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IN THIS ISSUE

Focus of the Month:
Antidepressant Roundup

Learning objectives for this issue: **1.** Summarize the state of current antidepressant medications now under development. **2.** Explain the ongoing debate over the effectiveness of antidepressant medications versus the placebo effect. **3.** Describe some of the methods researchers are using to try to predict a patient's response to an antidepressant. **4.** Understand some of the current findings in the literature regarding psychiatric treatment.

Is It Possible that Antidepressants Really Don't Work?

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Dr. Posternak has disclosed that he has no relevant relationships or financial interests in any commercial company related to this educational activity.

A heated debate over how well psychiatric medications actually work has led some authorities in our field to suggest that psychiatry is currently experiencing a "crisis of confidence" (Nierenberg AA et al, *J Clin Psychiatry* 2011;72(1):27–33). This debate has even begun to spill over into the mainstream media. Most recently, a *60 Minutes* exposé suggested that antidepressants *may not even work* for the majority of depressed patients for whom they're prescribed. Although you may be tempted to shrug off such criticism as another fringe assault on psychiatry, be warned that you do so at your own risk: the critics make a compelling case. After all, if they didn't, our leaders wouldn't be calling this a "crisis" right now. So what exactly is going on?

Irving Kirsch and the Placebo Response

The *60 Minutes* piece focused primarily on the work of Irving Kirsch, a psychologist currently at Harvard Medical School who has been studying

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Future Developments in Antidepressant Therapy

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Dr. Gable has disclosed that she has no relationships or financial interests in any company pertaining to this educational activity. Dr. Balt has disclosed that his spouse is employed as a sales representative for Bristol Myers Squibb.

In 2011 in the pages of *TCPR,* we asked, "What's new in antidepressant treatment?" The answer was "not much" (*TCPR,* April 2011). In 2012, unfortunately, the answer isn't very different.

Given the high cost ($1.8 billion) and long time (almost nine years, on average) to bring a new antidepressant to market, drug companies are putting fewer eggs into more selective baskets.

As you know, fluoxetine (Prozac) entered the U.S. market in 1987, setting off the introduction of a cascade of SSRIs—and, eventually, SNRIs—which have, collectively, become some of the most prescribed drugs in the United States (Olfson M and Marcus SC, *Arch Gen Psychiatry* 2009;66:848–856). We have seen six different SSRIs and three different SNRIs approved for major depression and a smattering of other indications. The final SSRI to enter the market, escitalopram (Lexapro), lost its patent and went generic in March of 2012. Duloxetine (Cymbalta), one of the SNRIs, will also lose its patent in 2013.

That leaves only a few new name-brand antidepressants left—and a more limited selection of free samples, too, for those of you who still use them. For the most part, these remaining name-brand medications are "me-too" drugs and patent extenders, like desvenlafaxine (Pristiq, the active metabolite of venlafaxine) and extended-release trazodone (Oleptro). Vilazodone (Viibryd), from Forest Labs, the people who brought you citalopram (Celexa) and escitalopram, could best be described as a combination of buspirone (BuSpar) and an SSRI. Drug companies are now turning their attention to

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the placebo response for more than three decades. In it, Kirsch asserted that depressed patients get better primarily because of the placebo effect, not because of the antidepressant medication itself. In response, the psychiatric community offered some rather weak rebuttals. Michael Thase, a prominent psychiatric researcher from the University of Pennsylvania, said that Kirsch "confused the results of studies with what goes on in practice" (ie, 'let's not let science get in the way of what we know to be true'). He concluded by confessing: "I wish our antidepressants were stronger."

Tom Laughren, director of the FDA's division of psychiatry products, admitted to *60 Minutes* that "the difference between improvement in drug and placebo is rather small." So small, in fact, that Great Britain has begun to train a new legion of psychotherapists after concluding that antidepressants don't work for most cases of mild to moderate depression.

