

New and Recent Drugs for Anxiety Disorders

Yujuan Choy, MD, and Franklin R. Schneier, MD

ABSTRACT

Serotonin reuptake inhibitors and benzodiazepines are currently the mainstays of treatment for anxiety disorders. Recent advances in novel anxiolytic agents with mechanisms of action at the γ -amino-butyric acid-ergic, serotonergic, and glutamatergic systems have garnered a great deal of interest as alternative treatment options. There has also been considerable research in expanding the indications of established agents, including antipsychotics and anti-convulsants, as monotherapy or adjunctive treatment. This article updates clinicians with the findings of recent controlled trials that examine the efficacy of novel drug treatments of anxiety disorders.

INTRODUCTION

Serotonin reuptake inhibitors (SRIs) are currently the first-line pharmacotherapy for most anxiety disorders, including obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), panic disorder, and social anxiety disorder (SAD). However, a significant number of patients do not fully respond to an adequate trial of an SRI. For example, at least 40% to 60% of OCD patients still exhibit symptoms after treatment.¹ Benzodiazepines are widely used for panic disorder, GAD, and SAD, but they are associated with unwanted cognitive side effects, a withdrawal syndrome, and potential for abuse. Use of tricyclic antidepressants and monoamine oxidase inhibitors is limited by their

Needs Assessment: Serotonin reuptake inhibitors and benzodiazepines are currently the mainstays of treatment for anxiety disorders. However, a significant number of patients do not fully respond to these drugs, and benzodiazepines are associated with unwanted side effects. This article updates clinicians with recent research findings of established and novel agents for the treatment of anxiety disorders.

Learning Objectives:

- Understand the need for new medication treatment of anxiety disorders
- Identify types of established drugs that may be helpful in anxiety disorders
- Identify novel agents that show efficacy in anxiety disorders

Target Audience: Primary care physicians and psychiatrists.

CME Accreditation Statement: This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Mount Sinai School of Medicine and MBL Communications, Inc. The Mount Sinai School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation: The Mount Sinai School of Medicine designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credit(s)*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Faculty Disclosure Policy Statement: It is the policy of the Mount Sinai School of Medicine to ensure objectivity, balance, independence, transparency, and scientific rigor in all CME-sponsored educational activities. All faculty participating in the planning or implementation of a sponsored activity are expected to disclose to the audience any relevant financial relationships and to assist in resolving any conflict of interest that may arise from the relationship. Presenters must also make a meaningful disclosure to the audience of their discussions of unlabeled or unapproved drugs or devices. This information will be available as part of the course material.

This activity has been peer-reviewed and approved by James C.-Y. Chou, MD, associate professor of psychiatry at the Mount Sinai School of Medicine, and Norman Sussman, MD, editor of *Primary Psychiatry* and professor of psychiatry at New York University School of Medicine. Review Date: November 20, 2008.

Dr. Sussman reports no affiliation with or financial interest in any organization that may pose a conflict of interest. Dr. Chou receives honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, and Pfizer.

To receive credit for this activity: Read this article and the two CME-designated accompanying articles, reflect on the information presented, and then complete the CME posttest and evaluation found on page 81. To obtain credits, you should score 70% or better. Early submission of this posttest is encouraged: please submit this posttest by December 1, 2010 to be eligible for credit. Release date: December 1, 2008. Termination date: December 31, 2010. The estimated time to complete all three articles and the posttest is 3 hours.

Dr. Choy is in private practice, is staff psychiatrist at the University of California, Irvine (UCI) Counseling Center, and is assistant clinical professor of psychiatry at the UCI Department of Psychiatry and Human Behavior. Dr. Schneier is associate professor of clinical psychiatry at Columbia University College of Physicians and Surgeons and research psychiatrist at the Anxiety Disorders Clinic at the New York State Psychiatric Institute in New York City.

Disclosures: Dr. Choy reports no affiliation with or financial interest in any organization that may pose a conflict of interest. Dr. Schneier is on the Scientific Advisory Board of Jazz and has received grant support from Forest and Pfizer.

Off-Label Disclosure: This article includes discussion of the following unapproved medications for anxiety disorders: haloperidol, risperidone, quetiapine, olanzapine, divalproex, topiramate, levetiracetam, tiagabine, lamotrigine, gabapentin, pregabalin, abercarnil, ocinaplon, gepirone, flesinoxan, lesopitron, ondansetron, deramciclane, D-cycloserine, LY354740, and LY544344.

Please direct all correspondence to: Yujuan Choy, MD, 4199 Campus Drive, Suite 550, Irvine, California 92612; Tel: 949-725-2951; Fax: 949-612-1569; E-mail: choyMD@gmail.com.

adverse side effect profiles. As a result, there has been a growing interest in evaluating anxiolytic properties of established drugs (eg, antipsychotics and anticonvulsants) and of novel agents that modify the γ -aminobutyric acid (GABA)-ergic, serotonergic, and glutamatergic receptor complexes. This article reviews published controlled studies that examine the efficacy of established and new drugs for the treatment of anxiety disorders. Most of the agents mentioned are not Food and Drug Administration approved for anxiety disorders, with the exception of duloxetine (approved for GAD) and fluvoxamine controlled release (CR; approved for OCD and SAD).

