The Carlat Psychiatry Report

AN UNBIASED MONTHLY COVERING ALL THINGS PSYCHIATRIC

VOLUME 4, NUMBER 3 WWW.THECARLATREPORT.COM MARCH 2006

Medications for Panic Disorder: An Update

All right, we can see you stifling that yawn, and we know what you're thinking: "What on earth is there to say about treating panic disorder other than to use SSRIs or benzos?"

Well, we're up for the challenge! There have been some new approvals over the past couple of years, as well as data on some off-label treatments that you may want to try on some of your more treatment-resistant patients.

It's true that SSRIs remain the mainstay of panic treatment, with Prozac (fluoxetine), Paxil (paroxetine), and Zoloft (sertraline) all officially indicated for this condition. Recently, Effexor XR (venlafaxine) won approval for panic as well, based on the results of two placebo-controlled trials that lasted 12 months each. These were fixed-dose studies, meaning that patients were assigned to several specific doses of Effexor XR (75 mg, 150 mg, and 225 mg). All three doses beat placebo, which is reassuring for those who prefer not to risk the possibility of Effexor-induced hypertension when using higher doses. (Summaries of this data are available

Continued on Page 3

IN THIS ISSUE:

Focus of the Month:
Medication Treatment of Anxiety

Benzodiazepines are Bad. Or Are They?

Nobody doubts that benzodiazepines ("benzos" or BZs) are effective in treating a wide range of anxiety disorders, but many believe that they are addictive, difficult and perhaps dangerous to stop taking, and that they cover up anxiety instead of truly treating it. Well, how valid are these concerns? After all, benzos offer some unique advantages: they work quickly, they are the only agents that can be used to treat an ongoing anxiety attack, they can be taken PRN, and they do not generally cause sexual side effects. So let's take a closer look at each of the concerns.

Benzos are addictive. It is crucial to understand three terms related to addiction: misuse, abuse, and dependence. *Misuse* refers to taking a medication other than how it is prescribed. Thus, a patient who is prescribed Klonopin (clonazepam) 1 mg TID who comes into your office and informs you that he increased the frequency to QID due to increased anxiety has misused his Klonopin prescription.

Abuse implies using a BZ specifically for inappropriate reasons such as to get high. How prone to abuse are BZs? Most clinical trials with placebo controls have found little evidence for preference of BZs over placebo (*Arch Gen Psychiatry* 1986; 43:533-41), though former alcoholics sometimes report positive mood changes in response to BZs. Epidemiological studies have consistently shown that the overwhelming majority of patients in the community, even former substance abusers, take fewer BZs than prescribed, rarely become

Continued on Page 2

Learning objectives for this issue: 1. List the medications frequently used for panic disorder. 2. Discuss the evidence regarding the advantages and disadvantages of benzodiazepines. 3. Outline the role of GABA and GABA receptors in anxiety.

This CME activity is intended for psychiatrists, psychiatric nurses, and other health care professionals with an interest in the diagnosis and treatment of psychiatric disorders.

Benzodiazepines are Bad. Or Are They?

Continued from Page 1

"dose escalators," and decrease rather than increase their dose over time (*J Clin Psychopharmaco*l 1992; 12:316-21). When true BZ abuse does occur, it is almost always in the context of other drug abuse. For example, in one study involving 30 patients who presented with BZ dependence (on an average dose of 140 mg/day of valium or its equivalent!), 28 of 30 were actively abusing other substances while the other two had a history of drug abuse (*J Clin Psychopharmacol* 1996; 16:51-57).

