THE CARLAT REPORT PSYCHIATRY

A CME Publication

Subscribe today! Call 866-348-9279

AN UNBIASED MONTHLY COVERING ALL THINGS PSYCHIATRIC

Daniel Carlat, MD
Editor-in-Chief

Volume 10, Number 1
January 2012
www.thecarlatreport.com

IN THIS ISSUE

Focus of the Month:
Natural Treatments in Psychiatry

Learning objectives for this issue: **1.** Describe the evidence for the effectiveness of Deplin (L-methylfolate). **2.** Describe the evidence for the effectiveness of Nuedexta (dextromethorphan (DM) and quinidine sulfate). **3.** Explain the effectiveness of complementary and alternative medicine for mood disorders. **4.** Understand some of the current findings in the literature regarding psychiatric treatment.

Deplin: Is it Just Folate by Another Name?

Steve Balt, MD
Research fellow
Addiction Pharmacology Research Laboratory
California Pacific Medical Center

Dr. Balt discloses that his spouse is employed as a sales representative for Bristol Myers Squibb.

Patients are probably asking you about Deplin, or L-methylfolate, a version of folic acid that is being marketed by Pamlab as an adjunctive treatment for depression. In a prior issue of *TCPR* (June 2009) we reviewed available information on Deplin, concluding that there's little evidence it is any more helpful for depression than much cheaper folic acid. Have we learned anything new in the last two years?

Interest in folate began in a landmark study by Victor Herbert in 1962. After eating a folate-free diet for four months, Herbert developed depressive symptoms and numerous hematologic abnormalities, all of which were reversed by folate supplementation (Herbert V, *Trans Assoc Am Physicians* 1962;307–320). While Herbert's symptoms may have been nonspecific and due to poor nutritional status, several epidemiologic studies over the years have shown a relationship between low serum and/or red blood cell folate and depression and other neuropsychiatric conditions (Frankenburg F, *Harv Rev Psychiatry* 2007;15(4):146–160). It isn't clear whether the correlation is due to a general nutritional deficiency—as in Herbert's case—but it is tempting to conclude that supplemental folate may help to treat mental illness.

L-methylfolate (Pamlab's Deplin) is also known as methyltetrahydrofolate (MTHF), a derivative of folic acid. Deplin

Continued on page 2

Nuedexta for Pseudobulbar Affect

Steve Balt, MD
Research fellow
Addiction Pharmacology Research Laboratory
California Pacific Medical Center

Daniel Carlat, MD
Associate clinical professor
Tufts University School of Medicine

Dr. Balt discloses that his spouse is employed as a sales representative for Bristol Myers Squibb. Dr. Carlat has disclosed that he has no relevant relationships or financial interests in any commercial companies pertaining to this educational activity.

Pseudobulbar affect (PBA), also known as pseudobulbar palsy, is a neurological condition in which patients have sudden outbursts of crying or laughing. While the episodes can be triggered by events that would ordinarily elicit genuine sadness or amusement, patients with PBA react with intense displays of emotion that they cannot control. The frequency of these episodes ranges from weekly to several times a day, and they can seriously impair social functioning.

By definition, PBA is a neurologic disease, occurring most often in ALS (amyotrophic lateral sclerosis), in which the prevalence of PBA is about 50%. PBA occurs less commonly in strokes, multiple sclerosis, Parkinson's disease, and brain injuries from tumors, strokes, or head trauma. Because so many different brain lesions can cause PBA, the actual pathophysiology is unclear, but a popular theory is that it is caused by a loss of voluntary motor control of the facial musculature.

Until now, the most established treatments for PBA were antidepressants—namely, tricyclics and SSRIs. Both have been shown to ease PBA symptoms in placebo-controlled trials. Among SSRIs,

Continued on page 3

Deplin: Is it Just Folate by Another Name?

Continued from page 1

is marketed as a "medical food," which is defined by the FDA as "a food which is formulated to be consumed under the supervision of a physician and which is intended for the specific dietary management of a condition for which **distinctive nutritional requirements,** based on recognized scientific principles, are established by medical evaluation."

