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Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Antidepressants

Learning Objectives

After reading these articles, you should be able to:

1. Analyze the pharmacological profile and clinical considerations of gepirone (Exxua) for treating major depressive disorder.
2. Understand the impact of SSRIs on temperamental traits.
3. Evaluate the benefits and limitations of Neuroscience-Based Nomenclature (NbN).
4. Summarize some of the current research findings on psychiatric treatment.

Gepirone: A First Look

Chris Aiken, MD. Editor-in-Chief, The Carlat Psychiatry Report. *Assistant Professor, NYU Langone Department of Psychiatry. Practicing psychiatrist, Winston-Salem, NC.*

Dr. Aiken has no financial relationships with companies related to this material.

On September 28, 2023, the FDA approved gepirone (Exxua) for major depressive disorder in adults. The medication is unlike any other antidepressant, and its approval process was unparalleled as well. In this article, I'll look at what gepirone brings to the table.

How it works

Gepirone is an azapirone, a class of medications that work as agonists at the serotonin 5-HT1A receptor. Buspirone was the original azapirone (Eison AS, *J Clin Psychopharmacol* 1990;10(3 Suppl):2S–5S). Compared to buspirone, gepirone has three times higher affinity for 5-HT1A, but otherwise the two are close pharmacologic relatives. Tandospirone is another sibling, an azapirone approved

Continued on page 2

Highlights From This Issue

Feature article—Gepirone is a new "antidepressant," but we're not convinced it's any better than buspirone.

Q&A on page 1—Thirty years ago, Peter Kramer predicted that SSRIs would change personality traits. He reflects on what we've learned since.

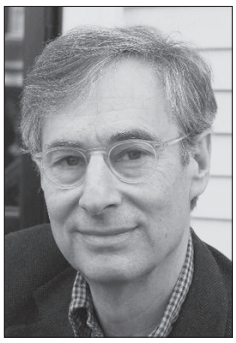
Research Update on page 6—Stimulant benefits start to plateau at around 40 mg/day for methylphenidate and 35 mg/day for amphetamine salts. Beyond the FDA-approved max, their harms generally outweigh their benefits.

Q&A With the Expert

Looking Back on Prozac
Peter D. Kramer, MD

Emeritus Professor of Psychiatry and Human Behavior, Brown University. Author of eight books, including the runaway bestseller Listening to Prozac *(Viking Adult, 1993) and* Death of the Great Man *(Post Hill Press, 2023).*

Dr. Kramer has no financial relationships with companies related to this material.



TCPR: You were one of the first to document changes in temperamental traits on selective serotonin reuptake inhibitor (SSRI) antidepressants. Tell us what you found.

Dr. Kramer: I was treating patients with psychotherapy in the late 1980s when fluoxetine (Prozac) came out, followed soon after by sertraline (Zoloft). These meds were having the kind of effects I tried to get in psychotherapy. Some patients had dramatic responses and felt better than they did before the depression. They were more confident, more comfortable socially, and free for the first time from anxious or obsessive personality traits (Kramer PD, *Lancet Psychiatry* 2016;3(1):e2–e3).

TCPR: Sounds like the kinds of traits people seek out.

Dr. Kramer: Yes. I thought there was an eerie consonance between what fluoxetine did and what the culture demanded. In particular, women were more assertive and men were quicker decision makers on the job. And I worried

Continued on page 4

Gepirone: A First Look

Continued from page 1

for both depression and anxiety in Asia. Other 5-HT1A agonists that are not in the azapirone class include vortioxetine, lurasidone, and aripiprazole.

Gepirone and buspirone also produce an active metabolite (1-PP) that may contribute to their anxiolytic effects. 1-PP is an alpha-2-antagonist, a mechanism shared by prazosin and mirtazapine, as well as yohimbine, a once-popular treatment for erectile dysfunction from the pre-Viagra era. This alpha-2-antagonism may create a drug interaction with alpha-2-agonists like guanfacine and clonidine, something that has been suggested by animal studies but is unexplored in humans.