LITERATURE SEARCH METHOD

A search of MEDLINE from January 2004 to March 2008 was conducted using the search terms: phobic disorders, anxiety disorders, social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder, obsessive-compulsive disorder, and panic disorder. Each of these disorders were combined with the terms for the antidepressants (duloxetine, fluvoxamine), antipsychotics (haloperidol, risperidone, quetiapine, olanzapine, ziprasidone, aripiprazole), antiepileptics (anticonvulsants, divalproex, carbamazepine, phenytoin, topiramate, levetiracetam, tiagabine, lamotrigine, gabapentin, pregabalin) and novel agents (abercarnil, ocinaplon, gepirone, flesinoxan, lesopitron, ondansetron, deramciclane, D-cycloserine, LY354740, LY544344). For agents that yielded controlled studies, and selected agents that did not yield studies (eg, haloperidol, lamotrigine), a repeat search was conducted for articles from 1990–2004. Only controlled trials in adults (≥ 18 years of age) that have a placebo group or another active agent (ie, active comparison trial) and published in English were included.

For most of the studies, the response rate is based on the clinician's ratings of much or very much improvement in the Clinical Global Impression (CGI) scale (ie, CGI response rate). Response rate can also be measured by the proportion of treatment responders based on the primary outcome measure, which is usually a scale specific to the particular disorder studied. For example, response rate for GAD can alternatively be measured by the number of patients who achieved a 50% decrease in the Hamilton Rating Scale for Anxiety (HAM-A). Response rate for OCD is commonly measured by the number of patients who achieved a 25% or 35% decrease in the Yale-Brown Obsessive Compulsive Scale. For consistency across the studies, the CGI response rate was reported when available. When there were inconsistencies in the response rate as measured by the CGI versus the primary outcome measures, this was noted in the article.

ANTIPSYCHOTICS

Numerous controlled trials have examined the efficacy of antipsychotics in treatment-resistant anxiety disorders, most often as an adjunct to SRI treatment. The best-established findings are for OCD, showing that 30% to 50% of OCD patients respond to antipsychotic augmentation, with better results for haloperidol and risperidone. Response can be apparent within 4 weeks. Treatment responses from other antipsychotics, such as quetiapine and olanzapine, have been inconsistent for OCD. For other anxiety disorders, including PTSD and SAD, there is limited evidence for the efficacy of antipsychotic treatments, with studies limited by small sample sizes and high placebo response rates.

Haloperidol

Haloperidol appears to be an effective adjunct for treatment-resistant OCD based on a small controlled study² of 34 patients. In this study, the addition of haloperidol to fluvoxamine over 4 weeks resulted in a 65% response rate, compared to 0% in the placebo group. There were no drop-outs, but 29% of the haloperidol patients required propranolol for akathisia despite prophylactic benztropine.

Risperidone

Three controlled studies showed that risperidone augmentation of SRIs over a period of 6–8 weeks decreased OCD symptoms in treatment-resistant patients, with a response rate of approximately 30% to 50%.^{3–5} One of the studies did not achieve statistical significance (40% vs. 0% response rate in risperidone and placebo group, respectively), but this might have been limited by the lack of power ($n=8$ per group).⁴ The presence of comorbid tic disorder or schizotypal personality disorder did not predict response, even though antipsychotics are considered helpful with these symptoms.³ Those who failed ≥ 2 medication trials³ or had less insight into their illness⁴ had poorer treatment outcomes. Interestingly, risperidone was helpful only in treatment-resistant cases. In patients with an initially good response, adding risperidone resulted in a weakened SRI effect.⁵

Risperidone treatment of PTSD has shown less consistent findings. Three studies reported that risperidone was helpful in alleviating PTSD symptoms in combat-related⁶ and non-combat-related PTSD,^{7,8} whether as an adjunct or as monotherapy. Two studies reported negative results.^{9,10} In these studies, risperidone did not decrease aggressive tendencies although it decreased irritability,⁹ and it did not decrease global PTSD symptoms or associated psychotic symptoms.¹⁰

In GAD, the addition of risperidone in treatment-resistant patients did not improve anxiety symptoms.^{11,12} One of these studies had a large sample size ($n=417$).¹²

Risperidone was generally well tolerated in anxiety disorder patients at a dosage range of 0.5–4.0 mg/day, with most common side effects of sedation and increased appetite. Akathisia and extrapyramidal symptoms were reported in some studies. Since none of the studies extended use of risperidone beyond 12 weeks, the rate of potential long-term adverse effects such as tardive dyskinesia and weight gain in anxiety disorder patients is unknown.

