, K., Kissling, W., & Leucht, S. (2010). Second-generation antipsychotics for anxiety disorders. In The Cochrane Collaboration & S. Leucht (Eds.), *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd. Retrieved from <http://doi.wiley.com/10.1002/14651858.CD008120.pub2>

- Doblin, R. (2002). A clinical plan for MDMA (Ecstasy) in the treatment of posttraumatic stress disorder (PTSD): Partnering with the FDA. *Journal of Psychoactive Drugs*, *34*, 185-194.
- Feltner, D. E., Liu-Dumaw, M., Schweizer, E., & Bielski, R. (2011). Efficacy of pregabalin in generalized social anxiety disorder. *International Clinical Psychopharmacology*, *26*, 213-220.
- Feltner, D. E., Wittchen, H.-U., Kavoussi, R., Brock, J., Baldinetti, F., & Pande, A. C. (2008). Long-term efficacy of pregabalin in generalized anxiety disorder. *International Clinical Psychopharmacology*, *23*, 18-28.
- Food and Drug Administration. (2011, July 26). FDA drug safety communication: Serious CNS reactions possible when methylene blue is given to patients taking certain psychiatric medications. *FDA website*. Retrieved July 26, 2011, from <http://www.fda.gov/Drugs/DrugSafety/ucm263190.htm>
- Fournier, J. C., DeRubeis, R. J., Hollon, S. D., Dimidjian, S., Amsterdam, J. D., Shelton, R. C., & Fawcett, J. (2010). Antidepressant drug effects and depression severity. *JAMA*, *303*, 47-53.
- Furieri, F. A., & Nakamura-Palacios, E. M. (2007). Gabapentin reduces alcohol consumption and craving: A randomized, double-blind, placebo-controlled trial. *The Journal of Clinical Psychiatry*, *68*, 1691-1700.
- Fusar-Poli, P., Allen, P., Bhattacharyya, S., Crippa, J. A. de S., Mechelli, A., Borgwardt, S., Martin-Santos, R., et al. (2009). Modulation of effective connectivity during emotional processing by $\Delta 9$ -tetrahydrocannabinol and cannabidiol. *The International Journal of Neuropsychopharmacology*, *13*, 421-432.

- Gabriele, A., & Packard, M. G. (2007). D-Cycloserine enhances memory consolidation of hippocampus-dependent latent extinction. *Learning and Memory, 14*, 468-471.
- Gildenberg, P. L. (2005). Evolution of neuromodulation. *Stereotactic and Functional Neurosurgery, 83*, 71-79.
- Goddard, A. W., Brouette, T., Almai, A., Jetty, P., Woods, S. W., & Charney, D. (2001). Early coadministration of clonazepam with sertraline for panic disorder. *Archives of General Psychiatry, 58*, 681-686.
- Gonzalez-Lima, F., & Bruchey, A. K. (2004). Extinction memory improvement by the metabolic enhancer methylene blue. *Learning and Memory, 11*, 633-640.
- Greenberg, B. D., Gabriels, L. A., Malone, D. A., Rezai, A. R., Friehs, G. M., Okun, M. S., Shapira, N. A., et al. (2010). Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. *Molecular Psychiatry, 15*, 64-79.
- Griebel, G., Simiand, J., Serradeil-Le Gal, C., Wagnon, J., Pascal, M., Scatton, B., Maffrand, J.-P., et al. (2002). Anxiolytic- and antidepressant-like effects of the non-peptide vasopressin V1b receptor antagonist, SSR149415, suggest an innovative approach for the treatment of stress-related disorders. *Proceedings of the National Academy of Sciences of the United States of America, 99*, 6370-6375.
- Grilo, C. M., Money, R., Barlow, D. H., Goddard, A. W., Gorman, J. M., Hofmann, S. G., Papp, L. A., et al. (1998). Pretreatment patient factors predicting attrition from a multicenter randomized controlled treatment study for panic disorder. *Comprehensive Psychiatry, 39*, 323-332.