Most azapirones have short half-lives, but gepirone has overcome its five-hour half-life through extended-release coating, allowing once-a-day dosing. Buspirone, with a half-life of two to three hours, is dosed two to three times a day.

A controversial approval

The FDA rejected gepirone three times over the past 25 years before finally giving it a pass. What changed? It wasn't the data. The FDA requires two positive results from well-designed, adequately sized, randomized trials to earn approval, and gepirone has met that standard since 2008 (Bielski RJ et al, *J Clin Psychiatry* 2008;69(4):571–577; Feiger AD et al, *J Clin Psychiatry* 2003;64(3):243–249). But gepirone also has 13 trials in depression that were not positive, and that is why the FDA rejected it in the past. During the recent approval, the negative data were given a different weight.

The manufacturer (Fabre-Kramer Pharmaceuticals) did not respond to requests for scientific information, but a summary of the FDA's decision categorizes those unlucky 13 trials as follows:

- Seven negative, including four involving an active comparator where gepirone performed worse than placebo and the active comparator surpassed the placebo on the 17-item Hamilton Depression Rating Scale
- Three failed but "uninformative"
- Two excluded for using dosages outside the usual range
- One excluded due to data manipulation (a relapse prevention trial where 40 patients were removed after the blind was broken) (www.tinyurl.com/2s4dmyez)

Negative trials are common for antidepressants, but not at this rate. Among 74 trials reviewed by the FDA for approved antidepressants, 49% were negative, compared to 87% for gepirone (Turner EH et al, *N Engl J Med* 2008;358(3):252–260).

Turning to its positive studies, gepirone separated from placebo by three to four weeks, with continued improvement up to the eight-week end point. Its efficacy was similar to that seen in published trials of other antidepressants, albeit at the lower end of that range, with a number needed to treat of 6–8 for response and 7 for remission (www.tinyurl.com/3z6fkx72).

Gepirone's antidepressant effects do find further support in six other controlled trials, but most of these had limitations that excluded them from the FDA's consideration, such as a small sample size or a focus on specific subtypes like anxious or atypical depression.

Overall, the evidence supporting gepirone in depression is weak but positive and in the same league as that for buspirone. Buspirone was explored as monotherapy for depression in the 1990s and was effective in four industry-sponsored placebo-controlled trials, although most of them enrolled patients with high levels of anxiety (Kishi T et al, *Psychol Med* 2014;44(11):2255–2269). In contrast to these monotherapy depression trials, buspirone actually failed in most of the antidepressant augmentation trials where it is often used. This may be because augmentation trials involve a more difficult-to-treat population. Gepirone has not been tested as antidepressant augmentation.

Other uses

Gepirone is being explored for generalized anxiety disorder (GAD) and sexual dysfunction. Only a few studies are available for GAD. There, gepirone appears to work, though it may be less effective than buspirone (Rossano F et al, *Eur Neuropsychopharmacol* 2023;76:23–51). In sexual dysfunction, the data are suggestive but far from

Continued on page 3

Mailing Information

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Gepirone: A First Look
Continued from page 2

definitive. Specifically, gepirone improved sexual function in women and men with depression—this was a secondary finding in some of the large trials where it failed to work as an antidepressant (Fabre LF et al, *J Sex Med* 2012;9(3):821–829).

Side effects

Gepirone's main advantage over other antidepressants is its lack of weight gain and sexual side effects. However, there are other medication options that are free from those problems as well, such as bupropion, trazodone, vilazodone, and possibly vortioxetine (mirtazapine also spares libido but is not weight neutral)—all have a more reliable track record in treating depression.

Like buspirone, gepirone is well tolerated, with common side effects of dizziness, headache, and gastrointestinal distress. It is weight-neutral and nonsedating. Unlike buspirone, it comes with a warning about QTc prolongation and a recommendation to "perform an ECG prior to initiation, during dosage titration, and periodically during treatment." The risk here is a potentially fatal arrhythmia (torsades de pointes) and is greater in patients with electrolyte disturbances.