Quetiapine

Four small, controlled studies^{13–16} have examined the efficacy of quetiapine as an augmenting agent for treatment-resistant OCD. Two studies^{13,14} reported positive results with response rates of 40%¹³ and 71%,¹⁴ whereas two subsequent studies^{15,16} showed no difference between quetiapine and placebo. In one of the negative studies,¹⁵ there was an unusually high placebo response rate of 47% (compared to 40% in treatment group). Quetiapine was well tolerated with few drop-outs secondary to side effects. Additionally, quetiapine was not shown to be effective as a monotherapy treatment of SAD.¹⁷ Approximately 40% of quetiapine patients responded to treatment, compared to 0% in placebo, but this was not statistically significant in a sample of 15 patients.

Olanzapine

Olanzapine yielded an approximately 40% response rate in two studies^{18,19} when used as an adjunct in treatment-refractory OCD patients. Whereas one study¹⁸ found significant results with a 46% response to drug versus 0% placebo response rate, the other study¹⁹ found equivalent response rates of 41% for drug and placebo.

In the treatment of PTSD, one augmentation study²⁰ also reported a high placebo response rate of 60%, which was equal to that of the olanzapine-treated group. In another study,²¹ olanzapine resulted in a greater improvement of PTSD-specific symptoms, but there was no significant difference in global response rates between drug and placebo (30% vs. 11%, respectively).

Two studies^{22,23} showed promising results for olanzapine as an augmentation agent in GAD²² and as monotherapy in SAD.²³ In the GAD study, there was a significantly higher rate of CGI responders to adjunctive olanzapine (56%) compared to placebo (8%). However, there was no significant difference in the primary outcome measure (HAM-A). In the SAD study, there was no significant difference in CGI response

rates between medication and placebo (43% vs. 0%), but the olanzapine-treated patients had superior outcomes based on the social anxiety-specific scales.

Olanzapine was generally tolerated at doses from 2.5–20 mg/day, but patients complained of weight gain and sedation.

ANTICONVULSANTS

Antiepileptics have also received considerable attention in the treatment of anxiety disorders, particularly the new-generation anticonvulsants, but with mixed findings. The benzodiazepines, which have anticonvulsant properties, have long been a mainstay of anxiety disorder treatment. Of the other older anticonvulsants, only divalproex has been studied in controlled trials,²⁴ but it did not yield any effect in the treatment of PTSD. Of the new-generation anticonvulsants, topiramate, levetiracetam, and tiagabine have not shown any efficacy in the treatment of anxiety disorders. Topiramate was not effective in the treatment of PTSD whether as a monotherapy²⁵ or as an adjunct to antidepressants and group therapy.²⁶ It was associated with significant cognitive side effects, and the drop-out rate was 55% in one of the studies.²⁶ Likewise, levetiracetam did not demonstrate any efficacy in the treatment of SAD.²⁷ Tiagabine is a selective GABA-reuptake inhibitor²⁸ that was ineffective in two large placebo-controlled trials^{28,29} for the treatment of PTSD²⁹ and GAD,²⁸ as well as in a small ($n=40$) active comparison trial for GAD.³⁰

However, several other new-generation anticonvulsants—lamotrigine, gabapentin, and pregabalin—appeared to have some benefit. In a small study³¹ of 15 patients, lamotrigine was superior to placebo in the treatment of PTSD, with 50% of lamotrigine-treated patients versus 25% of placebo patients responding to treatment. Lamotrigine was well tolerated with mild side effects that included drowsiness, poor concentration, sweating, unsteadiness, forgetfulness, and sexual side effects.

Gabapentin and pregabalin are structural analogs of GABA, but their mechanism of action is thought to involve selective binding to the $\alpha_2\delta$ subunit of voltage-dependent calcium channels in the central nervous system.³² Both drugs are predominately excreted by the kidney, and do not have significant drug-drug interactions.

There are two controlled studies^{33,34} of gabapentin in the treatment of anxiety disorders. In panic disorder, gabapentin was not effective in reducing panic symptoms. In SAD, gabapentin was more effective than placebo, but the amount of improvement was modest. Patients were still quite symptomatic at endpoint (average Liebowitz Social Anxiety Scale of 60) and only 32% of the patients had a >50% reduction in SAD symptoms. In addi-

tion, 38% of the gabapentin-treated patients dropped out of the study because of adverse effects or lack of efficacy. Most common side effects included sedation, dizziness, and dry mouth.

Pregabalin has been approved in Europe as a treatment for GAD. Five large controlled trials³⁵⁻³⁹ reported that pregabalin was effective in the acute treatment of GAD. Montgomery and colleagues³⁹ noted that one negative study was not published. All of the published studies reported a statistically significant reduction of general anxiety with a 46% to 61% response rate. In addition, one study⁴⁰ reported that pregabalin was efficacious during a 6-month maintenance treatment of GAD; acute-responders relapsed at a lower rate compared to placebo over a 24-week period (42% vs. 65%, respectively). Pregabalin was also investigated as a treatment of SAD.⁴¹ In patients with SAD, pregabalin 600 mg decreased social anxiety symptoms compared to placebo. Common side effects included dizziness, somnolence, headaches, dry mouth, blurry vision, incoordination, ataxia, and weight gain. There were no significant withdrawal symptoms when medication was discontinued.

