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Steve Balt, MD
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Depression

Learning objectives for this issue:
1. Describe how inflammation is tied to depression. **2.** Discuss how clinical trial information is reported in the psychiatry literature.
3. Explain how ketamine is used as a treatment for depression.
4. Understand some of the current findings in the literature regarding psychiatric treatment.

Fire in the Mind: The Depression-Inflammation Connection

Kelly Brogan, MD
Clinical Instructor in Psychiatry
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Dr. Brogan has disclosed that she has no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

We have all bumped up against the limits of the current model of antidepressant treatments for depression: the patient who comes in with a laundry list of failed medication trials, or a number of other complaints depicting a portrait of malaise—aches, pains, anhedonia, fatigue, brain fog, digestive woes—that don't really respond to currently available agents. What if shifting our thinking about underlying causes might hold the answer to treatment of these individuals?

It may be time to refine—perhaps even to discard—the monoamine hypoth-

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In Summary

- The diverse manifestations of depressive illness, and the frequently incomplete response to conventional antidepressants, suggest that our current models for depression may be outdated or inaccurate.
- Elevated levels of inflammatory cytokines, such as IL-1, IL-6, and TNF, may be at the heart of depression.
- Thinking of depression as an inflammatory syndrome may lend itself to more effective interventions, such as anti-inflammatory drugs, diets, and lifestyle interventions.

Q&A With the Expert

Ketamine for Depression

Sanjay J Mathew, MD

Associate Professor of Psychiatry & Behavioral Sciences
Baylor College of Medicine
Staff Physician, Michael E. Debakey VA Medical Center
Houston, TX

Dr. Mathew has disclosed that he has worked as a paid consultant for AstraZeneca, Naurex, Bristol-Myers Squibb, and Roche/Genentech. Dr. Balt has reviewed this interview and found no evidence of bias in this educational activity.

TCPR: Dr. Mathew, there is a lot of buzz around ketamine as a treatment for depression. What are the effects of ketamine in depression trials thus far?
Dr. Mathew: The studies so far have been very consistent. Typically, a slow, constant infusion of a subanesthetic dose—0.5 mg/kg—of ketamine is given over 40 minutes. To put this in perspective, the anesthetic dose is generally 2 to 3 mg/kg, so we are talking about one-sixth to one-fourth the usual anesthetic dose. During the infusion, patients often report dissociative-like symptoms, a sense of derealization, depersonalization, and changes in their perceptions of their body. For instance, they may view their limbs as unusually large or there may be feelings of levitation, such as floating above the bed. These are described usually 10 to 15 minutes into the infusion. For some patients there is a sense of relief, like a big weight has been lifted off of them. Feelings of chronic body pain can improve during the infusion as well. There are sometimes other side effects, including blurred vision, dizziness, and nausea that

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esis and explore a new perspective on chronic depression: the inflammatory model. First introduced in 1991 (Smith RS, *Med Hypotheses* 1991;35:298–306) and ripe to address the complexity and heterogeneity of what we call "depression," the inflammatory model may hold clues for the understanding and treatment of this scourge, as it has for such conditions as cardiovascular disorders, diabetes, cancer, and autoimmune pathology.

Alterations in serotonin-related physiology and stress hormones, the targets for our current treatments, may actually be downstream manifestations of this more primary driver. In other words, clinical depression may be the "fever" for which there are many disparate but related triggers. Let's take a tour of the basic tenets.

Relief Through Reduction of Inflammation

For starters, an increasing number of trials have examined the role of anti-inflammatory agents in the treatment of depression. In one recent randomized, controlled trial, a subset of patients resistant to antidepressant treatment and identified by serum markers of inflammation, most notably C-reactive protein (CRP) >3mg/L, were responsive to treatment with the TNF-alpha antagonist infliximab (Remicade) (Raison CL et al, *JAMA Psychiatry* 2013;70:31–41). Elevations in CRP were also shown to precede the onset of depressed mood in asymptomatic elderly patients without a history of the illness (van den Biggelaar AH et al, *Exp Gerontol* 2007;42:693–701).