Dependence is frequently labeled once a patient has difficulty coming off a BZ. However, this may represent physiological dependence in the same way that patients may have withdrawal symptoms when coming off Paxil (paroxetine) or Effexor XR (venlafaxine XR). Physiological dependence is certainly a risk for patients who take BZs daily for an extended period of time, but usually is not much of a concern for short term use (i.e., less than 3-6 months – see *JAMA* 1983;250:767-771). It is often impossible, however, to distinguish between a true BZ withdrawal syndrome and the unmasking of an underlying anxiety disorder syndrome, and because of this, there is no way to clearly estimate the prevalence of BZ dependence. The best insight that we can offer is to examine success rates of BZ discontinuation for patients who present for that specific purpose. In this situation, between 40-50% of BZ-dependent individuals can successfully be withdrawn from their BZ and remain BZ free thereafter (*Arch Gen Psychiatry* 1990; 47:899-915). Keep in mind, however, that there is no way to know whether the remaining patients were unsuccessful because their anxiety disorder reemerged or rather that they were truly unable to stop because of withdrawal symptoms. Benzodiazepines certainly can be abused--most of us have had patients who show up in the ER mimicking symptoms of panic and then get angry and leave when questioned about their frequent visits, or who have a number of doctors and prescriptions on file at a variety of pharmacies. Active substance abusers should not be given BZs, but, according to a comprehensive review on this topic (*Am J Addictions* 1991; 10:48-68), they *can* safely be given to alcoholics in recovery.

Two "New" Benzos: Pushing the Patent Envelope

- **Xanax XR** was approved for panic disorder in January of 2003, and is essentially good old Xanax (alprazolam) packaged in a delivery system that releases it gradually into the bloodstream; because of this, you can dose it QD or BID instead of QID. While FDA approval was fairly recent, Xanax XR has been kicking around Pharmacia & Upjohn for quite a while. Back in 1995, a paper was published comparing Xanax IR with Xanax XR in 14 volunteers with histories of sedative abuse. Hands down, they rated Xanax IR as more abusable than placebo, whereas Xanax XR did not differ from placebo along this dimension (*Clin Pharmacol Ther* 1995; 57:356-65). Whether it poses any advantages over long half-life BZs such as Klonopin remains to be seen. FYI, you won't see many more ads pushing Xanax XR, because its patent just expired, and it is now available as a generic from Mylan Laboratories.
- **Klonopin wafers** (clonazepam) have been available at pharmacies since May of 2003, although they were initially approved by the FDA back in 1997. Standard Klonopin pills were first approved back in 1975 and are available generically. The wafers are being pushed by Solvay as unique because they disintegrate on the tongue, and for this reason can be taken "discreetly" (yes, this is their language). The clinically helpful aspect of this "new" product is that it comes in two lower dosage forms than standard Klonopin – 0.125 mg and 0.25 mg. So gradual dosage titration is easier. As with Xanax XR, Klonopin Wafer's patent recently expired, and Barr Pharmaceuticals received FDA approval in August 2005 to market a generic version.

BZs are difficult or dangerous to stop taking. Because BZs induce physiological dependence, they do need to be tapered for patients who have been taking them for more than 6 months. The oft-cited 25% per week tapering guideline is too difficult for most patients, according to the major study to examine this issue (*Arch Gen Psych* 1990; 47:908-915). Instead, go 25% for the first two weeks, then slow the taper way down, to 10% per week or less. The specter of danger arises with the concern about withdrawal seizures. In a study of 153 BZ-dependent patients, a 3% withdrawal seizure rate was reported, and these patients were on very high doses of BZs that were often stopped abruptly (*Pharmacopsychiatry* 1995; 28:257-62). If you are concerned about seizures in particular patients, you can prescribe an anti-seizure medication such as Depakote or Tegretol and inform them not to drive over the next few days. If they decline this plan, you can recommend a short stay in the nearest psychiatric facility to monitor their withdrawal symptoms.

Benzos only "cover up" the underlying anxiety disorder and do not treat the source. The same

Continued on Page 3

Benzodiazepines are Bad. Or Are They?

Continued from Page 2

concern was expressed not so long ago about antidepressants for treating depression, but today most people accept the validity of treating symptoms. There is, however, some evidence that BZs inhibit the gains that can be made from cognitive-behavioral therapy (CBT). Since CBT works by teaching patients how to manage their anxiety, patients on BZs may be deprived of the opportunity of experiencing their anxiety and learning how to overcome it. This is a real concern, and should prompt a collaborative discussion with your patient and the CBT therapist.