No other antidepressant comes with that mandate. The reason is that gepirone prolongs the QTc by an average of 18 msec at a high dose (100 mg instant release). A similar degree of prolongation caused the FDA to restrict citalopram's dosing to 40 mg. What is missing from the FDA's report is how much gepirone prolongs the QTc in normal doses (≤72.6 mg extended release). Likely it is less, but an accidental glass of grapefruit juice could send the serum level higher (see drug interactions in the "Gepirone Quick Facts" table).

When to use gepirone

With the cardiac risks of a tricyclic and the efficacy of buspirone (rough comparisons), gepirone is not first-line for depression. Most patients who move to second- and third-line options need something more effective, like a monoamine oxidase inhibitor, a tricyclic, or ketamine, so it's hard to find a place for gepirone there. Perhaps there are patients who will benefit from the azapirone mechanism, but it's hard to justify the cardiac risks when a safer option with comparable antidepressant data exists: buspirone. Buspirone also has an intriguing synergy with melatonin (see the "Buspirone-Melatonin Combo" sidebar).

Gepirone should be dosed with a meal, as food increases its levels by 20%–30%, based on area under the curve (AUC). The average dose in the trials was 70 mg/day (range 55–85 mg/day), but the FDA-approved max is 72.6 mg. A lower maximum dose is suggested for the elderly (36.3 mg) because they achieve higher serum levels of the drug.

Gepirone Quick Facts	
FDA indication	Major depressive disorder
Other uses	Possible benefits in generalized anxiety disorder
Dosage	Start 18.2 mg QD x3 days, 36.3 mg QD x3 days, then 54.5 mg QD; max 72.6 mg QD (36.3 mg QD in elderly). Take with food.
Side effects	Dizziness, insomnia, headache, nausea, gastrointestinal distress
Interactions	CYP3A4 inhibitors raise levels (eg, grapefruit juice, fluvoxamine, nefazodone). Inducers lower levels (eg, carbamazepine, oxcarbazepine, topiramate, modafinils). Gepirone may interfere with alpha-2-agonists (clonidine, guanfacine).
Contraindications	Do not use if QTc >450 msec (potentially fatal torsades de pointes). ECG recommended before treatment and periodically during therapy.

CARLAT TAKE

Gepirone brings new risks and questionable efficacy to the treatment of depression, while sparing patients from weight gain and sexual side effects.

Buspirone-Melatonin Combo

In 2012, Mauricio Fava and colleagues came across a novel antidepressant combination while screening compounds for potential neuroprotective effects. The treatment showed promise in early studies but failed to gain further traction because the industry had little interest in a combo of two generic drugs: buspirone and melatonin.

The combo was tested against placebo and buspirone alone in a double-blind randomized trial involving 134 patients with major depression. After six weeks, the buspirone-melatonin combo separated from placebo (number needed to treat = 5), but buspirone alone did not (Fava M et al, *J Psychiatr Res* 2012;46(12):1553–1563). The improvements were not driven by changes in sleep, as one might expect from a melatonin combo. Instead, a secondary analysis suggested that improvements in cognition drove the antidepressant effects (Targum SD et al, *J Psychiatr Res* 2015;68:392–396).

The doses in this combo pill (buspirone 15 mg QHS with melatonin-SR 3 mg QHS from Mellen Medical Products) were surprisingly low. They were based on optimal levels arrived at in animal studies.

Learn more in our podcast episode, "How Buspirone Mixed with Melatonin to Make an Antidepressant," available at www.tinyurl.com/mt737xrz.

QUICK TAKE

The buspirone-melatonin combo gets a thumbs-up for safety, but we'd like to see more studies before recommending it in routine practice.

Expert Interview
Continued from page 1

about whether there would be some implicit coercion. If these medication effects were reliable, I could see a boss saying to their employee, "If we're going to keep you on this job, we're going to expect you to take that medicine."