- Gross, C., Zhuang, X., Stark, K., Ramboz, S., Oosting, R., Kirby, L., Santarelli, L., et al. (2002). Serotonin 1A receptor acts during development to establish normal anxiety-like behaviour in the adult. *Nature*, *416*, 396-400.
- Groves, D. A., & Brown, V. J. (2005). Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. *Neuroscience and Biobehavioral Reviews*, *29*, 493-500.
- Guastella, A. J., Richardson, R., Lovibond, P. F., Rapee, R. M., Gaston, J. E., Mitchell, P., & Dadds, M. R. (2008). A randomized controlled trial of D-cycloserine enhancement of exposure therapy for social anxiety disorder. *Biological Psychiatry*, *63*, 544-549.
- Gutman, D. A., Owens, M. J., Skelton, K. H., Thirivikraman, K. V., & Nemeroff, C. B. (2003). The corticotropin-releasing factor 1 receptor antagonist R121919 attenuates the behavioral and endocrine responses to stress. *Journal of Pharmacology and Experimental Therapeutics*, *304*, 874-880.
- Harris, D. S., Baggott, M., Mendelson, J. H., Mendelson, J. E., & Jones, R. T. (2002). Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology*, *162*, 396-405.
- Hatzidimitriou, G., McCann, U. D., & Ricaurte, G. A. (1999). Altered serotonin innervation patterns in the forebrain of monkeys treated with (+/-)3,4-methylenedioxymethamphetamine seven years previously: Factors influencing abnormal recovery. *The Journal of Neuroscience*, *19*, 5096-5107.
- Heilig, M. (2004). The NPY system in stress, anxiety and depression. *Neuropeptides*, *38*, 213-224.

- Heilig, M., McLeod, S., Brot, M., Heinrichs, S. C., Menzaghi, F., Koob, G. F., & Britton, K. T. (1993). Anxiolytic-like action of neuropeptide Y: Mediation by Y1 receptors in amygdala, and dissociation from food intake effects. *Neuropsychopharmacology*, *8*, 357-363.
- Heinrichs, S. C., De Souza, E. B., Schulteis, G., Lapsansky, J. L., & Grigoriadis, D. E. (2002). Brain penetrance, receptor occupancy and antistress in vivo efficacy of a small molecule corticotropin releasing factor type I receptor selective antagonist. *Neuropsychopharmacology*, *27*, 194-202.
- Henry, M., Fishman, J. R., & Youngner, S. J. (2007). Propranolol and the prevention of post-traumatic stress disorder: Is it wrong to erase the “sting” of bad memories? *The American Journal of Bioethics*, *7*, 12-20.
- Hertzberg, M. A., Moore, S. D., Feldman, M. E., & Beckham, J. C. (2001). A preliminary study of bupropion sustained-release for smoking cessation in patients with chronic posttraumatic stress disorder. *Journal of Clinical Psychopharmacology*, *21*, 94-98.
- Hofmann, S. G., Meuret, A. E., Smits, J. A. J., Simon, N. M., Pollack, M. H., Eisenmenger, K., Shiekh, M., et al. (2006). Augmentation of exposure therapy with D-cycloserine for social anxiety disorder. *Archives of General Psychiatry*, *63*, 298-304.
- Hofmann, S. G., Smits, J. A. J., Asnaani, A., Gutner, C. A., & Otto, M. W. (2011). Cognitive enhancers for anxiety disorders. *Pharmacology, Biochemistry, and Behavior*, *99*, 275-284.
- Holmes, A., Heilig, M., Rupniak, N. M. J., Steckler, T., & Griebel, G. (2003). Neuropeptide systems as novel therapeutic targets for depression and anxiety disorders. *Trends in Pharmacological Sciences*, *24*, 580-588.