So, are benzos "bad"? Not inherently. Like most drugs, they do have potential side effects, including drowsiness, cognitive impairment, and decreased coordination. While they should generally be reserved as a second-line treatment after SSRIs and CBT, and should be avoided in active substance abusers, they are a useful tool in our armamentarium and, when managed appropriately, incur minimal risk. ❖

Benzos: Not as bad as advertised

This article was contributed by Michael Posternak, M.D., of TCPR's editorial board. He reports no relevant financial disclosures.

Medications for Panic Disorder: An Update

Continued from Page 2

on the Wyeth website – www.wyeth.com.)

Lexapro (escitalopram), which has become a best-selling SSRI based on excellent marketing by Forest and a possible advantage in terms of side effects, is indicated for GAD as well as depression, so you'd assume that winning the panic disorder indication would be a slam dunk. However, the FDA recently issued Forest two consecutive "non-approvable" letters for the panic disorder indication. According to the Forest website, the FDA was not impressed by some of the research methods used in its placebo-controlled trials. Whether Lexapro is really not effective for panic is unclear, but this news does tend to temper our enthusiasm for the youngest SSRI on the block.

To treat panic disorder, start at half the usual dose of an SSRI to minimize initial jitteriness. Adding benzos at the outset is very common clinically, and over the past few years some good studies have been published bolstering this practice (*Arch Gen Psychiatry* 2001; 58:681-686, *J Psychopharm* 2003; 17:276-82). Both studies involved adding Klonopin (clonazepam) to an SSRI and compared this to adding placebo. Using Klonopin quickens response dramatically, but after four weeks there is no difference in response rates. In both studies, patients had little problem gradually tapering off Klonopin after this short-term treatment.

Aside from SSRIs, SNRIs, benzos, and CBT (cognitive behavioral therapy), what else can we offer our patients with panic disorder? Here is a laundry list of things to try, some of them with more robust research evidence than others:

Wellbutrin (bupropion). This is a blessedly low-side-effect drug that has been unfairly maligned as ineffective or anxiety. While Wellbutrin can be

Continued on Page 6

Q&A With the Expert

This Month's Expert: Andrew Goddard, M.D., on The Role of GABA in Anxiety

Professor of Psychiatry and Radiology; Director, Adult Outpatient Clinic and Anxiety Program, Indiana University Department of Psychiatry

Dr. Goddard has disclosed that he was or is the recipient of research grants from Cephalon and Pfizer Pharmaceuticals; and was or is a consultant for AstraZeneca; and was or is a member of the speakers bureau of Pfizer Pharmaceuticals. The editors of *The Carlat Psychiatry Report* have closely reviewed the content of Dr. Goddard's interview and have determined that there are no financial conflicts of interest regarding this educational activity. The author has disclosed that D-cycloserine, gabapentin, lamotrigine, pregabalin, and tiagabine have not been approved by the U.S. Food and Drug Administration for use in the treatment of anxiety. Please consult product labeling for the approved usage of these drugs.

TCR: Dr. Goddard, you've done a lot of neurobiological research in anxiety disorders. It's a very complex area, but basically what goes on in patients' brains when they have a panic attack?

Dr. Goddard: It is complex, and initially researchers focused on the actions of monoamines in both depression and anxiety.

TCR: Remind us what the monoamines are.

Dr. Goddard: They are perhaps the most well known neurotransmitters: serotonin, norepinephrine, and dopamine. They have been at the center of thinking about depression and anxiety for a long time. The "monoamine theory" of depression holds that depression is caused by a depletion of norepinephrine and serotonin.

TCR: Is anxiety thought to result from the same thing?

Dr. Goddard: One theory is that panic results from spontaneous overactivity in the locus coeruleus (LC), which is the part of the brain where most of the noradrenergic neurons are located. One idea is that when somebody has a panic attack they have this sort of storm or surge of noradrenaline neurotransmission in the LC. An important inhibitory input to this structure is from serotonergic neurons. The serotonin system comes on line to modulate the LC overactivity that leads to the panic. So essentially, what SSRIs do is to increase that normal compensatory mechanism, enhancing that inhibition.

TCR: So that's a nice, neat theory: SSRIs increase serotonin input into the locus coeruleus, which dampens norepinephrine, easing anxiety.