Celecoxib (Celebrex), the anti-inflammatory COX-2 inhibitor, has been found in randomized, placebo-controlled trials to be superior to placebo in antidepressant augmentation (Müller N et al, *Mol Psychiatry* 2006;11:680–684). In the setting of psoriasis treatment with etanercept (Enbrel), mood was improved independent of psoriatic relief (Tyring S et al, *Lancet* 2006;367:29–35). Thinking of depression as an inflammatory syndrome, therefore, may lend itself to more effective interventions, particularly in cases unresponsive to or incompletely responsive to antidepressants (Caravalho LA et al, *J Affect Disord* 2013;148(1):136–140).

Similarly, several studies show SSRIs may work primarily through immunomodulatory pathways and not through "serotonin reuptake," as classically believed. Antidepressants may downregulate inflammatory cytokines such as interleukin 6 (IL-6) and enhance secretion of anti-inflammatory immune messengers such as IL-10 (DeBerardis D et al, *Int J Immunopath Pharmacol* 2010;23(2):417–422).

In addition, antidepressants can activate growth factors like brain-derived neurotrophic factor (BDNF), and they have been found to enhance glucocorticoid receptor sensitivity, bringing the HPA axis back in line for some patients, but potentially overshooting with chronic exposure (Carmine M et al, *Psychoneuroendocrinology* 2004:29;423–447).

Even outside of the pharmaceutical realm, curcumin, a bioflavinoid in the Indian spice turmeric with elaborate anti-inflammatory mechanisms, was recently found to be as effective as fluoxetine (Prozac), at a dose of 1 g daily, in small a randomized study (Sanmukhani et al, *Phytother Res* 2013, online ahead of print).

While not yet rigorously studied, anti-inflammatory diets may also play a significant role in reversing mood and anxiety symptoms. Perhaps the greatest leverage comes from elimination of gluten-containing grains. A significant proportion of celiac patients suffer from depression and neuropsychiatric disease (including OCD and ataxia), possibly related to greater intestinal permeability, local and systemic inflammation, and immune complexes that compromise blood-brain barrier function. When patients with celiac disease are maintained on lab-standard, gluten free diets, these symptoms frequently improve (Jackson et al, *Psychiatr Q* 2012;83(1):91–102).

Case reports have been in the literature for over a decade describing dramatic clinical benefits from dietary modification, particularly from low carb (<40 g daily), high natural fat, moderate protein or "ketogenic diets" (Phelps JR et al, *Neurocase* 2013;19(5):423–426). Probiotics may also serve to enhance anti-inflammatory effects and self-nonself recognition patterns, while diminishing intestinal permeability and modifying behavioral symptoms such as anxiety (Messaoudi et al, *Br J Nutr* 2011;105:755–764).

Inflammatory Cytokines: Associative and Causative

The efficacy of anti-inflammatory drugs and diets raises the possibility that inflammatory cytokines may lie at the heart of the biology of depression. As an example, one of the most predictable side effects of interferon therapy for hepatitis C is depression. In fact, 45% of patients on interferon develop clinical depression, which appears to be related to elevated levels of IL-6 and TNF (Alavi M et al, *J Gastroenterol Hepatol* 2012;27(5):957–965).

Cytokines can also be induced by lipopolysaccharide (LPS), an endotoxin produced by gram-negative bacteria, and which is used in animal models to induce depression-like syndromes. Mice that lack

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IL1-B (a cytokine that mediates inflammatory response), however, are protected against these LPS-mediated "depressive symptoms" (ie, lost interest in sugar water), suggesting that these inflammatory messengers may be a key part of the depression equation (Lawson et al, *J Neuroinflammation* 2013;10:54).

A primary concept in the inflammatory model of depression is the bidirectional nature of immune signals in the peripheral and central nervous system. As we all remember from our immunology courses, inflammation is triggered by the presentation of environmental antigens to T-cells. Since our greatest interface with the environment is the 70%-plus of our immune system housed in our gut wall, disturbances in gut microbiota can trigger systemic inflammation, as can autoimmunity, head injury, childbirth, and infection.