TCPR: What have we learned in the 30 years since your book came out?

Dr. Kramer: One theory is that antidepressants change emotional biases. They make it easier for people to think good things about themselves or see the good in the events that happen to them. The patients become more flexible, less stuck in negative emotions, and better able to learn and adapt to reality.

TCPR: How do they help learning?

Dr. Kramer: For example, when a young child has an eye disorder or has to wear a patch at a critical moment for brain development, that child's brain may favor the unpatched eye for the rest of their life, to the point that they have trouble with binocular vision (this is called amblyopia). In studies of rodents, similarly patched in infancy, researchers were able to create a new critical learning period by administering fluoxetine later in life. They patch the dominant eye while the rodent is on the SSRI, and the nondominant eye starts learning again so that later the two eyes work in concert. This result may be related to fluoxetine's effects on neuroplasticity and neurogenesis, but it's not yet clear that this technique works in humans with amblyopia (Huttunen HJ et al, *Sci Rep* 2018;8(1):12830).

TCPR: How does that translate to therapy?

Dr. Kramer: A lot of what we do in treatment is to open up new periods of learning, whether through psychotherapy, medication, or possibly in the future with psychedelics. People just get less stuck. They go around in circles less. When we see that window open, we say, "Maybe this would be a good time to see if you could restart that friendship or reapproach the problems in your marriage."

TCPR: It's learning new paradigms, new ways to approach problems.

Dr. Kramer: Yes, and experiencing new feelings. I had anhedonic patients whom I wrote about in *Listening to Prozac* who didn't believe anyone was happy. They thought people were faking it. They had chronic, low-level depression and had never experienced happiness before taking the SSRI.

TCPR: How do you talk to a patient about the temperamental changes they might expect on an SSRI?

Dr. Kramer: I don't set up expectations. What I do is look for those windows of change. As the patient tells a story from their life, I might pick up that they are more assertive, less sensitive to rejection, or more able to experience pleasure. I'd point out new capacities and say, "This used to be very hard for you. Maybe facing disappointment will be easier now and you can take a chance on entering relationships."

"Antidepressants like SSRIs can do more than alleviate depression; they can enhance traits such as assertiveness and social comfort, raising important ethical questions about their use."

Peter D. Kramer, MD

TCPR: Do these temperamental effects differ among the antidepressant classes?

Dr. Kramer: Nobody knows the answer, but my sense is that the SSRIs have more of an effect on assertiveness—something like alpha status, hierarchy status, or dominance hierarchy effects. My sense is that those newer drugs did more of that. On the other hand, bupropion seems less likely to cause emotional numbing or apathy.

TCPR: Last year, we covered a study that compared outcomes for depression with mirtazapine vs an SSRI. Those with neurotic traits responded better to the SSRI (Naito M et al, *J Affect Disord* 2022;314:27–33).

Dr. Kramer: Yes, I would agree with that. Neuroticism is a technical term that describes people who are easily overwhelmed by stress and prone to negative emotions like anxiety, sadness, anger, and jealousy. Other studies have found that the response to SSRIs in depression is largely attributable to changes in this vulnerability. Also, the loss of neuroticism added extra protection against depression—the benefits of SSRIs lasted longer in these patients (Tang TZ et al, *Arch Gen Psychiatry* 2009;66(12):1322–1330; Quilty LC et al, *J Affect Disord* 2008;111(1):67–73).

TCPR: Your book was controversial. Some psychiatrists worried it would lead people to take antidepressants cosmetically, to improve their personality.

Dr. Kramer: When I coined the term, I wasn't recommending cosmetic psychopharmacology, which is using medication to move from one normal state to another that is more socially rewarded or desirable. The question I raise is: If we had a medication that could reliably change normal people from—say—shy to bold, should we use it for that purpose? At the time, I thought that lots of medications like this were on the horizon, but after 40 years, the serotonergic antidepressants are still the best example of the potential for cosmetic effects along these lines.