Kirsch first dropped the placebo bombshell on psychiatry in 1998, in an online journal article entitled "Listening to Prozac, but Hearing Placebo." He and his co-author analyzed the results of 19 published trials involving 2,318 patients, and found that the vast majority (75%) of benefit from antidepressant medication could be attributed either to spontaneous remission (the natural ups and downs of depression) or to the placebo response. They concluded at the time that the benefits of antidepressant medications were probably overstated. In 2008, Kirsch published a second meta-analysis that now included unpublished data obtained from pharmaceutical companies using the Freedom of Information Act. Combining the results of 35 published and unpublished trials (ie, trials where results usually didn't look so good), Kirsch reached a more damning conclusion: antidepressants offer almost no discernible benefit over placebo—other than in cases of severe depression (Kirsch I et al, *PLoS Med* 2008;5(2):e45).

Kirsch's two main points can be summarized as follows: (1) The majority (perhaps 50% to 75%) of benefit that subjects report from antidepressants is attributable to placebo or passage of time, and far less to a true drug effect; and (2) When the results of unpublished trials are taken into account, this difference falls well below the consensus opinion of what is generally accepted as clinically meaningful (except for the most severely depressed patients).

These findings have been corroborated by others (see for example, Fournier JC et al, *JAMA* 2010;303(1):47–53), and Kirsch's conclusions seem to have been accepted by leaders in the field. In a recent conference organized by Harvard's Andrew Nierenberg in response to Kirsch's work, a panel of experts concluded that clinicians should "expect greater antidepressant efficacy in patients with more severe depression than in patients with mild or moderate depression," and recommended psychotherapy for patients with mild or moderate depression (Nierenberg AA et al, *J Clin Psychiatry* 2011;72(1):27–33). Although some very recent meta-analyses do show modest benefit in less severe depression (for example, Gibbons RD et al, *Arch Gen Psychiatry* 2012;online ahead of print) the evidence supporting the short-term efficacy of antidepressant medications is unfortunately meager at best.

Reconciling Clinical Data with Everyday Experience

Even though clinical trials show only modest support for the efficacy of antidepressants, we've all seen how well they work in clinical practice. How do we account for this apparent discrepancy? Critics would say it's because we fail to appreciate how powerful the placebo effect is, and that most depressions usually remit on their own even without treatment. On both these counts they are almost undoubtedly correct—for example, in one study we found that as many as 85% of depressed patients spontaneously recover within one year, even without medications (Posternak MA et al, *J Nerv Ment Dis* 2006;194(5);324–329). But are there any other explanations?

One possibility is that the methodology used in antidepressant trials is flawed. In an article depicting the history of clinical trial methodology, my colleagues and I showed how clinical trial methods have remained almost completely unchanged over the past 50 years (Posternak MA et al, *Am J Psychiatry* 2002;159(2):191–200). Despite widespread recognition of the numerous flaws in these studies, why would pharmaceutical companies continue to use inefficient trial methods? The reason is actually quite simple: the primary goal of drug-funded studies is less about advancing science than about bringing an antidepressant to market. And the surest way to do that is for companies to do what the FDA requires of them—and no more. Changing trial design would mean going against a precedent that has arguably worked adequately for its intended purposes for decades.

Here's one example of a 1960s-era trial design flaw: subjects are given

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an antidepressant or a placebo for six weeks. They are then asked to come back every week to check in so that researchers can chart their progress. A typical drug trial, right? But that's a lot of contact with empathic listeners—and all that contact might help *everyone* in the trial get better, thereby increasing the placebo response. When we studied the impact of these frequent visits, by comparing these trials to others in which visits weren't so frequent, we found that they accounted for as much as 40% of the placebo response (Posternak MA and Zimmerman M, *Br J Psychiatry* 2007;190:287–292). These trial design flaws would make it a lot harder for an effective medication to look much better than placebo. As a result, these studies may actually *underestimate* how effective antidepressants are.

What Should We Do with This Information?