Cytokines such as IL-1, IL-6, and TNF-alpha are the messengers of distress and have all been shown to be elevated in a linear, dose-dependent way and in the setting of depression, (reviewed in Howren MB et al, *Psychosomat Med* 2009;71:171–186). These cytokines can traverse the blood brain barrier and may also stimulate afferent neurons (those that send sensory information toward the brain) such as the vagus (Wilson et al, *J Am Geriatr Soc* 2002;50:2041–2056).

Once there, glial cells called microglia, which act as the immune regulators of the brain, are activated. In activated microglia, an enzyme called IDO (indoleamine 2 3-dioxygenase) has been shown to direct tryptophan *away* from the production of serotonin and melatonin and *toward* the production of an NMDA agonist called quinolinic acid (Christmas DM et al, *Neuropsych Dis Treat* 2011:7;431–439).

In the postpartum period, for instance, IDO activation is related to symptoms of anxiety and depression, and is also thought to account for stimulation of NMDA receptors in the limbic system, which may contribute to intrusive thoughts/images and symptoms of anxiety. Furthermore, in a one-two punch of neurotoxicity, glial cells called astrocytes that are charged with removing excess glutamate through excitatory amino acid transporters are thought to be downregulated in the setting of inflammatory microglial activation (McNally et al, *CNS Spectr* 2008:13:6 501–510).

Stress as a Final Pathway for Inflammation?

We all know about the putative role of the hypothalamus-pituitary-adrenal (HPA) axis in depression, but interestingly, the monoamine hypothesis of depression has very little to say about HPA disruption. In the context of inflammation, however, cortisol, prolactin, and sex hormones are often dysregulated. In this model, depression is thought to represent a hypercortisolemic state which may result from elevated levels of inflammatory cytokines. Peripheral glucocorticoid resistance may exacerbate this elevation in cortisol and immune response, simultaneously, which would also drive changes in progesterone, insulin, and androgens.

This concept is reflected in the overlap between depression and "sickness syndrome" described by Miller, Raison, and Maes (Miller et al, *Biol Psychiatry* 2009;65(9):732–741) and characterized by lethargy, sleep disturbance, anorexia, anhedonia, and decreased social activity, mobility, and libido. They theorize that immune system hyperresponsivity has served us evolutionarily, but that the transduction of psychological stress into immune response, coupled by shifts in our relationship to our microbial environment, have rendered this system somewhat maladaptive. This may, in part, explain the efficacy of exercise (Cooney GM et al, *Cochrane Database Syst Rev* 2013;9:CD004366) and yoga (Yadav RK et al, *J Alt Comp Med* 2012;18(7):662–667) in the treatment of depression, as well as meditation in downregulation of inflammation (Dusek JA et al, *PLoS One* 2008;3(7):e2576).

Evidence suggests that inflammatory mediators acting on the brain may result in sickness behavior, depletion of tryptophan and monoamines, oxidative stress, and cellular dysfunction and apoptosis (Maes et al, *Metab Brain Dis.* 2009;24(1):27–53). Given the fundamental lack of clarity around etiology of depressive symptoms; the likelihood that depression represents a heterogeneous clinical entity with multiple different potential contributors; and the often limited benefits and notable side effects of today's antidepressants, consideration of inflammatory models may provide a new and more effective way of thinking about depression and its treatment.

TCPR'S VERDICT: The inflammatory hypothesis of depression paves the way for the study of effective interventions—diet, exercise, meditation, medications, such as NSAIDs—that have already shown promise in the treatment of metabolic inflammatory disorders and may represent a shift towards thinking of depression as a complex disorder with contributions from behavioral, neuroendocrine, and immune pathways.

Expert Interview

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occur generally within the first 40 minutes to one hour.

TCPR: How long do these effects last?