TCPR: Another criticism is that you weren't doing anything cosmetic but were simply treating undiagnosed dysthymic disorder with an SSRI (now called persistent depressive disorder).

Dr. Kramer: Perhaps that's true in part. Some of the patients I wrote about had dysthymic disorder, and we didn't appreciate back then how broad the personality effects of dysthymic disorder were. On the other hand, you do see these effects in studies of people who are squeaky clean—no depression. For example, studies find that healthy adults have better leadership traits and are more collaborative in gaming scenarios after taking an SSRI. They are better able to recognize happy faces and less reactive to fearful or angry ones (Knorr U et al, *Exp Clin Psychopharmacol* 2019;27(5):413–432).

TCPR: The changes you saw in psychiatric patients are pretty similar to what researchers have found in healthy adults.

Dr. Kramer: Yes, and they are consistent with animal studies. If you give fluoxetine to a nondominant

Continued on page 6

Neuroscience-Based Nomenclature: Significance to Psychiatrists

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The authors have no financial relationships with companies related to this material.

Jasmine presents with severe bipolar depression. You recommend lithium or an atypical antipsychotic, but she declines, explaining, "What I really need is something for depression, like an antidepressant."

Psychiatric medications are often categorized in ways that are confusing to patients. Antidepressants treat anxiety disorders, antipsychotics treat depression, and a new batch of medications (eg, esketamine, zuranolone, and gepirone) are now classified as "antidepressants" yet bear little resemblance to the original, monoaminergic drugs. In this article, we will look at a new classification system that aims to reduce this confusion.

Neuroscience-Based Nomenclature

The American College of Neuropsychopharmacology and a host of other organizations developed Neuroscience-Based Nomenclature (NbN) as an alternative to the long-standing classification for psychotropic drugs, the Anatomical Therapeutic Chemical (ATC) system. The ATC classification is driven by FDA approval, with familiar categories like antidepressants, antipsychotics, mood stabilizers, psychostimulants, anxiolytics, and hypnotics (Möller HJ et al, *Eur Arch Psychiatry Clin Neurosci* 2016;266(5):385–386).

NbN, by contrast, focuses on the chemical structure or action of medications. The system categorizes 130 psychotropics into 10 neurotransmitter profiles (eg, serotonin, glutamate) and nine modes of action (eg, reuptake inhibitor, antagonist). For example, lurasidone is a dopamine-serotonin antagonist, lamotrigine is a glutamate channel blocker, and ketamine is a glutamate antagonist.

It's difficult to pin down the mechanism of a drug and even more difficult to figure out whether a given mechanism is responsible for its effects. NbN presents an expert consensus in this unsettled area and clarifies some common misconceptions along the way. Gabapentin, for example, is not a GABA-ergic drug. Although it was designed to mimic the neurotransmitter GABA, it does not bind to the GABA receptors. In NbN, it is a glutamate channel blocker that decreases glutamate release by blocking calcium channels. Pregabalin and lamotrigine work in similar ways.

How might NbN improve clinical practice?

Here's how you can use NbN in practice.

Reduce stigma

When patients see that their medication is defined by pharmacologic properties rather than by a disorder, it underscores the fact that their condition is not their fault. The language of NbN conveys that the medication is intended to treat a physical problem and not a personal weakness (Caraci F et al, *Br J Clin Pharmacol* 2017;83(8):1614–1616). For example, aripiprazole is a dopamine and serotonin receptor antagonist under NbN. When it is used to treat major depression or Tourette's disorder, this description is less confusing than "antipsychotic."

Change how you discuss medications

The action-based NbN classification helps patients understand what their medication is doing. For example, the "antidepressant" zuranolone is classified as a neurosteroid and positive allosteric GABA modulator under NbN. Zuranolone is thought to treat postpartum depression by replacing allopregnanolone, a neurosteroid that falls after pregnancy.

Predict medication effects

The NbN app allows you to swipe right to see medications with a similar classification. Zuranolone, for example, shares a mechanism with benzodiazepines and shares in the anxiolytic, sedative, and rewarding qualities of these drugs. Understanding how a patient responded to benzodiazepines in the past can help us predict how they will respond to zuranolone.