NOVEL GABAERGIC AGENTS

Currently, benzodiazepines are the only FDA-approved, anxiolytic agents with a GABAergic mechanism of action. Other GABAergic agents have been investigated as potential anxiolytics, but two of these agents failed to show efficacy (tiagabine²⁸⁻³⁰ and abercarnil⁴²). Another agent (ocinaplon) was effective in decreasing anxiety based on one study.⁴³ Neither abercarnil nor ocinaplon are commercially available at present.

NEW INDICATIONS FOR SSRI/SNRI AGENTS

Recently, duloxetine and a controlled-release formulation of fluvoxamine received new FDA indications for anxiety disorders.

Duloxetine

Duloxetine is a serotonin norepinephrine reuptake inhibitor (SNRI) that received FDA approval for the treatment of GAD in 2007 based on three large placebo-controlled trials.⁴⁴⁻⁴⁶ A pooled analysis showed a response rate of 51% in duloxetine-treated patients compared to 33% in placebo.⁴⁷ Response was defined as $\geq 50\%$ reduction from baseline in HAM-A total score at endpoint, and remission was defined as a HAM-A total score ≤ 7 at endpoint. Remission was achieved in 30% of patients treated with duloxetine. The efficacy of duloxetine appeared to be comparable to that

of venlafaxine and SRIs, but no statistical comparison was conducted.⁴⁶ Duloxetine 60 mg and 120 mg were equally effective, but the higher dose resulted in greater adverse effects.⁴⁴ Duloxetine was also effective in the treatment of clinically significant pain, with improved GAD symptoms correlating with better pain control.⁴⁸

The most common side effects included nausea/vomiting, dizziness, sedation, fatigue, sweating, dry mouth, insomnia, constipation, and decreased libido. Discontinuation symptoms were absent in one study,⁴⁶ but problematic in another study.⁴⁴

Fluvoxamine Controlled Release

Fluvoxamine CR received FDA approval for the treatment of SAD and OCD in 2008. There are two large placebo-controlled trials in patients with SAD.^{49,50} One study⁴⁹ was positive but the response rate was not impressive: 33.9% in fluvoxamine CR versus 16.7% in placebo were considered treatment responders. The other study⁵⁰ was essentially negative with no difference in response rates between fluvoxamine CR and placebo groups (48% vs. 44%). For those who did respond, continued treatment for an additional 12 weeks resulted in further improvement, but the treated group still was no different from placebo (80% vs. 74%).⁵¹

During acute treatment, common side effects included headaches, nausea, somnolence, and insomnia, but there was no notable weight gain or sexual side effects. The incidence of sexual side effects became more prominent when the study was extended to 24 weeks (16% in fluvoxamine CR vs. 5% in placebo). Discontinuation symptoms or drug-drug interactions were not investigated.

There is one large placebo-controlled trial⁵² of fluvoxamine-CR for the treatment of OCD. Patients treated over a 12-week period with fluvoxamine CR 100–300 mg showed greater improvement in OCD symptoms compared to that of placebo, and significant differences were observed by week 2 of the study. A treatment response was achieved in 44% of fluvoxamine CR-treated patients, compared to 23% in placebo. Side effects were similar to those noted in the SAD studies, including sexual side effects. A higher percentage of fluvoxamine CR patients dropped out because of side effects (19% vs. 6% in placebo).

OTHER SEROTONERGIC AGENTS

Drugs that act on different serotonergic receptors have been investigated in the treatment of anxiety disorders.

Given the efficacy of buspirone in the treatment of GAD, other agents with partial or full agonist activity at the serotonin (5-HT)_{1A} receptors have been investigated as a poten-

tial non-benzodiazepine anxiolytic. However, these agents—gepirone,⁵³ flesinoxan,⁵⁴ and lesopitron⁵⁵—have not been shown to be efficacious and are not currently marketed.

Ondansetron is a selective antagonist at the 5-HT₃ subtype of serotonin receptors that is used in the treatment of nausea and vomiting in chemotherapy patients. A low dose of ondansetron (1 mg) was effective in reducing anxiety in GAD patients.⁵⁶ It was well tolerated with mild side effects, including cold-like symptoms, constipation, and headaches.

Deramciclane is an unmarketed novel anxiolytic agent with specific antagonism at 5-HT_{2A/2C} receptors. In a recent study,⁵⁷ deramciclane 60 mg decreased anxiety compared to placebo in patients with GAD. Medication was well tolerated with overall incidents of side effects comparable to placebo. Abrupt discontinuation did not result in withdrawal symptoms.

GLUTAMATERGIC AGENTS

Glutamate is a major mediator of excitatory neurotransmission in the central nervous system. The two major glutamate receptors are ionotropic receptors, which mediate fast synaptic transmission via ion-gated channels and include the *N*-methyl-D-aspartate (NMDA) receptor group, and metabotropic receptors, which mediate slower synaptic transmission via second messengers such as cyclic adenosine monophosphate. These receptors have recently been targeted for the development of anxiolytic agents.