A few takeaway points can be summarized:

1. **The efficacy of antidepressants in the short term is meager, but treatment involves more than just the short term.** Antidepressants almost always perform only *slightly* better than placebo in short-term trials—just well enough to bring them to market. But there's a lot of other stuff out there showing that antidepressants work (eg, long-term discontinuation studies that show higher rates of relapse even months after patients have been switched to placebo).
2. **The way we study antidepressants over the years may not be very good.** The continued reliance on the outdated Hamilton Depression Rating Scale (Zimmerman M et al, *J Clin Psychopharmacol* 2005;25(2):105–110); the financial pressure to rush subjects through studies; the use of research assistants rather than experienced clinicians; the frequent personal contact with subjects; and the lack of inter-rater reliability assessments are just a few (of many) design flaws that likely make antidepressants look worse than they actually are.
3. **Antidepressant efficacy trials have been conducted almost exclusively by the pharmaceutical industry.** With few exceptions, drug trials are designed to get FDA approval. Because antidepressants only need to show slight superiority to placebo, it should not come as a surprise that that's all that has been accomplished so far.
4. **The jury is still out.** Kirsch has provided a wake up call to the field, but bear in mind that his work only focuses on a tiny sliver of a very large pie.

As a result, where we go from here is anything but clear. It is disconcerting to admit that 50 years since their introduction, we still don't even know how well antidepressants work.

TCPR'S VERDICT Antidepressants may not be as wonderful as we've all come to believe, but might be better than the research has suggested. As of now, it seems premature to dramatically change the way we use them. It may be valuable, however, to keep in mind that most cases of depression do resolve on their own—and a little empathic support can go a long way.

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augmenting agents, like the atypical antipsychotics aripiprazole (Abilify) and quetiapine (Seroquel XR) (and others in clinical trials), but concerns about metabolic safety—not to mention cost—make these less attractive as first-line treatments.

Despite the panoply of options, treating depression remains more of an "art" than a science, as there are still no 100% reliable ways to predict a patient's response to a given antidepressant, and no way to determine the molecular basis of an individual patient's symptoms. Some psychiatrists have their own "favorite" antidepressants and use them regularly, switching or augmenting as needed. Some prefer to mix drugs from different classes to create combinations with novel mechanisms. This latter approach is not supported by the evidence. For example, a recent randomized trial showed that neither the combination of bupropion (Wellbutrin) plus escitalopram, nor mirtazapine (Remeron) plus venlafaxine (Effexor) provided any benefit over escitalopram alone (Rush AJ et al, *Am J Psychiatry* 2011;168(7):689–701).

Since most of the talk about new medication options focuses on the neurotransmitters involved, we will attempt to summarize the state of current antidepressants under development by separating them into groups based on the specific pathways they affect. Hopefully this gives a better sense of what may lie ahead in the antidepressant pipeline.

Melatonin System

The melatonin system seems like a reasonable target for antidepressants, since disturbances of circadian rhythm may cause depressed mood, fatigue, low energy, and poor concentration. **Agomelatine** (Valdoxan), a melatonin analogue approved in Europe, is similar to ramelteon (Rozerem), which was approved by the FDA in 2005 for insomnia characterized by difficulty with sleep onset. Both are melatonin (MT1 and MT2) receptor agonists, helping to promote sleep. Agomelatine is also a 5-HT2B and 5-HT2C receptor antagonist; its 5-HT2C antagonism hypothetically increases dopamine and norepinephrine release in the frontal cortex.

Does it work? Not very well. In trials comparing agomelatine to placebo or SSRIs, agomelatine was just about as effective as venlafaxine, fluoxetine, and sertraline—but not in all trials—and may actually be *worse* than paroxetine (Paxil). Furthermore, its efficacy relative to placebo was only, on average, a few HAM-D points (Hickie IB and Rogers NL, *Lancet* 2011;378:621–631). These observations, together with the finding of potential hepatotoxicity at higher doses, might explain why Novartis halted the development of agomelatine for the U.S.