Explain off-label use

NbN helps patients understand the rationale for off-label use. Bupropion's NbN classification as a norepinephrine and dopamine reuptake inhibitor and releaser overlaps with that of the psychostimulants, which explains its off-label use in ADHD.

Achieve more rational polypharmacy

Patients may respond better to combinations of medications that have different pharmacologic properties. For example, guanfacine, a central alpha-agonist, successfully augmented methylphenidate, a dopamine and norepinephrine reuptake inhibitor, in a large controlled trial of children with ADHD (Wilens TE et al, *J Atten Disord* 2017;21(2):110–119). On the other hand, the nomenclature alerts

Continued on page 7

Selections From Neuroscience-Based Nomenclature

Neurotransmitter	Action	Examples
Acetylcholine	Enzyme inhibitor	Antidementia (eg, donepezil)
Acetylcholine	Partial receptor agonist	Varenicline
Dopamine	Antagonist	Antipsychotics
GABA	Positive allosteric modulator	Benzodiazepines, zuranolone
Glutamate	Antagonist	Lamotrigine, ketamine, memantine
Histamine	Antagonist	Mirtazapine (low-dose), doxepin, hydroxyzine
Melatonin	Receptor agonist	Ramelteon
Norephinephrine	Reuptake inhibitor	Atomoxetine, nortriptyline
Opioid	Antagonist	Naltrexone
Orexin	Antagonist	Daridorexant, lemborexant, suvorexant
Serotonin	Partial receptor agonist	Buspirone

Research Update IN PSYCHIATRY

NEUROPSYCHIATRY

High-Dose Stimulants in Adult ADHD

Sy Clark, MD. Dr. Clark has no financial relationships with companies related to this material.

REVIEW OF: Farhat C et al, *JAMA Psychiatry* 2024;81(2):157–166

STUDY TYPE: Meta-analysis and network meta-analysis of randomized controlled trials

Finding the right stimulant doses for adult ADHD can be challenging. Practice guidelines—and patients—sometimes suggest exceeding the FDA's approved max doses of 60 mg daily for methylphenidate and 40 mg daily for amphetamine-dextroamphetamine. This study aimed to assess the effectiveness and safety of these higher, unlicensed doses.

The researchers included a total of 47 randomized controlled trials (29 tested methylphenidates; 18 tested amphetamines) with 7,714 participants (mean age 35 years, 56% male, 87% self-identified as White). They calculated standardized mean difference (SMD) in ADHD symptoms over the course of the studies. They also determined the mean dose associated with 50% and 95% (ED50, ED95) of a maximum change in symptoms when compared to placebo, and odds ratio (OR) of discontinuation. They then conducted a network meta-analysis of methylphenidates and amphetamines separately, comparing placebo, licensed, and unlicensed doses of stimulants.

For methylphenidates, the study showed that while increasing doses generally led to better symptom management, the benefits significantly diminished for doses above 40 mg daily: The ED50 was 25 mg daily, and the ED95 was 72.5 mg daily. The higher doses provided a small benefit above maximal licensed doses (SMD -0.23; p=0.03) but were associated with decreased tolerability compared to licensed doses (OR 2.02; p=0.01). Likewise, for amphetamines, there was an initial, sharp decrease in symptoms with increased doses, followed by minimal improvements beyond 35 mg daily (ED50 12.5 mg daily, ED95 30 mg daily).

CARLAT TAKE

While higher-than-normal stimulant doses may slightly reduce ADHD symptoms in adults, they often come with side effects. Rather than pushing the doses of stimulants higher and higher, try augmenting standard doses with exercise, a healthy diet, treating comorbid conditions, cognitive behavioral therapy, and nonstimulant medications.