D-cycloserine

D-cycloserine is a partial NMDA receptor agonist that was initially developed as a broad-spectrum antibiotic for tuberculosis. It is unique in that its application to anxiety disorders grew out of animal studies showing that it plays an important role in facilitating extinction of conditioned fear.⁵⁸ Unlike anxiolytics, D-cycloserine does not appear to directly reduce anxiety symptoms, but instead enhances learning that takes place during therapeutic exposure to feared situations. It has been studied only as an augmentation to behavioral therapy in which it was administered 1–4 hours prior to exposure sessions at doses ranging from 50–500 mg.

In the first clinical study,⁵⁹ D-cycloserine expedited treatment response in patients with height phobia, and treatment gains were maintained at 1- and 3-month follow-up. Since this trial, a number of other studies in SAD,^{60,61} spider fear,⁶² and OCD⁶³⁻⁶⁵ have been completed. Two placebo-controlled studies^{60,61} demonstrated that D-cycloserine was affective in augmenting the effects of

5-sessions of behavioral therapy for public-speaking fears in patients with SAD. Treatment gains were maintained at 1-month follow-up.⁶⁰ However, D-cycloserine did not affect treatment outcome in participants with subclinical spider fears in which >90% of participants responded to exposure therapy alone.⁶²

In two of three augmentation studies^{63,64} for OCD, D-cycloserine decreased OCD symptoms relative to pill placebo during mid-treatment, but this positive effect was lost by the end of treatment. In the other OCD study,⁶⁵ both D-cycloserine and pill-placebo patients responded equally well over time and at treatment endpoint. In these OCD studies, a full course of exposure therapy was given (up to 12 sessions or until a treatment response was achieved), whereas in the previous studies with height phobia and SAD, therapy was comparatively shorter, between 2–5 sessions. This suggests the possibility that prolonged and repeated administration of D-cycloserine during a full course of behavioral therapy may not be as effective as augmentation of an abbreviated course of exposure therapy. Alternatively, OCD may be more resistant to treatment augmentation. Nonetheless, a greater percentage of D-cycloserine patients completed treatment compared to pill placebo patients (93% vs. 65%),⁶³ suggesting that D-cycloserine may increase patient adherence to effective treatment. D-cycloserine was generally well tolerated with mild gastrointestinal distress, dizziness, fatigue, and anxiety. Given the preliminary results, it may be premature to use D-cycloserine in clinical settings at this time. Further controlled trials are still needed to establish the efficacy of D-cycloserine augmentation compared to standard cognitive-behavioral therapy alone.

LY354740/ LY544344

LY354740 is a metabotropic glutamate type 2 receptor agonist that negatively inhibits glutamate release and controls the release of GABA and other neurotransmitters.⁶⁶ In a small controlled study⁶⁶ of panic disorder patients, this agent performed worse compared to placebo. Interestingly, paroxetine 60 mg also did not fair better than placebo. However, LY354740 was reported to be efficacious in the treatment of GAD in a large placebo-controlled trial,⁶⁷ and its efficacy was comparable to lorazepam but with better tolerability. More recently, LY544344, a prodrug that increases LY354740 bioavailability, was shown to be effective in the acute treatment of GAD.⁶⁷ Unfortunately, this trial was prematurely terminated secondary to concerns over convulsions reported in animal studies. In the clinical study, no convulsions were observed, and LY544344 was well tolerated with minimal side effects.

CONCLUSION

The current interest in and need for new treatments for anxiety disorders has led to a search for expanding the use of established drugs as well as investigation of novel agents that modulate different neurotransmitter systems thought to influence anxiety symptoms. Recently, duloxetine received an FDA indication for GAD, and fluvoxamine CR was approved for OCD and SAD. All other agents discussed in this article are used off-label or have not been marketed.

Both antipsychotics and anticonvulsants have been considered in the treatment of anxiety disorders. Numerous controlled trials have indicated that treatment-resistant OCD patients may benefit from antipsychotic augmentation, particularly with haloperidol and risperidone. Studies for the antipsychotic treatment of other anxiety disorders have been less encouraging. Risperidone has not been effective in GAD and has limited benefits in PTSD; quetiapine has not been beneficial in SAD; and responses to olanzapine in patients with PTSD, GAD, and SAD have been inconsistent. Of the anticonvulsants studied, there is strong evidence for the efficacy of pregabalin in the acute and possibly maintenance treatment of GAD, and there is limited evidence for the efficacy of gabapentin in SAD and lamotrigine in PTSD.

In the treatment of GAD, the investigative GABAergic agent ocinaplon appeared beneficial, but its counterpart abercarnil was not effective. The novel serotonergic 5-HT_{1A} partial and full agonists either worsened or did not have any effect on anxiety symptoms. Ondansetron appeared to be effective, but findings of the investigative 5-HT_{2A/2C} receptor antagonist (deramciclone) were inconsistent.

Lastly, D-cycloserine showed promising results in enhancing the efficacy of behavioral therapy for height phobia and performance anxiety. However, it did not have any benefit as an augmenting agent during a longer treatment period in patients with OCD. Repeated administration of D-cycloserine may not be as effective as brief administration in enhancing learning and fear extinction during exposure therapy.