Dr. Mathew: By about two hours, the side effects almost always dissipate, and at that point a patient may describe feeling less depressed, more hopeful about the future, and more motivated to be productive. We've had several patients comment that they feel more activated and motivated to do things that they have long procrastinated, like going home and doing the dishes, sorting the mail, that sort of thing. It is important to note that patients are not necessarily giddy or euphoric or ecstatic. We have had very few patients who are giggling or hysterical. At the two-hour mark, patients are generally lucid, alert, and not sedated. By four hours, there appears to be continued improvement in positive thinking and hopefulness, and if they have had suicidal thoughts, those tend to be quite strongly attenuated. The 24-hour mark is when we have declared our primary outcomes in our depression studies—the Montgomery-Asberg Depression Rating Scale (MADRS) or the Hamilton Depression Rating Scale (HAM-D). The largest clini-

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Expert Interview
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cal effects of ketamine are found with lassitude, feelings of pessimism, and sad mood, as well as suicidal thoughts. There are also significant reductions in feelings of inner tension or anxious feelings.

TCPR: One key property of ketamine is that the effects seem to be long-lasting, even after a single infusion. Have you observed this?

Dr. Mathew: Yes, we and a number of groups have observed this. About 60% to 70% of patients have a positive response at 24 hours, a number that goes down a bit, to 50% to 60%, over the next 48 to 72 hours, but the response is generally maintained over this time frame. In our recent study in the *American Journal of Psychiatry,* we found that at seven days there was still persistence of benefit, although by that time the drug-versus-placebo difference was not statistically different (Murrough JW et al, *Am J Psychiatry* 2013;170(10);1079–1081). Among the patients who responded at seven days, we found that there were some very durable responders for an additional four weeks, all following a single infusion.

About 60% to 70% of patients have a positive response at 24 hours.

Sanjay J Mathew, MD

TCPR: Were any other medications given during the infusion in your study?

Dr. Mathew: Participants in our study were washed off of any other psychotropic drug, including antidepressants, for at least a seven day period prior to infusion. And the reason for that was that we want to look at other biological measures such as neurotrophic factors and brain-imaging markers, so we wanted to have as "clean" a sample as possible.

TCPR: People may argue that simply the psychoactive effects of ketamine—for instance, the transient dissociative symptoms and other unusual phenomena that people experience—might have antidepressant effects in and of themselves. Please explain how you took this into consideration in your study design.

Dr. Mathew: Instead of using a saline or an inert substance as a control, we randomized patients to ketamine or to midazolam (Versed), a commonly used anesthetic benzodiazepine. This was to make sure that patients were truly adequately blinded. Midazolam doesn't have the dissociative side effects of ketamine, but it does have the anxiolytic, sedative, and some of the transient cognitive side effects. We found that midazolam was effective as an antidepressant in only about 20% of patients at 24 hours, and it persisted at 72 hours. So the drug-versus-placebo difference in our study was significant. However, it's notable that when a treatment-resistant group of patients is given an intravenous medication that is not known to have any antidepressant properties, we still found 20% mounting a robust response. So we can't discount the power of expectations for these types of studies and for clinical practice as well.

TCPR: So you attribute midazolam's response rate primarily to the expectation that the medication will work. Is it possible that a rapidly acting psychotropic drug may disrupt the system so that the patient is no longer experiencing symptoms of depression?

Dr. Mathew: The patients who responded to midazolam said they felt lighter and more relaxed. That early anxiolytic effect might have influenced how they felt overall in terms of their mood. Nevertheless, in our study, the fact that the response rate was still significantly lower than with ketamine affirmed that there was something real about the ketamine antidepressant effect beyond its anxiolytic properties, and beyond its sedative or amnestic properties.

TCPR: Are there any predictors of the type of patient who might respond to ketamine?

Dr. Mathew: Researcher Carlos Zarate has found that a family history of alcohol dependence seems to be associated with early response in both unipolar and bipolar depression (Phelps LE, *Biol Psychiatry* 2009;65(2):181–184; Luckenbaugh D et al, *Bipolar Disord* 2012;14(8):880–887). His data also support that a previous history of suicide attempt is a predictor of good outcome. In addition, we have found that a history of childhood sexual abuse seems to be a predictor of good response, which is sort of at odds with much of the pharmacotherapy literature, in which early childhood trauma is a negative prognostic factor. We are looking at a number of other things as well, including a previous history of suicidal ideation and comorbid anxiety.