- Holmes, A., & Quirk, G. J. (2010). Pharmacological facilitation of fear extinction and the search for adjunct treatments for anxiety disorders--the case of yohimbine. *Trends in Pharmacological Sciences, 31*, 2-7.
- Insel, T. R., Cuthbert, B. N., Garvey, M. A., Heinssen, R. K., Pine, D. S., Quinn, K. J., Sanislow, C. A., et al. (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *American Journal of Psychiatry, 167*, 748–751.
- Ipser, J. C., Carey, P., Dhansay, Y., Fakier, N., Seedat, S., & Stein, D. J. (2006). Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders. In The Cochrane Collaboration & J. C. Ipser (Eds.), *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd. Retrieved from <http://doi.wiley.com/10.1002/14651858.CD005473.pub2>
- James, I. M., Burgoyne, W., & Savage, I. T. (1983). Effect of pindolol on stress-related disturbances of musical performance: Preliminary communication. *Journal of the Royal Society of Medicine, 76*, 194-196.
- Johansen, P., & Krebs, T. (2009). How could MDMA (ecstasy) help anxiety disorders? A neurobiological rationale. *Journal of Psychopharmacology, 23*, 389-391.
- Kaizar, E. E., Greenhouse, J. B., Seltman, H., & Kelleher, K. (2006). Do antidepressants cause suicidality in children? A Bayesian meta-analysis. *Clinical Trials, 3*, 73-98.
- Karl, A., Malta, L. S., & Maercker, A. (2006). Meta-analytic review of event-related potential studies in post-traumatic stress disorder. *Biological Psychology, 71*, 123-147.
- Katz, R. J., DeVeugh-Geiss, J., & Landau, P. (1990). Clomipramine in obsessive-compulsive disorder. *Biological Psychiatry, 28*, 401-414.

- Klein, D. F. (2011). Causal thinking for objective psychiatric diagnostic criteria. In P. E. Shrout, K. M. Keyes, & K. Ornstein (Eds.), *Causality and psychopathology: Finding the determinants of disorders and their cures* (pp. 321-337). New York: Oxford University Press.
- Komossa, K., Depping, A. M., Meyer, M., Kissling, W., & Leucht, S. (2010). Second-generation antipsychotics for obsessive compulsive disorder. In The Cochrane Collaboration & K. Komossa (Eds.), *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd. Retrieved from <http://doi.wiley.com/10.1002/14651858.CD008141.pub2>
- Koning, P. P., Figeo, M., Munckhof, P., Schuurman, P. R., & Denys, D. (2011). Current status of deep brain stimulation for obsessive-compulsive disorder: A clinical review of different targets. *Current Psychiatry Reports*, *13*, 274-282.
- Kramer, M. S., Cutler, N., Feighner, J., Shrivastava, R., Carman, J., Sramek, J. J., Reines, S. A., et al. (1998). Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science*, *281*, 1640-1645.
- Kringelbach, M. L., Jenkinson, N., Green, A. L., Owen, S. L. F., Hansen, P. C., Cornelissen, P. L., Holliday, I. E., et al. (2007). Deep brain stimulation for chronic pain investigated with magnetoencephalography. *Neuroreport*, *18*, 223-228.
- Krishnan, V., & Nestler, E. J. (2008). The molecular neurobiology of depression. *Nature*, *455*, 894-902.
- Krystal, J. H., Petrakis, I. L., Mason, G., Trevisan, L., & D'Souza, D. C. (2003). N-methyl-d-aspartate glutamate receptors and alcoholism: Reward, dependence, treatment, and vulnerability. *Pharmacology and Therapeutics*, *99*, 79-94.

- Krystal, J. H., Rosenheck, R. A., Cramer, J. A., Vessicchio, J. C., Jones, K. M., Vertrees, J. E., Horney, R. A., et al. (2011). Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD. *JAMA*, *306*, 493 -502.
- Kuriyama, K., Honma, M., Koyama, S., & Kim, Y. (2011). D-cycloserine facilitates procedural learning but not declarative learning in healthy humans: A randomized controlled trial of the effect of D-cycloserine and valproic acid on overnight properties in the performance of non-emotional memory tasks. *Neurobiology of Learning and Memory*, *95*, 505-509.
- Lakhan, S., & Callaway, E. (2010). Deep brain stimulation for obsessive-compulsive disorder and treatment-resistant depression: Systematic review. *BMC Research Notes*, *3*, 60.
- Langton, J. M., & Richardson, R. (2008). D-cycloserine facilitates extinction the first time but not the second time: An examination of the role of NMDA across the course of repeated extinction sessions. *Neuropsychopharmacology*, *33*, 3096-3102.
- Lee, J. L. C., Milton, A. L., & Everitt, B. J. (2006). Reconsolidation and extinction of conditioned fear: Inhibition and potentiation. *The Journal of Neuroscience*, *26*, 10051-10056.
- Levkovitz, Grisaru, N., & Segal, M. (2001). Transcranial magnetic stimulation and antidepressive drugs share similar cellular effects in rat hippocampus. *Neuropsychopharmacology*, *24*, 608-616.
- Löw, K., Crestani, F., Keist, R., Benke, D., Brünig, I., Benson, J. A., Fritschy, J.-M., et al. (2000). Molecular and neuronal substrate for the selective attenuation of anxiety. *Science*, *290*, 131-134.
- Madaan, V., & Wilson, D. R. (2009). Neuropeptides: Relevance in treatment of depression and anxiety disorders. *Drug News and Perspectives*, *22*, 319-325.