A survey of new and recent drugs for the treatment of anxiety disorders leaves much room for further investigation. Although there has been progress in some areas, such as antipsychotic augmentation of treatment-resistant OCD and use of novel agents for GAD, our arsenal of drugs for the treatment of anxiety disorders is currently still limited. Some potential anxiolytic targets that have been long-associated with anxiety in animal models, such as corticotropin releasing factor and neuropeptide Y, have not yet yielded published, controlled efficacy trials. Glutamatergic drugs are another area of active investigation. While we do have effective drug and psychotherapy treatments for each of the anxiety disorders, the field is still waiting for a treatment break-through in the order of magnitude as last seen with the establishment of the SRIs in the 1990s. **PP**

REFERENCES

- Pallanti S, Quercioli L. Treatment-refractory obsessive-compulsive disorder: methodological issues, operational definitions and therapeutic lines. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006;30(3):400-412.
- McDougle CJ, Goodman WK, Leckman JF, Lee NC, Heninger GR, Price LH. Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder. A double-blind, placebo-controlled study in patients with and without tics. *Arch Gen Psychiatry*. 1994;51(4):302-308.
- McDougle CJ, Epperson CN, Pelton GH, Wasylink S, Price LH. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2000;57(8):794-801.
- Hollander E, Baldini Rossi N, Sood E, Pallanti S. Risperidone augmentation in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. *Int J Neuropsychopharmacol*. 2003;6(4):397-401.
- Erzogovesi S, Guglielmo E, Siliprandi F, Bellodi L. Low-dose risperidone augmentation of fluvoxamine treatment in obsessive-compulsive disorder: a double-blind, placebo-controlled study. *Eur Neuropsychopharmacol*. 2005;15(1):69-74.
- Bartzokis G, Lu PH, Turner J, Mintz J, Saunders CS. Adjunctive risperidone in the treatment of chronic combat-related posttraumatic stress disorder. *Biol Psychiatry*. 2005;57(5):474-479.
- Reich DB, Winternitz S, Hennen J, Watts T, Stanculescu C. A preliminary study of risperidone in the treatment of posttraumatic stress disorder related to childhood abuse in women. *J Clin Psychiatry*. 2004;65(12):1601-1606.
- Padala PR, Madison J, Monahan M, et al. Risperidone monotherapy for post-traumatic stress disorder related to sexual assault and domestic abuse in women. *Int Clin Psychopharmacol*. 2006;21(5):275-280.
- Monnelly EP, Ciraulo DA, Knapp C, Keane T. Low-dose risperidone as adjunctive therapy for irritable aggression in posttraumatic stress disorder. *J Clin Psychopharmacol*. 2003;23(2):193-196.
- Hamner MB, Faldowski RA, Ulmer HG, Frueh BC, Huber MG, Arana GW. Adjunctive risperidone treatment in post-traumatic stress disorder: a preliminary controlled trial of effects on comorbid psychotic symptoms. *Int Clin Psychopharmacol*. 2003;18(1):1-8.
- Brawman-Mintzer O, Knapp RG, Nietert PJ. Adjunctive risperidone in generalized anxiety disorder: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2005;66(10):1321-1325.
- Pandina GJ, Canuso CM, Turkoz I, Kujawa M, Mahmoud RA. Adjunctive risperidone in the treatment of generalized anxiety disorder: a double-blind, prospective, placebo-controlled, randomized trial. *Psychopharmacol Bull*. 2007;40(3):41-57.
- Denys D, de Geus F, van Megen HJ, Westenberg HG. A double-blind, randomized, placebo-controlled trial of quetiapine addition in patients with obsessive-compulsive disorder refractory to serotonin reuptake inhibitors. *J Clin Psychiatry*. 2004;65(8):1040-1048.