Dr. Goddard: It's a nice theory, but we think it really doesn't explain the underlying pathology of panic. To understand this, researchers are delving into the GABA and glutamate systems.

TCR: What is GABA anyway?

Dr. Goddard: GABA (gamma aminobutyric acid) is a small amino acid neurotransmitter. It is basically a byproduct of glucose metabolism, and it is a byproduct of glutamate.

TCR: We've certainly been hearing a lot about glutamate lately in psychiatry.

Dr. Goddard: Yes, that's because glutamate is one of the main excitatory neurotransmitters in the brain, so it is one of the main "on buttons," if you will, to neural activity. And GABA is the flip side of that: it inhibits neural activity.

TCR: And a lot of us have heard about GABA in terms of the actions of both benzodiazepines and alcohol. Can you give us a brief review of what those two agents do to GABA?

Dr. Goddard: Sure. Native GABA (the GABA that we produce ourselves) acts in various brain regions by attaching to postsynaptic GABA-A receptors and opening ionic/chloride ion channels. Right next to the GABA-A receptors there is a specific benzodiazepine modulatory site. Benzodiazepines attach to this site on the receptor, and they enhance the opening of the ion channel. I think of it as turbocharging the efficacy of native GABA at the postsynaptic GABA-A receptor.

"This new research is fascinating, because it suggests an entirely new model of therapeutics and how to best combine psychotherapy and pharmacotherapy. Our usual clinical practice is to give standing doses of medications for anxiety and depression and maintain our patients on those. But it may be that there is a role for intermittent pharmacotherapy for anxiety disorders."

– Andrew Goddard, M.D.

TCR: But that's strange: Why do we have a specific benzodiazepine receptor in our brain? Do we have endogenous benzodiazepines?

Dr. Goddard: That's something of a mystery. Back in the 1970s, researchers discovered the opiate receptors in brain regions, which led to an intensive search for endogenous opiates. People eventually identified endorphins and enkephalins. And there was a similar search for endogenous benzodiazepines in the '80s and '90s. One molecule that has been identified in this search

Continued on Page 5

Q & A With the Expert

Continued from Page 4

is a neuropeptide called diazepam binding inhibitor (DBI), which is an inverse agonist at the benzo receptor. However CSF levels of DBI are normal in panic disorder which is a bit puzzling.

TCR: What about alcohol? How does that affect the GABA complex?

Dr. Goddard: Alcohol affects GABA in a very different way. There is no "alcohol receptor" in the GABA complex. Instead, alcohol seems to cause some stabilizing effect on the membrane of the GABA neurons and may cause extra GABA release by that mechanism. But it's not a simple "lock and key" story like the benzos.

TCR: All right, so we've covered how benzos and alcohol work on GABA. But how might GABA be involved in panic disorder?

Dr. Goddard: The short answer is that we don't know. It may be that subpopulations of the GABA-A receptors are deficient in some panic patients or that there are deficits in the production and release of GABA presynaptically. But many of us believe that the monoamines (serotonin and norepinephrine) are not the main players in anxiety, and that they basically serve to modulate or tweak the major systems, which are glutamate and GABA. Some interesting information relating to this story has come about through studying the actions of some of the newer anticonvulsants.

TCR: Can you give us a rundown of these medications, some of which are under investigation for the treatment of anxiety?

Dr. Goddard: Sure. There are five of them: tiagabine (Gabitril), pregabalin (Lyrica), gabapentin (Neurontin), lamotrigine (Lamictal), and D-cycloserine. Tiagabine is essentially a GABA reuptake inhibitor, in the same way that SSRIs are serotonin reuptake inhibitors. Part of the way in which the GABA chemical signal is ended is by reuptake into the presynaptic neuron. Tiagabine blocks the GABA reuptake transporter protein and so disrupts that process and makes GABA more likely to linger in the synapse.

TCR: And more GABA in the synapse may lead to an anti-anxiety effect?

Dr. Goddard: Yes, especially since tiagabine blocks GABA reuptake most strongly in areas of the brain that have a lot to do with anxiety, namely the amygdala and hippocampus, which are part of the limbic system.