There are no recognized "distinctive nutritional requirements" for depressed patients, but based on neurochemistry, it makes sense that folate might help. How? Well, folate is first converted into dihydrofolate (DHF), and then into L-methylfolate (Deplin). L-methylfolate is the "active" form of folate in the brain; it helps to form tetrahydrobiopterin (BH4), a crucial cofactor in the synthesis of serotonin, norepinephrine, and dopamine. In theory then (even though this has not been proven), low levels of folate could cause neurotransmitter deficiencies, which could then be corrected by L-methylfolate supplementation. Because L-methylfolate is involved in the synthesis of three monoamines, Dr. Stephen Stahl has dubbed Deplin a "trimonoamine modulator" (Stahl SM, *CNS Spectrums* 2007;12(10):739–744).

The promotional literature for Deplin, as well as several articles published over the last few years (many underwritten by Pamlab), imply that L-methylfolate is essential for BH4 synthesis, and that it is the only form of folate that can cross the blood-brain barrier. However, neither of these propositions is entirely true. BH4 can be generated in at least three ways unrelated to L-methylfolate, and it is unknown how significant the L-methylfolate pathway is (Ponzone A et al, *Med Res Rev* 2004;24(2)127–150). Furthermore, regular folic acid can, in fact, enter the brain without being transformed to L-methylfolate, although L-methylfolate may be the preferred substrate for the blood-brain barrier transporters (Hermann W and Obeid O, *Clin Chem Lab Med* 2007;45(12):1614–1620).

But is any of this even relevant for neurotransmitter synthesis? Probably not, since it's well known that the *CSF* folate level stays at a relatively constant concentration across wide variations in the *serum* folate (and, presumably, L-methylfolate) level (Obeid et al, *Clin Chem* 2007 53(2):326–333). So for the vast majority of our patients—except for those eating a folate-free diet for four months, perhaps—there's probably sufficient folate in the brain for monoamine synthesis, regardless of serum folate status.

A tenuous biochemical explanation notwithstanding, the key question is whether folate supplementation actually works for depression. A few small studies over the years have shown that folate and L-methylfolate may be somewhat helpful as adjunctive agents in the treatment of depression and other neuropsychiatric phenomena, but with no obvious advantage of L-methylfolate (see *TCPR,* June 2009). Earlier this year, however, at the 2011 European Congress of Psychiatry, two controlled studies of Deplin were made public. Neither has been published, but the results are available by request from Pamlab as a poster (Papakostas GI et al, *EPA 2011,* Vienna, Austria; 13 March 2011).

In the first study, 148 patients with SSRI-resistant depression were randomized to one of three groups. In each group, patients continued their SSRIs and used Deplin or placebo as an adjunct: 1. Deplin 7.5 mg/d for 30 days, then 15 mg/d for 30 days; 2. placebo for 30 days, then Deplin 7.5 mg/day for 30 days; or 3. placebo for 60 days. There was no statistically significant difference in outcomes among any of the three groups.

The second study was simpler. Seventy-five patients, also with SSRI-resistant depression, were randomized to 60 days of adjunctive treatment with either 15 mg/d of Deplin or placebo. In this trial, Deplin separated from placebo: 32.3% of Deplin-treated patients showed a response (ie, 50% reduction in HAM-D score), vs 14.6% of placebo patients (p=0.04), with a number needed to treat (NNT) of approximately 6. Mean reduction in HAM-D score was 5.6 points, vs 3 points for placebo (p=0.05). Deplin was well-tolerated, with only one dropout (vs two on placebo).

Thus, we have one positive study, and one larger negative study. Neither study compared Deplin with generic folic acid—and such a study is unlikely to be done (presumably because Pamlab is concerned that folic acid would be equivalent to Deplin). Thus, at this point, the clinical trial data on Deplin is suggestive, but by no means clear. We would need another positive controlled trial before being convinced it is effective.

But assuming for a moment that Deplin does successfully augment antidepressants, to whom should we prescribe it? Pamlab's answer is that Deplin is especially appropriate for

Continued on page 7

Nuedexta for Pseudobulbar Affect

Continued from page 1

fluoxetine (Prozac) 20 mg/day, citalopram (Celexa) 10 mg/day to 30 mg/day, and sertraline (Zoloft) 50 mg/day have been shown to be effective—but they are not FDA approved.