- Atmaca M, Kuloglu M, Tezcan E, Gecici O. Quetiapine augmentation in patients with treatment resistant obsessive-compulsive disorder: a single-blind, placebo-controlled study. *Int Clin Psychopharmacol*. 2002;17(3):115-119.
- Carey PD, Vythilingum B, Seedat S, Muller JE, van Ameringen M, Stein DJ. Quetiapine augmentation of SRIs in treatment refractory obsessive-compulsive disorder: a double-blind, randomised, placebo-controlled study [ISRCTN83050762]. *BMC Psychiatry*. 2005;5:5.
- Fineberg NA, Sivakumaran T, Roberts A, Gale T. Adding quetiapine to SRI in treatment-resistant obsessive-compulsive disorder: a randomized controlled treatment study. *Int Clin Psychopharmacol*. 2005;20(4):223-226.
- Vaishnavi S, Alamy S, Zhang W, Connor KM, Davidson JR. Quetiapine as monotherapy for social anxiety disorder: a placebo-controlled study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(7):1464-1469.
- Bystritsky A, Ackerman DL, Rosen RM, et al. Augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder using adjunctive olanzapine: a placebo-controlled trial. *J Clin Psychiatry*. 2004;65(4):565-568.
- Shapira NA, Ward HE, Mandoki M, et al. A double-blind, placebo-controlled trial of olanzapine addition in fluoxetine-refractory obsessive-compulsive disorder. *Biol Psychiatry*. 2004;55(5):553-555.
- Butterfield MI, Becker ME, Connor KM, et al. Olanzapine in the treatment of post-traumatic stress disorder: a pilot study. *Int Clin Psychopharmacol*. 2001;16(4):197-203.
- Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2002;159(10):1777-1779.
- Pollack MH, Simon NM, Zalta AK, et al. Olanzapine augmentation of fluoxetine for refractory generalized anxiety disorder: a placebo controlled study. *Biol Psychiatry*. 2006;59(3):211-215.
- Barnett SD, Kramer ML, Casat CD, Connor KM, Davidson JR. Efficacy of olanzapine in social anxiety disorder: a pilot study. *J Psychopharmacol*. 2002;16(4):365-368.
- Davis LL, Davidson JR, Ward LC, et al. Divalproex in the treatment of posttraumatic stress disorder: a randomized, double-blind, placebo-controlled trial in a veteran population. *J Clin Psychopharmacol*. 2008;28(1):84-88.
- Tucker P, Trautman RP, Wyatt DB, et al. Efficacy and safety of topiramate monotherapy in civilian posttraumatic stress disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68(2):201-206.
- Lindley SE, Carlson EB, Hill K. A randomized, double-blind, placebo-controlled trial of augmentation topiramate for chronic combat-related posttraumatic stress disorder. *J Clin Psychopharmacol*. 2007;27(6):677-681.
- Zhang W, Connor KM, Davidson JR. Levetiracetam in social phobia: a placebo controlled pilot study. *J Psychopharmacol*. 2005;19(5):551-553.
- Pollack MH, Roy-Byrne PP, Van Ameringen M, et al. The selective GABA reuptake inhibitor tiagabine for the treatment of generalized anxiety disorder: results of a placebo-controlled study. *J Clin Psychiatry*. 2005;66(11):1401-1408.
- Davidson JR, Brady K, Mellman TA, Stein MB, Pollack MH. The efficacy and tolerability of tiagabine in adult patients with post-traumatic stress disorder. *J Clin Psychopharmacol*. 2007;27(1):85-88.
- Rosenthal M. Tiagabine for the treatment of generalized anxiety disorder: a randomized, open-label, clinical trial with paroxetine as a positive control. *J Clin Psychiatry*. 2003;64(10):1245-1249.
- Hertzberg MA, Butterfield MI, Feldman ME, et al. A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. *Biol Psychiatry*. 1999;45(9):1226-1229.
- Lauria-Horner BA, Pohl RB. Pregabalin: a new anxiolytic. *Expert Opin Investig Drugs*. 2003;12(4):663-672.
- Pande AC, Pollack MH, Crockett J, et al. Placebo-controlled study of gabapentin treatment of panic disorder. *J Clin Psychopharmacol*. 2000;20(4):467-471.