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Q&A With the Expert

This Month's Expert

Predicting Antidepressant Response
Andrew Leuchter, MD

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Dr. Leuchter has disclosed that he has been a paid consultant to NeoSync Inc. on the NeoSync EEG Synchronized TMS device (NEST). Dr. Balt has reviewed this article and found no evidence of bias in this educational activity.

TCPR: Dr. Leuchter, is there a science to choosing an initial antidepressant for a depressed patient? Is it still predominantly personal preference or is there a better way to make that choice?

Dr. Leuchter: At this point, it is still very much clinician and patient preference. I don't think that there is any effective, proven way to predict medication response. I have been involved in research on biomarkers—we call them "response endophenotypes"—such as EEG, where we look at the physiologic response of the brain to a new drug and try to determine whether the drug will work for that patient. There have been several replication studies of our EEG work, but we would not yet advocate introducing this test into clinical practice.

TCPR: Can you describe very briefly some of the physiological changes that you might see on EEG?

Dr. Leuchter: These are functional changes in the prefrontal brain regions. We discovered that there are signals that emerge from the prefrontal regions that indicate whether patients are responding or are likely to respond to the medications they are receiving.

TCPR: How exactly does this work?

Dr. Leuchter: My research team and I record a baseline EEG and then record a second EEG after the patient is on a drug for one week. We look to see shifts in energy in certain frequency bands, specifically alpha and theta, that appear to be characteristic of early response to the drug.

TCPR: So you don't get specific readouts or specific patterns with individual drugs? Instead you see either a yes or a no response to whatever drug you are applying at that time?

Dr. Leuchter: We actually see both. When we put somebody on an initial medication—usually an SSRI—we see a signal of whether they are going to respond to that drug or not. Interestingly, in our studies we've found that if patients have a negative indicator in response to the SSRI, they are likely to have a positive indicator with regard to bupropion (Wellbutrin). Now, obviously, not everybody who fails to respond to an SSRI goes on to respond to bupropion, so it is not a one-to-one correspondence. But we do know that having a negative indicator on one drug seems to indicate a greater likelihood of having a positive indicator on a drug with a totally different mechanism of action. We have published these results (Leuchter AF et al, *Psych Research* 2009;169:132–138) but have not yet published independent replication of those findings. [Editor's note: for more on this, see also *TCPR,* November 2009.]

TCPR: That is something that we generally observe in practice, too. When patients fail one or multiple SSRI trials, they may have success with a trial of a different class of medication. So it sort of corroborates clinical experience.

Dr. Leuchter: Yes. What's interesting is that it corroborates clinical experience but not clinical trials. Reading the literature, we know that if we switch to a drug with a totally different mechanism of action that it does not statistically increase the chances of response. However, we have all had the clinical experience where many people who are SSRI-nonresponders turn out to be responders to an SNRI or a drug with an entirely different mechanism. It may be that without this type of biomarker, we cannot reliably identify those subjects who will benefit from a medication with a different mechanism of action.

TCPR: What is a "response endophenotype"?

Dr. Leuchter: It's a term we use for a behavioral or neurobiological feature that we can measure in a patient early in the course of treatment that may predict a patient's ultimate outcome.

TCPR: Another predictor of response would be pharmacogenetic testing. Although clinicians do not seem to use that regularly, where does it stand right now?

Dr. Leuchter: I think the reason that people don't use it regularly is because it hasn't been shown to work (Garriock HA et al, *Biol Psychiatry* 2010;67(2):133–138). There are multiple genes that confer risk for depression and that are involved in mediating drug response. So since we don't really have a good model for how people get depressed, it is very hard to have a good model for what genes we ought to look at when we attempt to predict response.

TCPR: Patients are often concerned about side effects. Is there any way to use either your endophenotype approach or another biomarker measure to predict whether a patient will have side effects from a given medication?