TCPR: How is this treatment being used in real-life clinical practice?

Dr. Mathew: There are a number private clinics now offering this treatment. Many of them use the 0.5 mg/kg protocol that we have studied, although there seems to be a lot of variability. Some clinics are doing bolus infusions over a couple of minutes, while others are doing different dosing, like 0.25 mg/kg over a longer period of time. Some practices are doing this under anesthesiologist monitoring with continuous EKG and pulse oximetry and nasal cannula, with the psychiatrist's role much like in ECT. There are other clinics being run completely by psychiatry without the same degree of monitoring.

TCPR: Would you advise the average office-based psychiatrist to do this? If so, what are some of the practical issues?

Dr. Mathew: From our experience, even among carefully selected patients, there will be a small number who experience significant changes in blood pressure and pulse, and some patients will have relatively dramatic elevations in those parameters. In our studies we did have a portion who needed intervention by the anesthesiologist with antihypertensive medications. So I urge caution for the clinical use of this. If we see those type of side effects in a small proportion of highly selected patients who don't have histories of hypertension or obstructive sleep apnea, and who have normal EKGs and are on no other psychotropic medications, it would suggest that in the general clinical practice you run into much higher risk.

TCPR: So there is really no accepted protocol for how often the infusion should be given, how many infusions should be given, when they stop, whether there should be maintenance infusions, and/or whether to use concurrent medications?

Dr. Mathew: That is correct. We don't know the best way to conduct repeated administration dosing strategies—for instance, should the regimen be three times a week over two weeks, or three times a week over three weeks? At what point do you taper? And how do you manage a patient who has responded beautifully to ketamine? There is some preclinical literature suggesting lith-

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Clinical Trials: Show Us the Data

Uri Cohen, MD

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

"It is no longer possible to pretend that a report of a clinical trial in a medical journal is enough to allow full independent scrutiny …." Fiona Godlee, Editor, *British Medical Journal (BMJ)*

Too often our literature presents an oversimplified picture driven by some agenda, usually commercial. We prescribers, or, more accurately, "research consumers," need a more complete and accurate description of what's *actually* observed in clinical trials. This would help us use the literature to inform the nuanced clinical judgments we face every day with each patient.

Several major campaigns are currently underway to promote greater transparency of clinical trial data. These include the AllTrials (www.alltrials.net) and the RIAT (Restoring Invisible and Abandoned Trials) initiatives. They are not aimed solely at researchers, regulators, or journal editors, nor do they follow the more familiar patterns of looking for potential conflicts of interest (COIs), limiting collaborations between academia and industry, or advancing particular ideological agendas. Instead, they're predicated on the idea of educating and empowering research consumers like us around what we need for clinical decision making, through access to clinically relevant information from trials themselves.

What gets published in the psychiatric literature (and, indeed, all medical literature) are highly condensed proxies of original, primary, clinical trial information. The true "methods" and "results" sections of a trial are the clinical study report (CSR) and raw data sets. These documents can be quite large, and very often they're seen in full only by the sponsor of the trial.

As clinicians we would be better served by complete and accurate access to all the trial data, to help us assess the true efficacy and side effects of an intervention.

One of the foremost illustrations of this is from the antidepressant literature. Study 329, was a multi-site trial of paroxetine (Paxil) in the treatment of adolescent depression sponsored by SmithKline Beecham (now GSK). It was summarized as supporting the conclusion that "paroxetine is generally well-tolerated and effective for major depression in adolescents" (Keller MB et al, *J Am Acad Child Adolesc Psychiatry* 2001;40(7):762–772).