Nuedexta is a combination of dextromethorphan (DM) and quinidine sulfate (Piore EP, *Drugs* 2011;71(9):1193–1207). You might reasonably ask why these two agents would have ever been considered as a treatment for PBA. DM is widely known as a cough suppressant. When taken at very high doses, it can cause hallucinations, a feeling of dissociation, and euphoria, which is why pharmacies now tightly limit its sale. DM causes these effects because it affects various neurotransmitters. It has SSRI properties, it is an NMDA receptor antagonist (glutamate stimulates this receptor), and a sigma 1 agonist (don't ask us about sigma 1—we don't know what it does and nobody else knows much about it either).

It was DM's NMDA antagonist properties that originally caught the attention of researchers interested in slowing the progression of ALS, which is thought to be caused in part by toxic effects of glutamate. While DM failed ALS trials, patients taking it told researchers that it seemed to diminish their PBA symptoms. So Avanir Pharmaceuticals conducted trials specifically targeting DM for PBA. Why did they combine it with quinidine? Because DM is very rapidly metabolized by 2D6, and quinidine is a potent inhibitor of 2D6. Delivering them together keeps DM levels high for long enough to have a therapeutic effect (Rosen H, *Drugs Today* 2008, 44(9):661).

The FDA approved Nuedexta based on data from a clinical trial of 326 patients with ALS and multiple sclerosis with clinically significant PBA (Pioro EP et al, *Ann Neurol* 2010;68(5):693–702). Nuedexta was more effective than placebo, both in terms of decreasing the number of emotional episodes, and on a numerical scale of PBA called the Center for Neurologic Studies–Lability Scale. Nuedexta comes in one dosage form: 20 mg of DM combined with 10 mg of quinidine (termed 20/10), and is given twice a day.

So why are you reading about a neurology drug in a psychiatry newsletter? Here's where it gets interesting. Even though PBA is formally "owned" by neurologists, psychiatrists often end up treating it. After all, many patients with neurologic diseases have comorbid depression or bipolar disorder, and differentiating between PBA and a psychiatric syndrome is not always clear-cut. To muddy the turf boundaries even more, some authors (including some affiliated with Avanir) recently proposed a new diagnostic classification, "Involuntary Emotional Expression Disorder" (IEED), which would incorporate PBA and other types of uncontrollable emotion (Cummings JL et al, *CNS Spectr* 2006,11(6):1–7). While the authors were careful to distinguish IEED from mania or depression, clinicians in everyday practice may have a harder time doing so. It's likely that some prescribers may resort to Nuedexta as an off-label alternative for their patients with mood disorders, even though there's no evidence to support this. Nevertheless, one author (a scientific advisor to Avanir) has published his thoughts on why Nuedexta could be effective for depression (Lauterbach EC, *Med Hypotheses* 2011,76(5):717–719), and clinical trials are under way for the treatment of neuropathic pain. We're eager to see the results.

So what about the cost? Well, as with many new drugs, one big problem with Nuedexta is sticker shock—it costs around $600/month, or $7,000 per year. In the absence of any head to head studies showing that Nuedexta works better than antidepressants for PBA, we recommend a trial of SSRIs or TCAs before jumping to Nuedexta. Of note, Nuedexta causes a small but significant increase in the QTc interval on EKG.

We would love to suggest you create your own version of this medication by prescribing generic DM and generic quinidine, but quinidine's lowest available dose is 10 times the dose you'd need, so that method wouldn't work. Plus, Avanir is vigorously defending its patent on their proprietary two-drug combination.

Perhaps an even better alternative would be to combine DM with an SSRI like fluoxetine, which is effective for PBA as monotherapy as well as being a potent 2D6 inhibitor itself. But be aware that combining DM with an SSRI could theoretically cause serotonin syndrome, since DM has some serotonin reuptake antagonist properties.

For PBA, save Nuedexta for third line use, after SSRIs and tricyclics.