- Malberg, J. E., & Seiden, L. S. (1998). Small changes in ambient temperature cause large changes in 3,4-methylenedioxymethamphetamine (MDMA)-induced serotonin neurotoxicity and core body temperature in the rat. *The Journal of Neuroscience*, *18*, 5086-5094.
- Marks, D. M., Thanaseelan, J., & Pae, C.-U. (2009). Innovations in clinical research design and conduct in psychiatry: Shifting to pragmatic approaches. *Psychiatry Investigation*, *6*, 1-6.
- Marshall, R. D., Beebe, K. L., Oldham, M., & Zaninelli, R. (2001). Efficacy and safety of paroxetine treatment for chronic PTSD: A fixed-dose, placebo-controlled study. *American Journal of Psychiatry*, *158*, 1982-1988.
- Mathew, S. J., Keegan, K., & Smith, L. (2005). Glutamate modulators as novel interventions for mood disorders. *Revista Brasileira de Psiquiatria*, *27*, 243-248.
- Mathew, S. J., Vythilingam, M., Murrough, J. W., Zarate Jr., C. A., Feder, A., Luckenbaugh, D. A., Kinkead, B., et al. (2011). A selective neurokinin-1 receptor antagonist in chronic PTSD: A randomized, double-blind, placebo-controlled, proof-of-concept trial. *European Neuropsychopharmacology*, *21*, 221-229.
- Mavissakalian, M. R. (2003). Imipramine vs. sertraline in panic disorder: 24-week treatment completers. *Annals of Clinical Psychiatry*, *15*, 171-180.
- McCann, U. D., Szabo, Z., Scheffel, U., Dannals, R. F., & Ricaurte, G. A. (1998). Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. *Lancet*, *352*, 1433-1437.
- McGaugh, J. L. (2000). Memory: A century of consolidation. *Science*, *287*, 248-251.
- McGaugh, J. L., & Roozendaal, B. (2009). Drug enhancement of memory consolidation: Historical perspective and neurobiological implications. *Psychopharmacology*, *202*, 3-14.

- Mechoulam, R., Parker, L. A., & Gallily, R. (2002). Cannabidiol: An overview of some pharmacological aspects. *Journal of Clinical Pharmacology*, *42*, 11S-19S.
- Milekic, M. H., & Alberini, C. M. (2002). Temporally graded requirement for protein synthesis following memory reactivation. *Neuron*, *36*, 521-525.
- Miller, G. (2010). Is pharma running out of brainy ideas? *Science*, *329*, 502 -504.
- Möhler, H. (2012). The GABA system in anxiety and depression and its potential for novel therapeutics. *Neuropharmacology*, *62*, 42-53.
- Monfils, M.-H., Cowansage, K. K., Klann, E., & LeDoux, J. E. (2009). Extinction-reconsolidation boundaries: Key to persistent attenuation of fear memories. *Science*, 1167975.
- Montgomery, S. A., Sheehan, D. V., Meoni, P., Haudiquet, V., & Hackett, D. (2002). Characterization of the longitudinal course of improvement in generalized anxiety disorder during long-term treatment with venlafaxine XR. *Journal of Psychiatric Research*, *36*, 209-217.
- Muehlbacher, M., Nickel, M. K., Nickel, C., Kettler, C., Lahmann, C., Gil, F. P., Leiberich, P. K., et al. (2005). Mirtazapine treatment of social phobia in women. *Journal of Clinical Psychopharmacology*, *25*, 580-583.
- Mullins, C. D., Shaya, F. T., Meng, F., Wang, J., & Bron, M. S. (2006). Comparison of first refill rates among users of sertraline, paroxetine, and citalopram. *Clinical Therapeutics*, *28*, 297–305.
- Muravieva, E. V., & Alberini, C. M. (2010). Limited efficacy of propranolol on the reconsolidation of fear memories. *Learning and Memory*, *17*, 306-313.