In fact, original documents from the trial itself, later made public by court order (something that has been rarely done for any study), have raised serious issues not just with the conclusions but, much more importantly, with how closely the published paper represented the clinical study report and data sets. In significant ways that would not be apparent to even the most careful reader or peer reviewer without the original trial information, effectiveness and adverse events were not accurately represented (see, for instance, Jureidini JN et al, *Int J Risk Safety Med* 2008;20(1–2):73–81). As of now, the ongoing handling of Study 329 remains emblematic of the broader issue of how limited access to raw data from clinical trials may undermine the integrity of our existing literature.

That legacy is particularly relevant to newer treatments of depression, including those discussed in this month's issue. We are moving away from an era of "blockbuster" medications towards one of more targeted and personalized care. As research consumers, whether or not we can reassure ourselves that we are being provided complete and accurate information from the trials on a particular intervention becomes even more important. A number of research sponsors are already engaging with clinical trial transparency initiatives, and it will be increasingly possible to differentiate between those researchers and companies that do—or do not—provide true transparency (see, for instance, Doshi P, *BMJ* 2013;347:f6754).

As information from trials and other sources grows, and related meta-analyses and "big data" syntheses expand, so too does the importance of access to the actual methods and data. Future issues of *TCPR* will examine these campaigns and initiatives in more detail. For now, I will close with this quote from Richard Lehman at *BMJ*: "Sharing of accurate and complete data is the basis for true evidence-based medicine... This is where the rebirth of humane scientific medicine must begin."

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Expert Interview

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ium may have some common mechanisms with ketamine. And so there are studies ongoing looking at this lithium/ketamine combination as a way to prolong the benefit of ketamine. There really isn't much literature guiding clinicians on this point. We decided initially three times a week because we were trying to follow an ECT model, and we felt three times a week over two weeks would be acceptable to patients and represent a minimal ECT course. But ultimately the treatment needs to be individualized.

TCPR: Let's discuss how ketamine works as an antidepressant. Can you explain the history behind the use of ketamine and other NMDA-based antidepressant approaches?

Dr. Mathew: Back in the '80s it was discovered by Skolnick and others that most standard antidepressants, including the tricyclics, down-regulated NMDA receptor activity. They also found that NMDA antagonists may have acute antidepressant properties in laboratory experiments. Then, a number of years later, a pilot study done at Yale (Berman RM et al, *Biological Psychiatry* 2000;47(4):351–354) found that low-dose ketamine could have very rapid antidepressant properties. Since that study was published in 2000, there have been a number of replications supporting the idea that NMDA receptor blockade can result in a very rapid effect whose time course is beyond the half-life of the drug. The elimination half-life of ketamine is approximately two to four hours, and most of these studies have supported the notion that there is a persistence of benefit certainly beyond the half-life and in some

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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.

SCHIZOPHRENIA

Metformin for Weight Loss in Schizophrenia

Obesity and metabolic impairments are widespread in both psychiatric and non-psychiatric populations. To make matters worse, weight gain, hyperlipidemia, and diabetes are common side effects of the pharmaceuticals we use to treat psychiatric illness. Exercise and diet can be effective interventions, but pharmacological options are scarce. Metformin, a common diabetes medication known to decrease hepatic gluconeogenesis and improve insulin sensitivity, has been studied for weight loss in nondiabetic patients.

To determine whether adjunctive metformin might cause weight loss in overweight patients with schizophrenia or schizoaffective disorder, researchers randomized 148 patients to metformin or placebo, in addition to their normal psychotropic regimen. All patients underwent weekly diet and exercise counseling. At baseline, patients were on at least one antipsychotic medication and all were overweight (BMI≥27). None had diabetes. At the end of 16 weeks, those who had taken metformin experienced, on average, a 3 kg (6.6 lb) weight loss, while those on placebo lost an average of 1 kg (2.2 lb). Metformin was also effective in reducing triglycerides (-7 mg/dL compared to +13 mg/dL for placebo) and HbA1c (-0.06% vs +0.01%), while other lipid parameters and glucose or insulin levels were not significantly different.