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Expert Interview

Continued from page 4

monkey and take the dominant monkey away, you can artificially create a new leader for the monkey troop. Now that we have, sadly, SSRIs in the water supply, there are crayfish that are being too bold in water that has a lot of these antidepressants in it. They come out of their underground holes more often than they should (Reisinger AJ et al, *Ecosphere* 2021;12(6):e03527).

TCPR: One more criticism. I've heard people say you were just causing hypomania.

Dr. Kramer: *(laughs)* Yes, I did hear that. None of these patients had hypomanic signs or went on to develop mania or mood cycling. That was not their fate.

TCPR: Any other traits you've seen change with SSRIs?

Dr. Kramer: I saw someone who was obsessive about collecting things. He spent a lot of time going to auctions, and after taking fluoxetine, he no longer felt the need to do that. This wasn't OCD, but more an obsessional personality trait. I also saw a woman who was less obsessional about taking care of her ailing mother.

TCPR: Did that raise some ethical questions?

Dr. Kramer: Indeed! But since then, studies have looked at whether SSRIs make people more or less charitable, and on the whole it's more. They are more empathic, less self-centered, and more outward looking (Crockett MJ et al, *Curr Biol* 2015;25(14):1852–1859).

TCPR: One thing that has stood in the way of "cosmetic psychopharmacology" is that we have a greater awareness of the risks with SSRIs, such as sexual dysfunction, withdrawal problems, decreased bone mineral density, and—in younger patients—rare suicidality.

Dr. Kramer: Yes, and the effects on temperament are not always positive. Patients can feel bland, apathetic, or emotionally numb on SSRIs. I think of an angry, rebellious undergraduate who didn't like the way fluoxetine took his rough edges off, saying, "This isn't me."

TCPR: But even if we reject that cosmetic use, I imagine your findings have a lot of relevance for patients who had a good response and then came off SSRIs.

Dr. Kramer: Yes, that can be a problem for people who experienced those positive temperamental changes. They come back saying, "I was really a better parent on that medicine," or, "I have a job interview coming up and I know I would have a better chance if you put me back on that medicine." This is a challenge. As psychiatrists, we are used to addressing those needs through psychotherapy, not medication. So people stay on them longer, which has created another problem. As they stay on them longer, we see more problems with SSRI withdrawal.

Continued on page 8

CME Post-Test

To earn CME or CE credit, log on to www.TheCarlatReport.com to take the post-test. You will be given two attempts to pass the test. You must answer 75% of the questions correctly to earn credit. Tests must be completed within a year from each issue's publication date. The Carlat CME Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Carlat CME Institute maintains responsibility for this program and its content. Carlat CME Institute designates this enduring material educational activity for a maximum of one (1) *AMA PRA Category 1 Credit*™. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Learning Objectives are listed on page 1.

1. Which statement accurately describes the unique pharmacological profile of gepirone (Exxua) (LO #1)?
   - [ ] a. Gepirone is a selective serotonin reuptake inhibitor (SSRI) with a long half-life, suitable for once-daily dosing
   - [ ] b. Gepirone belongs to the azapirone class, acting primarily as an agonist at the serotonin 5-HT1A receptor
   - [ ] c. Gepirone is contraindicated in patients with anxiety disorders due to its potential to worsen symptoms
   - [ ] d. Gepirone has a significant risk of weight gain and sexual dysfunction, similar to other antidepressants

2. Which of the following best describes one of the potential temperamental effects of SSRIs as discussed by Dr. Kramer (LO #2)?
   - [ ] a. Increased novelty seeking and risk-taking behavior
   - [ ] b. Enhanced assertiveness and reduced sensitivity to rejection
   - [ ] c. Increased novelty seeking and openness to experience
   - [ ] d. Heightened risk of hypomania and manic episodes

3. Which of the following is a potential benefit of using neuroscience-based nomenclature in clinical practice (LO #3)?
   - [ ] a. Simplified drug classification based on FDA approval categories
   - [ ] b. Enhanced understanding of how drugs affect neurotransmitter systems
   - [ ] c. Elimination of side effects associated with psychotropic medications
   - [ ] d. Identification of medications based on their efficacy in treating primary disorders