TCR: What about pregabalin (Lyrica) and gabapentin (Neurontin)?

Dr. Goddard: Pregabalin and gabapentin are pretty closely related chemically, sort of chemical cousins, if you will, and pregabalin is more potent and more bioavailable to the central nervous system than gabapentin. We really don't know how they might work in anxiolysis, but one theory is that they enhance presynaptic release of GABA through alterations in calcium metabolism.

TCR: How does Lamictal affect GABA?

Dr. Goddard: Lamictal may affect GABA indirectly. It seems to inhibit release of glutamate, thereby altering the excitatory/inhibitory balance between glutamatergic and GABAergic neurons.

TCR: That's interesting. So either inhibiting glutamate or increasing the action of GABA lead to anti-anxiety effects.

Dr. Goddard: Right, but the story is a bit more complicated than that. Surprisingly, it may be that some medicines that briefly increase glutamate activity could be useful therapeutically for some types of anxiety. For example, we know that glutamate is involved in laying down new memories. And memories--learning--is involved in anxiety. For instance, a patient develops a simple phobia by learning to associate, say, a snake with fear. We believe that this process is mediated by a brief increase in glutamate activity within the brain.

TCR: But if that's true, how would a medication that enhances glutamate be helpful?

Dr. Goddard: Because in order to extinguish a phobia, the brain has to lay down new memories to replace the old ones. Thus, one research group has shown that if you give phobia patients a hefty dose of D-cycloserine (a glutamate enhancer) before behavior therapy, you can significantly amplify the response to treatment.

TCR: Meaning that glutamate can work both both ways--allowing phobias to be learned in the first place, but aiding in their extinction if you bump up levels just before therapy?

Dr. Goddard: Exactly. And this is fascinating, because it suggests an entirely new model of therapeutics and how to best combine psychotherapy and pharmacotherapy. Our usual clinical practice is to give standing doses of medications for anxiety and depression and maintain our patients on those. But it may be that there is a role for intermittent pharmacotherapy in anxiety disorders that really hasn't been explored fully.

TCR: Is D-cycloserine available to prescribe?

Dr. Goddard: Yes, it is an old tuberculosis drug so it has been around since the '50s, and it is marketed under the trade name of Seromycin. I think the neuroscience group at Eli Lilly is interested in looking at the molecule more closely and possibly developing medications based on its structure.

TCR: Thank you, Dr. Goddard, for sharing these fascinating insights.

❖ ❖ ❖

Medications for Panic Disorder: An Update

Continued from Page 1

over-stimulating for the first several days, it definitely works over time for anxiety. One series of studies found no difference between Zoloft and Wellbutrin for the anxiety accompanying depression (*J Clin Psychiatry* 2001; 62:776-781), and an open-label study of Wellbutrin SR in 20 patients with panic disorder found it to be effective (*Psychopharm Bull* 2003; 37:66-72). It strikes us as unlikely that we'll ever see a large controlled trial of Wellbutrin for panic disorder, because all formulations except Wellbutrin XL are available generically, reducing the financial incentives for drug-makers to fund the necessary research.

Zyprexa (olanzapine). Two patients with panic disorder, both on Paxil, improved within days of starting Zyprexa 5 mg QD as augmentation (*J Clin Psychopharm* 2003; 23:100-101).

Abilify (aripiprazole). In a retrospective chart review study, a majority of patients with a variety of anxiety disorders responded to the addition of Abilify 15-30 mg QD to their SSRI (*Int Clin Psychopharmacol*; 2005 20:9-11).

Tricyclics. While it's generally accepted that tricyclics work as well as SSRIs for panic disorder (*J Clin Psych* 2004;65 [suppl 5]: 24-28), most psychiatrists are loathe to start anyone on them, because of lack of experience and the fear of side effects. Recently, researchers analyzed side effects specific to imipramine over one year of maintenance treatment, and found that it did indeed produce sustained dry mouth, sweating, tachycardia, and significant weight gain (*J Clin Psychopharm* 2002; 22:155-61).