Nuedexta—At a Glance	
Generic Name	Dextromethorphan/quinidine sulfate
Manufacturer	Avanir Pharmaceuticals, Inc
Approval date	October 29, 2010
Approval indication	Pseudobulbar affect (PBA)
Available in pharmacies	Available now
Dosages available	20/10 mg capsule
Target dose	20/10 mg twice daily
Average cost	$600/month
Likely marketing points	Only medication approved for PBA
Advantages over existing agents	No clear advantages over SSRIs; probably has fewer side effects than tricyclics

Q&A With the Expert

This Month's Expert

Complementary and Alternative Medicine for Mood Disorders

Marlene Freeman, MD

Associate professor of psychiatry, Harvard Medical School
Director of clinical services, Perinatal and Reproductive Psychiatry Clinical Research Program
Massachusetts General Hospital

Dr. Freeman has received research support from Lilly, GlaxoSmithKline, and Forest Pharmaceuticals for the study of duloxetine, Lovaza (omega-3 fatty acid), and escitalopram. She has also served as a consultant to Bristol Myers Squibb on measurement based care. Dr. Carlat has reviewed this article and found no evidence of bias in this educational activity.

TCPR: Dr. Freeman, you were the chair of a task force organized by the APA several years ago to study complementary and alternative treatments in psychiatry. How did you become interested in this area?

Dr. Freeman: I have done research with omega-3 fatty acids and mood disorders since my residency. I became more involved in the area of complementary and alternative medicine (CAM) because of an interest in perinatal psychiatry. There is a particularly compelling need for non-pharmacologic treatments for women who are trying to conceive, and who are pregnant or breastfeeding.

TCPR: And what was the goal of the APA task force?

Dr. Freeman: We were charged with creating an informative, clinically relevant report for practicing psychiatrists. We focused on major depression because that is the area where there has been the greatest number of systematic and controlled studies of CAM treatments in psychiatry.

TCPR: What qualifies as CAM?

Dr. Freeman: Defining CAM is challenging. One of the things that makes it so hard to have a concrete discussion on CAM is that it means different things to different people. It has a lay definition that basically means "any sort of treatment that is not considered mainstream." There is an epidemiologic study showing that 40 percent of adults in this country use at least one CAM treatment each year, and that Americans spend about 34 billion dollars out of pocket on CAM treatments (Barnes et al, *CDC National Health Statistics Report* #12;2007–2008). We need to inquire because patients may not tell their psychiatrists about CAM use, because they just don't think it is relevant or sometimes patients think we won't approve. When we ask about what medicines a patient is taking, we might expect patients would tell us about supplements, but if we don't specifically ask about supplements, they probably won't mention them.

TCPR: When we ask our patients about these remedies, how do you suggest we phrase the question? Should we ask about "dietary supplements"? Do most patients even know what we mean by that?

Dr. Freeman: I tend to ask this in two different ways, in two different parts of the initial interview. When I ask what medications patients are taking, I ask about any supplements or vitamins. Later in the interview, when I ask about use of alcohol, tobacco, and caffeine, I ask again about any supplements or "herbal remedies" or "nontraditional treatments." It is interesting because if I phrase the question in a slightly different way, I may get different answers.

TCPR: What are some of the CAM remedies that you feel comfortable enough with the evidence base to recommend them to your patients?

Dr.Freeman: I recommend exercise to almost every patient. It is rare that there is any contraindication to exercise. There haven't been large scale trials of exercise monotherapy that have been rigorously conducted and controlled for validated major depressive disorder, but the literature is compelling that there appear to be antidepressants effects (see for example Lawlor DA and Hopker SW, *BMJ* 2001;322:763–767). One of the tough things about getting evidence for exercise in the treatment of any disorder is that it is hard to really have a placebo controlled trial of exercise—some sort of condition where people don't know they are exercising.

TCPR: Any particular kind of exercise?

Dr. Freeman: It depends on exercise experience, the weather, finances (can they afford a gym membership, equipment, etc). For most patients, walking is doable, and is oftentimes more than they are already doing. I usually recommend, if they are not already exercising, 20 to 30 minutes of walking three to four times a week to start with.

TCPR: What else do you recommend?

Dr. Freeman: I recommend omega-3 fatty acids to most patients with mood disorders. The area where there is the most evidence is using omega-3 fatty acids as augmentation to a standard antidepressant (Lin PY and Su KP, *J Clin Psychiatry* 2007;68:1056–1061). The evidence for anxiety disorders is much less compelling. Some of the most famous benefits of omega-3 fatty acids are cardiovascular benefits, including decreasing high triglycerides. Considering that some of the medications that we use have

metabolic and lipid effects, I think it makes sense for patients who take those drugs to supplement with omega-3 fatty acids (Mozaffarian D and Wu JH, *J Am Coll Cardiol* 2011;58(20):2047–2067). This is an area in which we are currently conducting research.