All patients received weekly diet and exercise counseling, which seemed effective, as the placebo group lost 0.3 BMI points over the course of the trial. Metformin caused an additional weight loss, which increased over time. Whether the weight loss caused by metformin might persist or increase after 16 weeks is unknown.

The results suggest that metformin, at daily doses up to 2,000 mg/d (1000 mg BID) over a 4-month period, can cause weight loss in patients with psychotic disorders. Metformin was well tolerated, with only nausea as a common, transient, side effect. Patients at risk for lactic acidosis, a known adverse effect of metformin, were excluded from the study.

While it is tempting to conclude that metformin may prevent or reverse the weight gain caused by antipsychotics, this was not the focus of this study. Indeed, all subjects were on antipsychotic medication for the duration of the trial, but there was no determination as to whether their baseline obesity had been caused by antipsychotics (Jarskog LF et al, *Am J Psychiatry* 2013;170(9):1032–1040).

TCPR's TAKE: This study shows that metformin may cause a statistically significant weight loss and improvement in triglycerides in overweight patients with psychosis, and that diet and exercise counseling may also result in significant (although smaller) weight loss. It does not demonstrate that metformin can reverse the weight gain caused by antipsychotics, nor that it can be used prophylactically to prevent antipsychotic-associated weight gain.

Does Brintellix Bring Anything New?

Steve Balt, MD
Editor-in-chief

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

After a dry spell of new antidepressants—the last one to be approved was levomilnacipran (Fetzima), the active enantiomer of milnacipran (Savella) in July 2013—the FDA approved vortioxetine (Brintellix) in September. Vortioxetine is another serotonergic antidepressant. How exactly does it work, and what are its advantages over existing drugs?

Vortioxetine has several actions on serotonin-related targets. Like SSRIs, it's a serotonin reuptake inhibitor. It's also an agonist at 5-HT1A receptors as well as an antagonist of 5-HT3A and 5-HT7 receptors. (You may recall that buspirone (BuSpar), vilazodone (Viibryd), and aripiprazole (Abilify) are partial agonists of this receptor, among other functions.)

Thus, it sounds promising, but receptor-binding properties usually confer advantages that are only theoretical in nature. Therefore, a look at the data is appropriate.

Approval of vortioxetine was based on six short-term (6- to 8-week) studies of vortioxetine compared against placebo and/or duloxetine (Cymbalta) or venlafaxine (Effexor). These studies revealed that the effective doses of vortioxetine range from 5 to 20 mg/day, and also that vortioxetine was roughly similar in efficacy to venlafaxine but worse than duloxetine.

Other failed trials have been published, which generally used lower doses of vortioxetine (although some trials showed failure even at higher doses of 10 mg/day or 15 mg/day). A European trial found vortioxetine to be superior to agomelatine, an antidepressant whose manufacturer has not submitted it for FDA approval in the US due to lack of efficacy. As of summer 2013, there were 33 studies of vortioxetine registered with www.clinicaltrials.gov, for a range of diagnoses, so more data should be emerging.

In a longer-term trial, vortioxetine was found to be effective in preventing relapse in a 52-week study of adults with depression, although doses were low (2.5 to 10 mg/day) and the study was open-label, with no placebo control. A short-term trial in elderly patients (ages 65 and

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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 November 30, 2014. 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. Which of the following anti-inflammatory agents has NOT been associated with reduction in depression or elevation in mood in clinical studies, according to Dr. Kelly Brogan (Learning Objective #1)?
   [ ] a) Infliximab (Remicade) [ ] b) Celecoxib (Celebrex) [ ] c) Etanercept (Enbrel) [ ] d) Naproxen (Naprosyn)

2. A quintessential example of raw trial data not being faithfully represented in the published literature is Study 329, a multi-site trial of which popular antidepressant (LO #2)?
   [ ] a) Paroxetine (Paxil) [ ] b) Sertraline (Zoloft) [ ] c) Venlafaxine (Effexor) [ ] d) Fluoxetine (Prozac)