Dr. Leuchter: There are some promising leads that may have clinical applicability, particularly when it comes to drug metabolism, such as cytochrome P450 2D6 and 3A4 activity. Researchers have established that the rate at which a patient metabolizes some of these compounds is probably related to the likelihood of side effects or drug interactions (D'Empaire I et al, *J Psychiatr Pract* 2011;17(5):330–339). So I think some of this testing is ready for prime time. Of course there is the question of cost and whether you get more from the testing than you would from close clinical monitoring. The jury is still out on that.

TCPR: Another area of your research is placebo response. Could you summarize your work?

Dr. Leuchter: A decade ago, our group was the first to demonstrate that there were physiologic changes in the brains of placebo responders that were distinct from those of patients who didn't respond to placebo or who responded to active drug (Leuchter AF et al, *Am J Psychiatry* 2002;159(1):122–129). So "placebo response" is not just a psychological phenomenon, but a physiologic phenomenon. We also have promising findings to suggest that brain function even before treatment might indicate the likelihood that one will respond to placebo, and that there are certain genetic polymorphisms, specifically in MAO-A and COMT genes, that make one more likely to be a placebo responder—at least in the context of depression (Leuchter AF et al, *J Clin Psychopharmacol* 2009;29(4):372–377). We continue to pursue this work and have been looking more recently at the role of expectations and different personality variables as mediators of placebo response. We hope to report these results within the next few months.

"I don't think that there is any effective, proven way to predict medication response."

Andrew Leuchter, MD

TCPR: What types of physiological changes have you observed in placebo responders?

Dr. Leuchter: Like active-drug responders, they showed changes in neurophysiologic activity in the prefrontal region. However, these changes took longer to come on. In drug responders, we saw changes in many cases within 48 hours and certainly saw very significant changes by one week. The placebo responders didn't tend to show any change until about two weeks, and even then, the changes that we saw frequently were in the opposite direction of those that we saw in drug responders. Based on the particular symptoms that they showed, there was no way that you could distinguish the placebo responder from the drug responder. But physiologically they looked different. We saw decreases in prefrontal cordance [a measure of regional brain activity] in the drug responders and increases in prefrontal cordance in placebo responders.

TCPR: Does that change normalize over time after the placebo effect wears off?

Dr. Leuchter: Well, actually, it normalizes in both groups; they tend to come back to their pretreatment baseline over time. That makes sense with the drug effect because if you block reuptake, for instance, the brain does eventually re-equilibrate. In placebo responders, why they get back to their baseline is an interesting question.

TCPR: Based on your research, are there patient-centered factors that predict a better response to a treatment, whether it is a placebo or an antidepressant?

Dr. Leuchter: There certainly appear to be some. Some of these are seemingly common sense factors, such as: the greater the expectation people have for a positive outcome of treatment, the more likely they are to respond to treatment. The interesting thing is that expectations seem to play a different role in medication responders than they do in placebo responders.

TCPR: Would it help outcomes if we simply assess a person's expectations at baseline?

Dr. Leuchter: I think it would. There was an interesting study last year on placebo response where the conclusion was that a placebo works *even if you know you're getting it.* But when you look at the study, people were told it was a study of placebo response, and they would either get a placebo or be put into a control condition. Those who did *not* receive placebo were disappointed, and therefore may have responded more poorly in the study (Kaptchuk TJ et al, *PLoS One* 2010;5(12):e15591).

TCPR: It's hard to do a placebo-controlled placebo trial.

Dr. Leuchter: Exactly.

TCPR: What are your suggestions for enhancing patients' expectations in an appropriate and ethical way?

Dr. Leuchter: We live in an age where people have to be fully informed of what they are getting and the consequences of those choices. But we should harness expectations whenever we can. When I prescribe a new medication for a patient, I always tell the patient, "You know, I think that this medicine that we are going to prescribe for you now is really going to help you." If I didn't

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market in October of 2011. It's not clear whether it will ever become available here.