- Nemeroff, C. B. (2003). Anxiolytics: Past, present, and future agents. *Journal of Clinical Psychiatry, 64*, 3-6.
- Norberg, M. M., Krystal, J. H., & Tolin, D. F. (2008). A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. *Biological Psychiatry, 63*, 1118-1126.
- Oetting, A. I., Levy, J. A., Weiss, R. D., & Murphy, S. A. (2011). Statistical methodology for a SMART design in the development of adaptive treatment strategies. In P. E. Shrout, K. M. Keyes, & K. Ornstein (Eds.), *Causality and psychopathology: Finding the determinants of disorders and their cures* (pp. 179-205). New York: Oxford University Press.
- Osuch, E. A., Benson, B. E., Luckenbaugh, D. A., Geraci, M., Post, R. M., & McCann, U. (2009). Repetitive TMS combined with exposure therapy for PTSD: A preliminary study. *Journal of Anxiety Disorders, 23*, 54-59.
- Otto, M. W., Basden, S. L., McHugh, R. K., Katak, K. M., Deckersbach, T., Cather, C., Goff, D. C., et al. (2009). Effects of D-cycloserine administration on weekly nonemotional memory tasks in healthy participants. *Psychotherapy and Psychosomatics, 78*, 49-54.
- Otto, M. W., McHugh, R. K., Simon, N. M., Farach, F. J., Worthington, J. J., & Pollack, M. H. (2010). Efficacy of CBT for benzodiazepine discontinuation in patients with panic disorder: Further evaluation. *Behaviour Research and Therapy, 48*, 720-727.
- Otto, M. W., Smits, J. A. J., & Reese, H. E. (2006). Combined psychotherapy and pharmacotherapy for mood and anxiety disorders in adults: Review and analysis. *Focus, 4*, 204-214.

- Paul, G. L. (1969). Behavior modification research: Design and tactics. In C. M. Franks (Ed.), *Behavior therapy: Appraisal and status* (pp. 29-62). New York: McGraw-Hill.
- Pitman, R. K., Sanders, K. M., Zusman, R. M., Healy, A. R., Cheema, F., Lasko, N. B., Cahill, L., et al. (2002). Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. *Biological Psychiatry, 51*, 189-192.
- Pittenger, C., Coric, V., Banasr, M., Bloch, M., Krystal, J. H., & Sanacora, G. (2008). Riluzole in the treatment of mood and anxiety disorders. *CNS Drugs, 22*, 761-786.
- Pollack, M. H., Hoge, E. A., Worthington, J. J., Moshier, S. J., Wechsler, R. S., Brandes, M., & Simon, N. M. (2011). Eszopiclone for the treatment of posttraumatic stress disorder and associated insomnia. *Journal of Clinical Psychiatry, 72*, 892-897.
- Pollack, M. H., Kinrys, G., Krystal, A., McCall, W. V., Roth, T., Schaefer, K., Rubens, R., et al. (2008). Eszopiclone coadministered with escitalopram in patients with insomnia and comorbid generalized anxiety disorder. *Archives of General Psychiatry, 65*, 551-562.
- Pollack, M. H., Mangano, R., Entsuah, R., Tzanis, E., Simon, N. M., & Zhang, Y. (2007). A randomized controlled trial of venlafaxine ER and paroxetine in the treatment of outpatients with panic disorder. *Psychopharmacology, 194*, 233-242.
- Pollack, M. H., Otto, M. W., Roy-Byrne, P. P., Coplan, J. D., Rothbaum, B. O., Simon, N. M., & Gorman, J. M. (2008). Novel Treatment Approaches for Refractory Anxiety Disorders. *Focus, 6*, 486-495.
- Post, A., & Keck, M. E. (2001). Transcranial magnetic stimulation as a therapeutic tool in psychiatry: What do we know about the neurobiological mechanisms? *Journal of Psychiatric Research, 35*, 193-215.