Beta-blockers. Many psychiatrists are accustomed to prescribing beta-blockers such as propranolol and atenolol to treat situation-specific social phobia like stage-fright, or to alleviate lithium-induced tremor. In one study, the beta-blocker pindolol was compared with placebo as augmentation of Prozac treatment in 25 patients with treatment-resistant panic disorder. Pindolol outperformed placebo robustly. The dosage of pindolol used was 2.5 mg TID (roughly equivalent to propranolol 20 mg TID), and it was well tolerated in all patients (*J Clin Psychopharm* 2000; 20:556-559). However, using beta-blockers as monotherapy for panic has yielded mixed results (see, for example, *J Clin Psychopharm* 1989; 9:22-7).

Buspirone. Unfortunately, buspirone, which is as effective as any medication for generalized anxiety disorder (GAD), doesn't work for panic disorder (*Acta Psychiatr Scand* 1993; 88:1-11), although one small case series found it helpful as an adjunct to benzodiazepines, which might be a nice way of avoiding the benzo dosage creep that occurs in some patients (*Am J Psychiatry* 1989; 146:914-916).

Gabitril (tiagabine). Gabitril (a Cephalon product) has been knocking on the door of the antianxiety market for several years now but hasn't yet won approval for anything beyond adjunctive treatment of epilepsy. Published placebo-controlled studies for GAD have been unimpressive (*J Clin Psychiatry* 2005; 66:1401-1408), showing no separation from placebo on the primary measure. Nonetheless, open trials have been intriguing, particularly those that used Gabitril as adjunctive treatment for patients with anxiety disorders who were unresponsive to the initial agent. In one study, for example, 13 of 17 patients achieved a response with add-on Gabitril (mean dose 13 mg QD), and 10 patients achieved remission (*Ann Clin Psychiatry* 2005; 17:167-172). The main side effects to watch for are dizziness, sedation, jitteriness, and tremor. See the Gabitril medication fact sheet on our web site (www.TheCarlatReport.com) for more information.

Neurontin (gabapentin). One lonely placebo-controlled trial showed no drug/placebo difference on the Panic and Agoraphobia Scale in 103 patients with panic disorder (*J Clin Psychopharm* 2000; 20:467-471). Nonetheless, many clinicians are convinced that Neurontin can be helpful for refractory anxiety in select patients.

Lyrica (Pregabalin). Lyrica appears to have a more promising future in psychiatry than either Gabitril or its cousin Neurontin. Three placebo-controlled studies using Lyrica for GAD have been published, all of which were positive (*J Clin Psychopharm* 2003; 23:240-249, *J Clin Psychopharm* 2004; 24:141-149, *Arch Gen Psychiatry* 2005; 62:1022-1030). In fact, Lyrica compared favorably to both Xanax (alprazolam) and Ativan (lorazepam) in these studies. The best dose to shoot for appears to be 200 mg TID. Side effects are similar to those with Gabitril, namely, dizziness and sedation. It does appear to cause weight gain of about 2 kg over four weeks. While it hasn't received FDA approval for GAD (it is currently approved for treatment of neuropathic pain), it did receive the green light from Europe's Committee for Medicinal Products for Human Use (CHMP), meaning that it will likely receive approval from the European Commission (Europe's FDA) within the next few months. We're not aware of any good studies of Lyrica for panic disorder, but the impressive GAD data bodes well for this condition. ❖

TCPR VERDICT: ***Panic disorder: Think outside the SSRI/benzo box***

CME Post-Test

To earn CME credit, you must read the articles and complete the quiz below, answering at least four of the questions correctly. Mail a photocopy or fax the completed page to **Wolters Kluwer Health, Office of Continuing Education, 530 Walnut Street, 8th Floor East, Philadelphia, PA 19106**; **fax: (215) 521-8637**. **For customer service, please call (215) 521-8635.** Only the first entry will be considered for credit and must be received by WKH by February 28, 2007. Acknowledgment will be sent to you within 6 to 8 weeks of participation.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Wolters Kluwer Health and Clearview Publishing, LLC. Wolters Kluwer Health is accredited by the ACCME to provide continuing medical education for physicians.