34. Pande AC, Davidson JR, Jefferson JW, et al. Treatment of social phobia with gabapentin: a placebo-controlled study. *J Clin Psychopharmacol*. 1999;19(4):341-348.
35. Pande AC, Crockatt JG, Feltner DE, et al. Pregabalin in generalized anxiety disorder: a placebo-controlled trial. *Am J Psychiatry*. 2003;160(3):533-540.
36. Feltner DE, Crockatt JG, Dubovsky SJ, et al. A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. *J Clin Psychopharmacol*. 2003;23(3):240-249.
37. Pohl RB, Feltner DE, Fieve RR, Pande AC. Efficacy of pregabalin in the treatment of generalized anxiety disorder: double-blind, placebo-controlled comparison of BID versus TID dosing. *J Clin Psychopharmacol*. 2005;25(2):151-158.
38. Rickels K, Pollack MH, Feltner DE, et al. Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. *Arch Gen Psychiatry*. 2005;62(9):1022-1030.
39. Montgomery SA, Tobias K, Zornberg GL, Kasper S, Pande AC. Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder: a 6-week, multicenter, randomized, double-blind, placebo-controlled comparison of pregabalin and venlafaxine. *J Clin Psychiatry*. 2006;67(5):771-782.
40. Feltner D, Wittchen HU, Kavoussi R, et al. Long-term efficacy of pregabalin in generalized anxiety disorder. *Int Clin Psychopharmacol*. 2008;23(1):18-28.
41. Pande AC, Feltner DE, Jefferson JW, et al. Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: a placebo-controlled, multicenter study. *J Clin Psychopharmacol*. 2004;24(2):141-149.
42. Rickels K, DeMartinis N, Aufdembrinke B. A double-blind, placebo-controlled trial of abecarnil and diazepam in the treatment of patients with generalized anxiety disorder. *J Clin Psychopharmacol*. 2000;20(1):12-18.
43. Lippa A, Czobor P, Stark J, et al. Selective anxiolysis produced by ocinaplon, a GABA(A) receptor modulator. *Proc Natl Acad Sci U S A*. 2005;102(20):7380-7385.
44. Koponen H, Allgulander C, Erickson J, et al. Efficacy of Duloxetine for the Treatment of Generalized Anxiety Disorder: Implications for Primary Care Physicians. *Prim Care Companion J Clin Psychiatry*. 2007;9(2):100-107.
45. Rynn M, Russell J, Erickson J, et al. Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial. *Depress Anxiety*. 2008;25(3):182-189.
46. Hartford J, Kornstein S, Liebowitz M, et al. Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial. *Int Clin Psychopharmacol*. 2007;22:167-174.
47. Allgulander C, Hartford J, Russell J, et al. Pharmacotherapy of generalized anxiety disorder: results of duloxetine treatment from a pooled analysis of three clinical trials. *Curr Med Res Opin*. 2007;23(6):1245-1252.
48. Russell JM, Weisberg R, Fava M, Hartford JT, Erickson JS, D'Souza DN. Efficacy of duloxetine in the treatment of generalized anxiety disorder in patients with clinically significant pain symptoms. *Depress Anxiety*. 2008;25(7):E1-E11.
49. Davidson J, Yaryura-Tobias J, DuPont R, et al. Fluvoxamine-controlled release formulation for the treatment of generalized social anxiety disorder. *J Clin Psychopharmacol*. 2004;24(2):118-125.
50. Westenberg HG, Stein DJ, Yang H, Li D, Barbato LM. A double-blind placebo-controlled study of controlled release fluvoxamine for the treatment of generalized social anxiety disorder. *J Clin Psychopharmacol*. 2004;24(1):49-55.
51. Stein DJ, Westenberg HG, Yang H, Li D, Barbato LM. Fluvoxamine CR in the long-term treatment of social anxiety disorder: the 12- to 24-week extension phase of a multicentre, randomized, placebo-controlled trial. *Int J Neuropsychopharmacol*. 2003;6(4):317-323.
52. Hollander E, Koran LM, Goodman WK, et al. A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder. *J Clin Psychiatry*. 2003;64(6):640-647.
53. Rickels K, Schweizer E, DeMartinis N, Mandos L, Mercer C. Gepirone and diazepam in generalized anxiety disorder: a placebo-controlled trial. *J Clin Psychopharmacol*. 1997;17(4):272-277.
54. van Vliet IM, Westenberg HG, den Boer JA. Effects of the 5-HT1A receptor agonist flesinoxan in panic disorder. *Psychopharmacology (Berl)*. 1996;127(2):174-180.
55. Fresquet A, Sust M, Lloret A, et al. Efficacy and safety of lesopitron in outpatients with generalized anxiety disorder. *Ann Pharmacother*. 2000;34(2):147-153.
56. Freeman AM, 3rd, Westphal JR, Norris GT, et al. Efficacy of ondansetron in the treatment of generalized anxiety disorder. *Depress Anxiety*. 1997;5(3):140-141.
57. Naukkarinen H, Raassina R, Penttinen J, et al. Deramciclane in the treatment of generalized anxiety disorder: a placebo-controlled, double-blind, dose-finding study. *Eur Neuropsychopharmacol*. 2005;15(6):617-623.
58. Davis M. Role of NMDA receptors and MAP kinase in the amygdala in extinction of fear: clinical implications for exposure therapy. *Eur J Neurosci*. 2002;16(3):395-398.
59. Ressler KJ, Rothbaum BO, Tannenbaum L, et al. Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. *Arch Gen Psychiatry*. 2004;61(11):1136-1144.
60. Hofmann SG, Meuret AE, Smits JA, et al. Augmentation of exposure therapy with D-cycloserine for social anxiety disorder. *Arch Gen Psychiatry*. 2006;63(3):298-304.
61. Guastella AJ, Richardson R, Lovibond PF, et al. A randomized controlled trial of D-cycloserine enhancement of exposure therapy for social anxiety disorder. *Biol Psychiatry*. 2008;63(6):544-549.
62. Guastella AJ, Dadds MR, Lovibond PF, Mitchell P, Richardson R. A randomized controlled trial of the effect of D-cycloserine on exposure therapy for spider fear. *J Psychiatr Res*. 2007;41(6):466-471.
63. Kushner MG, Kim SW, Donahue C, et al. D-cycloserine augmented exposure therapy for obsessive-compulsive disorder. *Biol Psychiatry*. 2007;62(8):835-838.
64. Wilhelm S, Buhlmann U, Tolin DF, et al. Augmentation of behavior therapy with d-cycloserine for obsessive-compulsive disorder. *Am J Psychiatry*. 2008;165(3):335-341.
65. Storch E, Merlo L, Bengtson M, et al. D-cycloserine does not enhance exposure-response prevention therapy in obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2007;22:230-237.
66. Bergink V, Westenberg HG. Metabotropic glutamate II receptor agonists in panic disorder: a double blind clinical trial with LY354740. *Int Clin Psychopharmacol*. 2005;20(6):291-293.
67. Dunayevich E, Erickson J, Levine L, et al. Efficacy and tolerability of an mGlu2/3 agonist in the treatment of generalized anxiety disorder. *Neuropsychopharmacology*. 2008;33(7):1603-1610.