Glutamate System

One well-known disadvantage of current antidepressants is their slow onset of action. A series of trials at the NIMH (which have received much popular attention in the last several months) has shown that **ketamine,** an antagonist of the N-methyl-D-aspartic acid (NMDA) subtype of the glutamate receptor, can have a powerful and rapid antidepressant effect. And yes, it's *that* ketamine, also used as an anesthetic/sedative by veterinarians and pediatric anesthesiologists and abused on the streets as "Special K." In one NIH-funded study of 18 patients with treatment-resistant depression who received an infusion (0.5 mg/kg) of ketamine, a 50% reduction in HAM-D score ("response") was seen in half the patients within two hours. Within 24 hours, 71% met criteria for response and 29% for remission, and 35% of subjects maintained their response one week later (Zarate C et al, *Arch Gen Psychiatry* 2006;63:856–864).

Basic research shows that ketamine raises intracellular levels of a protein called mTOR and increases dendritic spines in pyramidal cells of the frontal cortex, which might account for its antidepressant effect. Ketamine must be given intravenously, and may cause dissociative side effects. Some facilities are now studying repeated ketamine infusions, for example at weekly intervals, to observe for prolonged responses. This treatment remains off-label but is an intriguing possibility for the acute treatment of severe depression, including suicidality (DiazGranados N et al, *J Clin Psychiatry* 2010;71(12):1605–1611).

Acetylcholine System

Acetylcholine may be involved in the control of mood, cognition, and attention. We know, for example "pro-

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Research Updates IN PSYCHIATRY

Section Editor, Glen Spielmans, PhD

Glen Spielmans, PhD, has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

DEPRESSION

Can a Blood Test Diagnose Depression?

Psychiatrists have long wondered whether someday we might have an objective way to diagnose depression, in much the same way an internist orders a blood test or X-ray. A recent article suggests that just such a test might be on the horizon. Is it the real deal?

Investigators obtained blood samples from depressed and non-depressed patients. They measured levels of nine "biomarker" proteins and performed a calculation to get an "MDDScore." The details of the calculation are undisclosed, proprietary information, but the end result is straightforward: a number on a scale of 0 to 100, where anything over 50 suggests depression. In a pilot study of 36 depressed and 43 non-depressed patients, the average MDDScores were 85.5 for depressed patients and 32.9 for others. A follow-up replication study of 34 depressed patients found an average score of 81. There were a few false negatives and positives, but the sensitivity and specificity were high, at about 91% and 81%, respectively.

Investigators selected the biomarkers from an initial set of 110 candidates because they helped to distinguish depressed people from non-depressed people. Markers included metabolic, inflammatory, and neurotrophic proteins, among others. Interestingly, in the published study, only four markers were consistently (and significantly) different between the two populations. Whether these four were weighted more heavily in the MDDScore calculation is unknown.

While the results are certainly impressive, they should be taken with a grain of salt. For one thing, there's no known reason why these nine (or in the paper, only four) proteins should be elevated in depression, or whether they normalize with treatment. Also, subjects were all relatively healthy, not taking NSAIDs or antidepressants, and had no other psychiatric complaints or "unstable medical disorders." The authors also did not control for demographic factors.

Furthermore, the authors point out that the test cannot differentiate bipolar from unipolar depression (although they're investigating this) or, for that matter, any other psychiatric condition; it cannot be used to predict vulnerability to depression in someone without clinical symptoms; and it does not reflect the severity or prognosis of a patient's depression. Nevertheless, the article's sponsor, Ridge Diagnostics, has already begun marketing the test (at $745 a pop) directly to clinicians and patients (Papakostas GI et al, *Molecular Psychiatry* 2011;online ahead of print).

TCPR's Take: There may indeed be some biochemical differences between some depressed patients and non-depressed individuals, and this study may give us some early hints. But the question is certainly still in the research stage. Individuals with depressive symptoms but a negative test still deserve treatment, while a positive MDDScore in the *absence* of subjective complaints presents an entirely different dilemma. Until the science is made a bit more transparent and more data are obtained—preferably with patients that resemble those we see in practice, and with more controls—we recommend that you save yourself the $745 and steer clear of this test.