- Powers, M. B., Smits, J. A. J., Otto, M. W., Sanders, C., & Emmelkamp, P. M. G. (2009). Facilitation of fear extinction in phobic participants with a novel cognitive enhancer: A randomized placebo controlled trial of yohimbine augmentation. *Journal of Anxiety Disorders, 23*, 350-356.
- President's Council on Bioethics. (2003). *Beyond therapy: Biotechnology and the pursuit of happiness*. Washington, DC: Government Printing Office.
- Przybylski, J., Roulet, P., & Sara, S. J. (1999). Attenuation of emotional and nonemotional memories after their reactivation: Role of beta adrenergic receptors. *The Journal of Neuroscience, 19*, 6623-6628.
- Quirk, G. J., & Mueller, D. (2007). Neural mechanisms of extinction learning and retrieval. *Neuropsychopharmacology, 33*, 56-72.
- Rachman, S. (1990). The determinants and treatment of simple phobias. *Advances in Behaviour Research and Therapy, 12*, 1-30.
- Ravindran, L. N., & Stein, M. B. (2009). Pharmacotherapy of PTSD: Premises, principles, and priorities. *Brain Research, 1293*, 24-39.
- Ravindran, L. N., & Stein, M. B. (2010). The pharmacologic treatment of anxiety disorders. *Journal of Clinical Psychiatry, 71*, 839-854.
- Reneman, L., Lavalaye, J., Schmand, B., de Wolff, F. A., van den Brink, W., den Heeten, G. J., & Booij, J. (2001). Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy"): Preliminary findings. *Archives of General Psychiatry, 58*, 901-906.
- Ressler, K. J., Rothbaum, B. O., Tannenbaum, L., Anderson, P., Graap, K., Zimand, E., Hodges, L., et al. (2004). Cognitive enhancers as adjuncts to psychotherapy: Use of D-cycloserine

- in phobic individuals to facilitate extinction of fear. *Archives of General Psychiatry*, *61*, 1136-1144.
- Rickels, K., Downing, R., Schweizer, E., & Hassman, H. (1993). Antidepressants for the treatment of generalized anxiety disorder: A placebo-controlled comparison of imipramine, trazodone, and diazepam. *Archives of General Psychiatry*, *50*, 884-895.
- Rodriguez, C. I., Kegeles, L. S., Flood, P., & Simpson, H. B. (2011). Rapid resolution of obsessions after an infusion of intravenous ketamine in a patient with treatment-resistant obsessive-compulsive disorder. *The Journal of Clinical Psychiatry*, *72*, 567-569.
- Roesler, R., & Schröder, N. (2011). Cognitive enhancers: Focus on modulatory signaling influencing memory consolidation. *Pharmacology, Biochemistry, and Behavior*, *99*, 155-163.
- Rojas, J. C., Bruchey, A. K., & Gonzalez-Lima, F. (2012). Neurometabolic mechanisms for memory enhancement and neuroprotection of methylene blue. *Progress in Neurobiology*, *96*, 32-45.
- Rothbaum, B. O., & Davis, M. (2003). Applying learning principles to the treatment of post-trauma reactions. *Annals of the New York Academy of Sciences*, *1008*, 209-211.
- Rudolph, R. L., Fabre, L. F., Feighner, J. P., Rickels, K., Entsuah, R., & Derivan, A. T. (1998). A randomized, placebo-controlled, dose-response trial of venlafaxine hydrochloride in the treatment of major depression. *Journal of Clinical Psychiatry*, *59*, 116-122.
- Rush, A. J. (2007). Limitations in efficacy of antidepressant monotherapy. *The Journal of Clinical Psychiatry*, *68 Suppl 10*, 8-10.