3. According to Dr. Sanjay Mathew, what is the mechanism by which ketamine is thought to exert its antidepressant effects (LO #3)?
   [ ] a) AMPA receptor antagonist [ ] b) NMDA receptor antagonist
   [ ] c) NR2B receptor antagonist [ ] d) Selective norepinephrine reuptake inhibitor

4. The six short-term trials that were the basis of the FDA approval of vortioxetine (Brintellix) had which of the following results (LO #4)?
   [ ] a) Vortioxetine was roughly similar in efficacy to duloxetine but worse than venlafaxine.
   [ ] b) Vortioxetine was roughly similar in efficacy to venlafaxine but worse than duloxetine.
   [ ] c) Vortioxetine was superior in efficacy to venlafaxine and duloxetine.
   [ ] d) Vortioxetine was roughly similar in efficacy to venlafaxine and duloxetine.

5. In the 2013 Jarskog et al study, participants who took metformin for 16 weeks lost an average of how much weight, compared to an average 1 kg (2.2 lb) weight loss for those who took placebo (LO #4)?
   [ ] a) 1.5 kg (3.3 lb) [ ] b) 2 kg (4.4 lb) [ ] c) 3 kg (6.6 lb) [ ] d) 5 kg (11 lb)

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Expert Interview

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patients several weeks, and these were by and large treatment-resistant patients.

TCPR: There are other NMDA antagonists, however, like memantine (Namenda), which don't seem have any antidepressant effects. So what is it about ketamine?

Dr. Mathew: What is unique about ketamine? Ketamine binds within the channel of the NMDA receptor, specifically at same site as phencyclidine (PCP, "angel dust"), but with less affinity. This is important to its therapeutic effect. On the other hand, memantine is a relatively weak NMDA blocker, and other drugs that are available, like amantadine (Symmetrel), have weak NMDA receptor activity. By blocking NMDA, you may be preferentially engaging AMPA receptor activity, and AMPA receptor activity may be important for many of the downstream effects, including those underlying the long duration of action. So while the initial pharmacologic target is NMDA, one of the theories is that AMPA receptor potentiation is actually critical to the mechanism of action. That may also be more unique to the ketamine story than some of the other NMDA-like substances. And the way we know this preclinically is that when you block AMPA receptors you can undo some of the behavioral effects of ketamine in the animals.

TCPR: Given what we know about how ketamine works, what other molecules or other agents are on the horizon that might take advantage of this NMDA mechanism?

Dr. Mathew: One study is looking at the isomer of ketamine—S-ketamine—in an intranasal form for treatment-resistant depression. S-ketamine has a higher affinity at the PCP site, so the idea would be that can you use lower doses, achieve equal efficacy with fewer side effects and less dissociation. There are also a number of drugs that modulate NMDA-receptor functioning, but are more selective for specific subunits of the NMDA receptor (for example, NR2B receptor antagonists), which are now in clinical trials and being investigated. An NMDA channel blocker known as AZD6765, developed by AstraZeneca, is now in late phase 2 studies. Finally, there is a glycine site agonist called GLYX-13 (developed by Naurex) that is a partial NMDA agonist that is being studied in Phase 2 trials.

TCPR: Thank you, Dr. Mathew.

Does Brintellix Bring Anything New?

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older) also found it similar in efficacy to duloxetine.

The advantages of vortioxetine over existing agents remain to be seen. One possible advantage, which is already being discussed in the literature, is a "pro-cognitive" benefit due to its 5-HT7 antagonist properties. Compounds with this property have shown some benefit in animal models of learning and memory. Existing data in humans are minimal. As for side effects, the most common was dose-related nausea (reported by roughly 25% of subjects), while weight gain was negligible.

TCPR'S VERDICT: Vortioxetine might be more than just a "me-too" drug, as its pharmacodynamic properties are slightly different from any existing agent on the market. But the data demonstrate no clear advantages over currently available drugs, and its cost is likely to be substantially higher than what's available now. Further head-to-head trials with other antidepressants, as well as specific studies on purported advantages of vortioxetine, for example, in cognition, are necessary.