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think it was going to help, I wouldn't be prescribing it. So there is actually nothing misleading about it. To some extent raising expectations can become a self-fulfilling prophecy. In clinical trials, the placebo response may be an annoyance. In clinical practice, placebo response is our "friend."

TCPR: Do patients benefit from an explanation of a drug's mechanism?

Dr. Leuchter: Yes, and there are two main reasons. One is that some patients won't go for the treatment unless you "medicalize" it. So if you make it sound like a medical treatment and explain the mechanism through which drugs work, I think that increases acceptability and maybe adherence. Secondly, it's a way to increase confidence and positive expectation because it is not just that you are saying, "I think this is going to help you." You are also saying, "I think I know *why* this is going to help you."

TCPR: When it comes to treatment-resistant depression, is the problem that we just don't have the right tool to treat it, or is it largely a patient's negative expectation: "Well, the last medication didn't do anything for me so the chances are that nothing else will"?

Dr. Leuchter: Treatment resistance is a very complex phenomenon, and to some extent when individuals are treatment-resistant it is because we don't have the right molecules—the right treatment—to correct whatever biological abnormality exists. At the same time, there probably is an element of pharmaco-conditioning going on. We have an article coming out soon that shows that when you expose individuals to one unsuccessful treatment after another you probably are conditioning them in some ways not to respond to the next treatment. When they have the experience again and again of taking a pill and not getting better, at some point negative conditioning may start to play a role. Jerome Frank, when he wrote *Persuasion and Healing: A Comparative Study of Psychotherapy,* said that one of the goals of therapy was the restoration of hope, and I think there is a lot of truth to that. We are in the business not just of prescribing treatment, but also encouraging patients to believe that the treatment is likely to benefit them. We are not really doing the patient full service unless we address their hopefulness or their hopelessness.

TCPR: Thank you, Dr. Leuchter.

CME Post-Test

To earn CME or CE credit, you must read the articles and log on to www.TheCarlatReport.com to take the post-test. You must answer at least four questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be taken by May 31, 2013. As a subscriber to *TCPR,* you already have a username and password to log on www.TheCarlatReport.com. To obtain your username and password or if you cannot take the test online, please email info@thecarlatreport.com or call 978-499-0583.

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Below are the questions for this month's CME post-test. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Note: Learning objectives are listed on page 1.

1. In one NIH-funded study, what percentage of patients with treatment-resistant depression who received an infusion (0.5 mg/kg) of ketamine met criteria for "response" within 24 hours (Learning Objective #1)?
   [ ] a) 29% [ ] b) 35% [ ] c) 50% [ ] d) 71%

2. In an NIH-funded study of depressed patients receiving IV scopolamine (4 mg/kg), what percentage of participants achieved remission after three infusions three to four days apart (LO #1)?
   [ ] a) 5% [ ] b) 18% [ ] c) 56% [ ] d) 89%

3. According to research by Andrew Leuchter, MD, which of the following has NOT been shown to predict placebo response in the treatment of depression (LO #3)?
   [ ] a) which antidepressants the patient has failed in the past [ ] b) EEG changes shortly after initiating treatment
   [ ] c) genetic polymorphisms in MAO-A and COMT genes [ ] d) patients' expectations and specific personality variables

4. In Papakostas GI et al's study, investigators obtained blood samples from depressed and non-depressed patients and measured what factor (LO #4)?
   [ ] a) Levels of monoamines [ ] b) Levels of biomarker proteins [ ] c) Levels of RNA [ ] d) Levels of blood sugar

5. In a 2006 study by Posternak MA et al, the researchers found what percentage of depressed patients spontaneously recover within one year, even without medications (LO #2)?
   [ ] a. only 20% [ ] b. 45% [ ] c. 60% [ ] d. as many as 85%

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cholinergic" drugs such as physostigmine, an inhibitor of cholinesterase, have the potential to exacerbate depression. You may recall that there are two subtypes of acetylcholine receptors. The anticholinergic drug **scopolamine,** which binds to the muscarinic subtype, may have a rapid antidepressant effect similar to ketamine. In an NIH-funded study of 18 depressed patients receiving intravenous scopolamine (4 mg/kg), antidepressant effects were seen within four days, and 56% achieved remission after three infusions three to four days apart (Furey ML and Drevets WC, *Arch Gen Psychiatry* 2006;63(10):1121–1129).