- Rush, A. J., George, M. S., Sackeim, H. A., Marangell, L. B., Husain, M. M., Giller, C., Nahas, Z., et al. (2000). Vagus nerve stimulation (VNS) for treatment-resistant depressions: A multicenter study. *Biological Psychiatry*, *47*, 276-286.
- Sara, S. J. (2000). Retrieval and reconsolidation: Toward a neurobiology of remembering. *Learning and Memory*, *7*, 73-84.
- Schelling, G., Roozendaal, B., & De Quervain, D. J.-F. (2004). Can posttraumatic stress disorder be prevented with glucocorticoids? *Annals of the New York Academy of Sciences*, *1032*, 158-166.
- Schmitt, R., Gazalle, F. K., Lima, M.-cio S. de, Cunha, Ã., Souza, J., & Kapczinski, F. (2005). The efficacy of antidepressants for generalized anxiety disorder: A systematic review and meta-analysis. *Revista Brasileira de Psiquiatria*, *27*, 18 - 24.
- Schutters, S. I. J., Van Megen, H. J. G. M., Van Veen, J. F., Denys, D. A. J. P., & Westenberg, H. G. M. (2010). Mirtazapine in generalized social anxiety disorder: a randomized, double-blind, placebo-controlled study. *International Clinical Psychopharmacology*, *25*, 302-304.
- Siegmund, A., Golfels, F., Finck, C., Halisch, A., Raeth, D., Plag, J., & Stroehle, A. (2011). D-cycloserine does not improve but might slightly speed up the outcome of in-vivo exposure therapy in patients with severe agoraphobia and panic disorder in a randomized double blind clinical trial. *Journal of Psychiatric Research*, *45*, 1042-1047.
- Simon, N. M., Connor, K. M., Lang, A. J., Rauch, S., Krulewicz, S., LeBeau, R. T., Davidson, J. R. T., et al. (2008). Paroxetine CR augmentation for posttraumatic stress disorder refractory to prolonged exposure therapy. *The Journal of Clinical Psychiatry*, *69*, 400-405.

- Simon, N. M., Otto, M. W., Worthington, J. J., Hoge, E. A., Thompson, E. H., LeBeau, R. T., Moshier, S. J., et al. (2009). Next-step strategies for panic disorder refractory to initial pharmacotherapy. *Journal of Clinical Psychiatry, 70*, 1563-1570.
- Snyder, J. S., Soumier, A., Brewer, M., Pickel, J., & Cameron, H. A. (2011). Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. *Nature, 476*, 458-461.
- Strange, B. A. (2003). An emotion-induced retrograde amnesia in humans is amygdala- and adrenergic-dependent. *Proceedings of the National Academy of Sciences, 100*, 13626-13631.
- Tam, S. W., Worcel, M., & Wyllie, M. (2001). Yohimbine: A clinical review. *Pharmacology and Therapeutics, 91*, 215-243.
- Tancer, M., & Johanson, C.-E. (2003). Reinforcing, subjective, and physiological effects of MDMA in humans: A comparison with d-amphetamine and mCPP. *Drug and Alcohol Dependence, 72*, 33-44.
- Tedeschini, E., Fava, M., & Papakostas, G. I. (2011). Placebo-controlled, antidepressant clinical trials cannot be shortened to less than 4 weeks' duration. *The Journal of Clinical Psychiatry, 72*, 98-118.
- Thase, M. E., Friedman, E. S., Biggs, M. M., Wisniewski, S. R., Trivedi, M. H., Luther, J. F., Fava, M., et al. (2007). Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: A STAR*D report. *The American Journal of Psychiatry, 164*, 739-752.
- Urschel, H. C., Hanselka, L. L., & Baron, M. (2011). A controlled trial of flumazenil and gabapentin for initial treatment of methylamphetamine dependence. *Journal of Psychopharmacology, 25*, 254-262.

