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Pharmacological 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 two broad approaches to the development of innovative anxiety treatments: the continued development of drugs based on specific neuroreceptors and the pharmacological manipulation of fear-related memory. We highlight directions for future research, as neither of these approaches is ready for routine clinical use.

Keywords

Pharmacotherapy; Anxiety disorders; Antidepressants; Memory consolidation; Psychedelics

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

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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, and psychedelic and narcotic drugs. The results have largely been disappointing so far; in many cases, however, we identify concrete questions for future research, many of which may 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. The few studies comparing SNRIs to SSRIs show similar responses. 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 Dysphoric Disorder, and 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 30–50% 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 2–4 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. 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 2 and 6 weeks to produce an initial "partial" 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 4–6 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 is consistent with this in 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 10–12 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 (i.e., not having achieved remission). 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" to 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 in whom, the placebo effect contributes to antidepressant response. In a recent meta-analysis, Fournier et al. (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. However, a recent study with a much larger and more complete database suggests that initial severity of depression is unrelated to antidepressant response (Gibbons, Hur, Brown, Davis, & Mann, 2012). The relationship of response to initial severity should be systematically examined in the anxiety disorders as well.

Most data on the causes of treatment nonresponse, response, and relapse are correlational. Even classic randomized controlled trials (RCTs) do not reveal what causes these classes of effects at the level of individual patients. Meta-analyses can provide some guidance through estimates of individual versus combined treatment effects, but these studies often 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, Levy, Weiss, & Murphy, 2011). This novel approach should be used to examine

the optimal treatment sequence for partial or nonresponders to initial anxiety treatments. Other multi-stage clinical trial designs have been developed that allow investigators to estimate true drug response from placebo response at the individual level (e.g., Marks, Thanaseelan, & Pae, 2009).

2.1.2. Other antidepressants—Extensive studies of TCAs show that they have similar efficacy to SSRIs for panic disorder (PD; e.g., Mavissakalian, 2003) and generalized anxiety disorder (GAD; e.g., Schmitt et al., 2005). 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, including dry mouth, blurred vision, constipation, urinary retention, cardiac arrhythmia, tachycardia, sedation, postural hypotension, dizziness, and headache. Nonetheless, TCAs may 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 foods that contain tyramine (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 Megen, 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 by acting on a chloride ion channel (Davidson, 1989). They were initially considered first-line treatments for anxiety because of their tolerability and equal efficacy to TCAs, but 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 potent, short-term effects (e.g., flying on an 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 (Westra, Stewart, & Conrad, 2002), 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). However, for select individuals with significant residual anxiety after antidepressant treatment, these agents may help achieve total symptom remission.

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 (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 dependence (Urschel, Hanselka, & Baron, 2011).

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 and hands trembling) of anxiety within 30–60 min; 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 2–4 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). Because 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 6 weeks and will add a different agent if symptoms do not fully remit within 12 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 (e.g., addition of an atypical antipsychotic medication such as risperidone, olanzapine, or quetiapine).

Very few studies have empirically evaluated the efficacy of 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 an (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). 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. A study of similar scale has not been conducted in the anxiety disorders.

For severe, treatment-resistant cases of anxiety, augmentation of the antidepressant with an atypical antipsychotic (e.g., risperidone and quetiapine) has been shown to be effective. This strategy appears to be effective for OCD (Ipser et al., 2006; Komossa et al., 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, & Rüther, 2007; Otto, Smits, & Reese, 2005), 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., 2005) and should be reserved for patients with severe anxiety who require medication (Zwanzger, Diemer, & Jabs, 2008). However, limited data have 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 first-line 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 proved to be incrementally more effective than SSRIs.

Similarly, GABA-A subunits (e.g., α_2), which mediate the anxiolytic effect of benzodiazepines (Löw et al., 2000), have been targeted. However, the development of some α_2 agents was terminated due to adverse effects (Möhler, 2012), and none have 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 GAD and PTSD, eszopiclone produced greater specific anxiolytic effects compared to placebo when added to an SSRI (Pollack et al., 2011; Pollack, Kinrys, et al., 2008; Pollack, Otto, 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 monamine 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 & Schröder, 2011).

Substance P, a member of the tachykinin family of neuropeptides, acts on brain tachykinin (NK_1) receptors involved in anxiety and stress responses (Holmes et al., 2003). Clinical trials of NK_1 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). Corticotropinreleasing factor (CRF), a neuropeptide found in amygdala and other key anxiety-related areas, acts on the CRF_1 and CRF_2 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 has failed to show consistent evidence for efficacy and safety (Gutman, Owens, Skelton, Thrivikraman, & 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 investment of time and capital for a 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 is typically administered immediately before (or after) exposure therapy sessions on a short-term basis and has no direct anxiolytic effects. 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 session 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 (de Kleine, Hendriks, Kusters, Broekman, & van Minnen, 2012; Siegmund et al., 2011).

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 did not augment exposure therapy in comparison to placebo at post-treatment, but did augment exposure therapy at 1-week follow-up. The side effect profile of yohimbine includes increased anxiety (one of the effects it is intended to prevent), blood pressure, and 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 & Drug Administration, 2011). Initial human trials of low-dose, oral 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 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 emotional memories 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 the pathogenesis 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 destabilizing process in which remembering a memory makes the memory temporarily susceptible to new information (Przybyslawski, Roullet, & 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 the 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 eight 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, this side effect may be 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, Aerni, Schelling, & Roozendaal, 2009; de Quervain et al., 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, whereas memory consolidation is a well established phenomenon, 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 coupled with long-duration exposure (Cain, Blouin, & Barad, 2004), lead 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? 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 to decreased amygdala activation (Bergamaschi et al., 2011; Vollenweider & Kometer, 2010; Vollenweider, Liechti, Gamma, Greer, & Geyer, 2002), effects that appear to be the opposite of baseline abnormalities found in various anxiety disorders. 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 (1.5–1.7 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 adjunctive MDMA might provide a critical window during which it could improve the learning and habit change that occur during psychotherapy. This benefit might be realized in as few as one to three drug sessions, according to Doblin (2002). These hypotheses are premature given the available data, and they 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 postadministration 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 °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 tolerated, 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, the 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, de, 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 to evaluate 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. 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 "on average, 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 innovations in drug development to occur.

New pharmacological treatments for anxiety are being developed along two broad paths: continued drug development focused on highly specific neuroreceptor targets and the pharmacological manipulation of memory to enhance adaptive processes and block maladaptive processes. 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 their efficacy and safety in animal models have rarely 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 a better return on investment.

Pharmacological manipulation of memory and learning is a relatively new and highly innovative field. Research has shown such manipulation to be not only theoretically plausible but also 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.[1] Much basic research is needed to determine the generality of these drugs' effects on nontarget memory processes and their long-term efficacy as augmenting agents. 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.

[1]This argument also applies to many other novel medications we have discussed. Most new medications are first tested in patients who could instead be treated with existing first-line medications, such as SSRIs. In most cases, however, a more efficient use of precious research funds would be to test new medications exclusively in patients who have not responded to initial treatment.

How can future research facilitate progress in the development and application of pharmacological treatments for anxiety disorders? The most critical questions on the application side concern the optimal parameters and sequencing of existing treatments as well as 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 their patients' unique genetic profiles. On the novel treatment development side, basic questions concerning 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.

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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	

Note: 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.
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.

[a]Higher dosage than for other anxiety disorders.

[b]Clomipramine (Anafranil).

[c]Examples include bupropion (Wellbutrin), mirtazpine (Remeron), nefazodone (Serzone).