Another investigational antidepressant, **S-mecamylamine** (TC-5214), binds to the nicotinic subtype of the acetylcholine receptor. This is the same receptor responsible for the effect of varenicline (Chantix) and, of course, nicotine. An initial trial of TC-5214, a "nicotinic receptor modulator," in 265 subjects found an average six-point decrease in HAM-D scores, but two phase III trials failed to replicate these findings. In March 2012, AstraZeneca announced that it would no longer be pursuing this agent due to the negative clinical trial data.

Serotonin System

While it doesn't look like there are any more SSRIs on the horizon, drugs that affect the serotonin system remain targets for antidepressant development. **Vortioxetine** (Lu-AA-21004), from Lundbeck and Takeda Pharmaceuticals, is currently in phase III trials. It is a partial agonist of 5-HT1A receptors (like buspirone), but it also blocks 5-HT3 and 5-HT7 receptors. The function of these receptors in depression is not well understood (although the 5-HT7 antagonist properties might remind you of the novel antipsychotic lurasidone [Latuda]). A six-week, placebo-controlled trial of 429 subjects showed response (68%) and remission (49%) rates that were comparable to venlafaxine and superior to placebo (Connolly KR and Thase ME, *Expert Opin Emerg Drugs* 2012;online ahead of print).

There may still be a market for multifunctional reuptake inhibitors, too. Forest Labs is conducting phase III trials of levomilnacipran, the active enantiomer of milnacipran, an SNRI like duloxetine and venlafaxine. Milnacipran is already marketed in the U.S. as Savella. However, most psychiatrists are probably unfamiliar with it, because its sole FDA indication (received in 2009) is for fibromyalgia. It's not clear why Forest never sought approval of milnacipran for depression in the U.S. (it's approved overseas for this indication); perhaps because earlier research showed no benefit over SSRIs or TCAs (Nakagawa A et al, Milnacipran versus other antidepressive agents for depression. *Cochrane Database of Systematic Reviews,* 2009).

Norepinephrine System

Finally, a study of a novel norepinephrine reuptake inhibitor called **edivoxetine** showed favorable response (49%) and remission (30%) rates in a 10-week, placebo-controlled trial (Pangallo B et al, *J Psychiatr Res* 2011;45(6):748–755). Eli Lilly is currently conducting four separate phase III

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trials of this agent. The company is seeking an indication for adjunctive treatment of depression (basically converting an SSRI alone into an "SNRI-style" regimen) and for ADHD, where it may replace its sister drug Strattera (atomoxetine), also from Lilly, which is projected to lose its patent protection in 2016.

The future treatment options for depression appear to be limited. But rather than give up hope, we might see this as a golden opportunity to refine our use of existing treatments, or characterize exactly which medications are most appropriate for specific patients.

In addition, a "back-to-basics" emphasis on evidence-based psychotherapies (practiced by us or our colleagues) might help us treat our patients more effectively. Finally, we might see more use of somatic interventions such as transcranial magnetic stimulation (TMS) or deep brain stimulation (DBS). The FDA's regulatory hurdles are somewhat lower for these interventions, but that means we need to be even more diligent in looking for the evidence that these treatments work.

TCPR'S VERDICT

Even though glutamate- and acetylcholine-based drugs might hold some promise in the future, other new antidepressant pathways seem to have led to dead ends, at least so far. For now, it's probably best to understand the currently available drugs but not hold out hope that the next miracle cure is right around the corner.

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