4. What do findings by Farhat et al suggest about the effectiveness of higher, unlicensed doses of methylphenidate for adults with ADHD (LO #4)?
   - [ ] a. Doses above 60 mg show significantly greater symptom reduction compared with lower doses
   - [ ] b. The benefits of methylphenidate diminish significantly at doses greater than 40 mg because of decreased tolerability
   - [ ] c. Doses beyond FDA-approved limits significantly reduce the risk of discontinuation compared with lower doses
   - [ ] d. Symptom improvement with methylphenidate peaks at 50 mg and remains consistent regardless of further dose increases

5. Which factor contributed to the FDA's approval of gepirone for major depressive disorder (LO #1)?
   - [ ] a. Strong evidence from numerous positive trials with consistent efficacy over a variety of subtypes
   - [ ] b. Lack of adverse effects relative to other antidepressants
   - [ ] c. Improved medication adherence due to the extended-release formulation allowing once-daily dosing
   - [ ] d. A reconsideration of negative trial data and a reevaluation of its overall risk-benefit profile

Neuroscience-Based Nomenclature: Significance to Psychiatrists

Continued from page 5

us to potential risks when medications with overlapping mechanisms are combined. Examples include serotonin syndrome with buspirone (a partial serotonin agonist) and selective serotonin reuptake inhibitors, or hypertension from the combined norepinephrine-reuptake effects of atomoxetine and venlafaxine.

Getting Started With NbN

Learning how to use the new nomenclature isn't difficult:

- Try the NbN3 app, free on Apple and Android devices.
- The NBN website is a great introduction (www.nbn2r.com).
- Make time to learn about the classification. Use webinars, podcasts, or continuing medical education programs. For example: www.tinyurl.com/bdwfnrtv

A drawback of NbN

Complex language such as "norepinephrine and dopamine reuptake inhibitor" can be confusing, and it isn't necessary in straightforward situations where—say—an antidepressant is being started for major depression.

Like the ATC classification, NbN can also give a false sense of certainty. Psychopharmacologic mechanisms do a better job of explaining a drug's benefits than they do its side effects. Psychedelics supposedly induce a spiritual, transcendent state through serotonin-2A agonism, but antagonists at this same receptor (eg, cariprazine, trazodone, and the tricyclics) treat depression without affecting spirituality.

CARLAT VERDICT

NbN gives us a new way to talk about medications, cutting through the stigma of the traditional classifications. Just remember that the categories are simplifications and do not imply deeper understanding of pathophysiology. This option also presents an alternative method of discussing medication purpose with patients—physicians who prescribe psychoactive therapies can use a combination of present categorical descriptions and NbN nomenclature when discussing prescription treatment options with patients.

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Expert Interview
Continued from page 6

TCPR: How do you stop SSRIs?

Dr. Kramer: Very slowly. My sense is that the brain gets acclimated to the medication, and as we come off, I don't want the brain to notice what is going on. If patients were on an antidepressant with a short half-life like paroxetine, I might switch to or add fluoxetine, which in most cases has a long half-life. Typically I would lower the dose by 20% at a time over the course of a year, trying not to end in February in New England when seasonal depression might peak. Better to aim for May.

TCPR: What was it like being Donald Trump's psychiatrist?

Dr. Kramer: *(laughs)* My latest book, *Death of the Great Man,* is a novel about a psychiatrist who is dragooned into the treatment of a narcissistic, buffoonish, autocratic national leader in his corrupt and disastrous second term. It made me think about what a person such as Donald Trump would be like close up, and what it's like to work with extremely dislikeable patients. The doctor in the novel is very dedicated. He tries to see the best in his patient, as I did with difficult patients in my own practice. Perhaps, in imagination, I was overly empathetic. I wrote the book before the events of January 6, 2021. What happened that day surprised me. I underestimated how bad things could get.

TCPR: Thank you for your time, Dr. Kramer.

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