Wolters Kluwer Health designates this educational activity for a maximum of one (1) AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Please identify your answer by placing a check or "X" mark in the box accompanying the appropriate letter.

1. FDA-approved medications for panic disorder include
- [ ] a. Paxil, Zoloft, Effexor XR, and Lexapro.
- [ ] b. Paxil, Prozac, Zoloft, and Cymbalta.
- [ ] c. Paxil, Prozac, Zoloft, and Effexor XR.
- [ ] d. Paxil, Klonopin, and Lorazepam.

2. Lyrica (pregabalin)
- [ ] a. Is indicated for the treatment of seizures.
- [ ] b. Appears to be effective for GAD.
- [ ] c. Is effective for panic disorder but not GAD.
- [ ] d. Is indicated for treatment of bipolar disorder.

3. Seizures related to benzodiazepine withdrawal are frequently reported in the medical literature.
- [ ] a. True [ ] b. False

4. Klonopin wafers differ from standard Klonopin in that
- [ ] a. Wafers dissolve on the tongue and come in 0.5 mg strength.
- [ ] b. Wafers are a controlled release form of Klonopin.
- [ ] c. Wafers dissolve on the tongue and come in 0.125 mg and 0.25 mg forms.
- [ ] d. Wafers are the generic version of Klonopin.

5. According to Dr. Goddard, effective panic treatment involves the inhibition of GABA.
- [ ] a. True [ ] b. False

PLEASE NOTE: WE CAN AWARD CME CREDIT ONLY TO SUBSCRIBERS

First Name	Last Name	
Street Address		
City	State	Zip
Phone	Fax	E-mail

Your evaluation of this CME activity (i.e., this issue) will help guide future planning. Please respond to the following questions:

1. Did the content of this activity meet the stated learning objectives? [ ] Yes [ ] No
2. On a scale of 1 to 5, with 5 being the highest, how do you rank the overall quality of this educational activity? [ ] 5 [ ] 4 [ ] 3 [ ] 2 [ ] 1
3. As a result of meeting the learning objectives of this educational activity, will you be changing your practice behavior in a manner that improves your patient care? Please explain. [ ] Yes [ ] No

4. Did you perceive any evidence of bias for or against any commercial products? Please explain. [ ] Yes [ ] No

5. How long did it take you to complete this CME activity? ___ hour(s) ___ minutes
6. **Important for our planning:** Please state one or two topics that you would like to see addressed in future issues.

Tales from the History of Psychiatry:
The Birth of "Panic Disorder"

In the dark old days of American Psychiatry, most patients were diagnosed with schizophrenia and prescribed Thorazine (chlorpromazine) or its equivalent. One of the true pioneers of rational medication treatment is Donald Klein of Columbia University, who in 1962 was a psychiatrist practicing at Hillside Hospital in New York. He and his colleague Max Fink published an early study in Archives of General Psychiatry in which they documented the responses of a variety of patients to imipramine vs. chlorpromazine. One patient in particular (diagnosed as schizophrenic) suffered an "atypical" syndrome of paroxysmal episodes of fear and agitation that would last for several minutes and then subside. He did not respond to Thorazine, but these episodes diminished on robust doses of imipramine. Klein later labeled these "paroxysmal" episodes "panic attacks," but it was not until 1980 that the concept of panic disorder gained acceptance in American psychiatry. It was in that year that David Sheehan and colleagues published a seminal article on "Endogenous Anxiety". Soon thereafter, Upjohn introduced Xanax (alprazolam), and panic disorder was rapidly transformed from an unknown disorder to one of the most commonly treated conditions in psychiatry.

Sheehan DV, Ballenger J, and Jacobsen G: Treatment of endogenous anxiety with phobic, hysterical, and hypochondriacal symptoms. *Archives of General Psychiatry*. 1980;37:51-57.

The Carlat Psychiatry Report

P.O. Box 626
Newburyport, MA 01950

This Month's Focus:
Medication Treatment of Anxiety

Next Month in *The Carlat Psychiatry Report:* Alternative Treatments in Psychiatry, with articles on dietary supplements, herbals, and an interview with natural medication expert David Mischoulon, M.D., of Massachusetts General Hospital.