- Vaiva, G., Ducrocq, F., Jezequel, K., Averland, B., Lestavel, P., Brunet, A., & Marmar, C. R. (2003). Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma. *Biological Psychiatry, 54*, 947-949.
- Van Ameringen, M., Mancini, M., Oakman, C., Walker, J., Kjernisted, J., Chokka, P., Johnston, D., et al. (2007). Nefazodone in the treatment of generalized social phobia: A randomized, placebo-controlled trial. *Journal of Clinical Psychiatry, 68*, 288-295.
- Vollenweider, F. X., Gamma, A., Liechti, M., & Huber, T. (1998). Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naïve healthy volunteers. *Neuropsychopharmacology, 19*, 241-251.
- Vollenweider, F. X., & Komater, M. (2010). The neurobiology of psychedelic drugs: Implications for the treatment of mood disorders. *Nature Reviews: Neuroscience, 11*, 642-651.
- Vollenweider, F. X., Liechti, M. E., Gamma, A., Greer, G., & Geyer, M. (2002). Acute psychological and neurophysiological effects of MDMA in humans. *Journal of Psychoactive Drugs, 34*, 171-184.
- Wang, P. S., Lane, M., Olfson, M., Pincus, H. A., Wells, K. B., & Kessler, R. C. (2005). Twelve-month use of mental health services in the United States: Results from the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*, 629-640.
- Warden, D., Rush, A. J., Carmody, T. J., Kashner, T. M., Biggs, M. M., Crismon, M. L., & Trivedi, M. H. (2009). Predictors of attrition during one year of depression treatment: A roadmap to personalized intervention. *Journal of Psychiatric Practice, 15*, 113-124.
- Wassermann, E. M., & Lisanby, S. H. (2001). Therapeutic application of repetitive transcranial magnetic stimulation: A review. *Clinical Neurophysiology, 112*, 1367-1377.

- Watanabe, N., Churchill, R., & Furukawa, T. (2007). Combination of psychotherapy and benzodiazepines versus either therapy alone for panic disorder: A systematic review. *BMC Psychiatry*, *7*, 18.
- Webb, A. J. S., Fischer, U., & Rothwell, P. M. (2011). Effects of β -blocker selectivity on blood pressure variability and stroke: A systematic review. *Neurology*, *77*, 731-737.
- Westra, H. A., Stewart, S. H., & Conrad, B. E. (2002). Naturalistic manner of benzodiazepine use and cognitive behavioral therapy outcome in panic disorder with agoraphobia. *Journal of Anxiety Disorders*, *16*, 233-246.
- Zakzanis, K. K., & Young, D. A. (2001). Memory impairment in abstinent MDMA ("Ecstasy") users: A longitudinal investigation. *Neurology*, *56*, 966-969.
- Zarate, C. A., Jr, Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., Charney, D. S., et al. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry*, *63*, 856-864.
- Zobel, A. W., Nickel, T., Künzel, H. E., Ackl, N., Sonntag, A., Ising, M., & Holsboer, F. (2000). Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: The first 20 patients treated. *Journal of Psychiatric Research*, *34*, 171-181.
- Zuardi, A. W. (2008). Cannabidiol: From an inactive cannabinoid to a drug with wide spectrum of action. *Revista Brasileira de Psiquiatria*, *30*, 271-280.
- Zwanzger, P., Diemer, J., & Jabs, B. (2008). Comparison of combined psycho- and pharmacotherapy with monotherapy in anxiety disorders: Controversial viewpoints and clinical perspectives. *Journal of Neural Transmission*, *116*, 759-765.

Table 1. *Non-Psychiatrists' Guide to Pharmacotherapy Interventions for the Anxiety Disorders*

	SP	PTSD	PD	SAD	GAD	OCD
Selective Serotonin Reuptake Inhibitor (SSRI)		1	1	1	1	1 ^a
Shift to Different SSRI or SNRI		2	2	2	2	2
Augmentation with Additional SSRI or SNRI		3	3	3	3	3
Other antidepressants (MAOIs, other) ^c		4	3	3	2	4
Tricyclic Antidepressants		3	2	3	3	1 ^b
Augmentation with Atypical Antipsychotics		4	4	4	4	4
Anticonvulsants			4	4	4	
Azapirones					3	
Beta Blockers	2			3		
Benzodiazepines	2		3	3	4	

Notes.

1 = First-line intervention: multiple randomized control trials (RCTs) showing efficacy.

2 = Secondary intervention: often used as an intervention for non- or partial-response of first-line intervention, with some RCTs showing efficacy, though evidence may be mixed.

3 or 4 = Alternative intervention after 1st and 2nd line interventions, often with less RCT support or more significant side effect profile.

^a Higher dosage than for other anxiety disorders

^b Clomipramine (Anafranil)

SP = specific phobia; PTSD = posttraumatic stress disorder; PD = panic disorder; SAD = social anxiety disorder; GAD = generalized anxiety disorder; OCD = obsessive-compulsive disorder; SNRI = serotonin norepinephrine reuptake inhibitor; MAOI = monoamine oxidase inhibitor