TCPR: Which kind of omega-3s should we be recommending?

Dr. Freeman: The ones that have been studied for depression are eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA). I recommend a supplement that contains EPA plus DHA, in a ratio of at least 2:1 or 3:2 of EPA to DHA. I tell patients to aim for a dose of the EPA plus the DHA to equal at least a gram a day. Some positive studies have used even higher ratios of EPA : DHA. The doses that have been demonstrated most consistently to be helpful are in the lower dose range, so about 1 to 2 grams a day versus some of the studies that have looked at enormous doses like 6 to 9 grams a day (Freeman MP et al, *J Clin Psychiatry* 2006;67:1954–1067). And I also tell patients to steer away from most of the plant source products, which is what you find in supplemented foods, such as enriched breads. These products contain alpha-linolenic acid, also an omega-3 fatty acid, but not the kind that has been associated with mood benefits.

TCPR: A lot of people say, "Well I eat salmon every day." Is that enough?

Dr. Freeman: Yes. Salmon is a great source of omega-3 fatty acids, and if someone is eating salmon every day there would be no need to supplement. That is just not typical of the American diet. There have been concerns raised about some fish and mercury, and fish intake has fallen, particularly among women of childbearing potential.

TCPR: So exercise and omega-3 fatty acids. What else do you recommend?

Dr. Freeman: For patients with depression treated with antidepressants, I recommend that they take a standard multivitamin with folate (ie folic acid). There have been augmentation studies showing a benefit from adding folic acid in typical doses to an SSRI (Freeman MP et al, *Journal of Clinical Psychiatry* 2010;71(6):669–681). This is particularly true among women. There was a randomized controlled trial of patients on fluoxetine who were randomized to get either folate or placebo, and the folate was significantly better than placebo, but the effect was more robust among women (Coppen A and Bailey J, *J Affect Disord* 2000;60:121–130). For women of reproductive age, it is a good idea to take folic acid to decrease the likelihood of birth defects if they get pregnant.

TCPR: What is a standard dose of folate?

Dr. Freeman: The typical dose in a multivitamin is about 400 to 500 mcg. The study that showed significant benefit (and more robust benefit among women) used 500 mcg.

TCPR: Is there anything else you recommend to patients?

Dr. Freeman: For some patients who prefer not to be on a standard antidepressant, the evidence for SAMe (S-adenosyl L-methionine) as a monotherapy is good. There have been quite a number of studies and meta-analyses showing a benefit of SAMe as a monotherapy compared to placebo, at least equivalent in effectiveness to some of the older antidepressants (S-Adenosyl-LMethionine (SAMe) for Depression, Osteoarthritis, and Liver Disease. Agency for Healthcare Research and Quality, Rockville, MD, August 2002). Like many CAM treatments, insurance is not likely to reimburse for SAMe, and some patients have noted it is expensive, so it may have limited usefulness.

TCPR: Do you recommend anything else that is not an oral supplement?

Dr. Freeman: I recommend light boxes often, especially if there is a history of seasonal mood worsening. The main caution with light therapy is that if there is any underlying bipolar diathesis, the patient has to be carefully monitored for symptoms of hypomania, and all patients should be alerted to stop using if they are feeling too revved up. In Massachusetts, where I practice, there are a lot of patients who get seasonal mood worsening, but light boxes have also been shown to be beneficial for depression that is not seasonal (Golden RN et al, *Am J Psych* 2005;162:656–662). The data for acupuncture in depression have not been consistent, but there have been a couple of well-designed studies showing benefit for depression in pregnancy (Manber R et al, *Obstet Gynecol* 2010;115(3):511–520). Sometimes patients have to decide where to invest their time and their resources, among all of the available options. If patients are not in psychotherapy, I usually advise them to pursue that first.

TCPR: And then there is the whole field of relaxation exercises, massages, etc. Do you ever recommend those?

Dr. Freeman: There have been studies of massage for depression during pregnancy that had some really interesting results. There was one study where all the patients got psychotherapy and then half were randomized to also get massage as well. Both groups did well in the study, but the groups that received massage had more adherence to the protocol, which seems like it would be an expected outcome (Field T, *J Psychosomatic Obstet Gynaecol* 1999;20(1):31–38). Another study showed significant benefit, though there are certainly a lot of variables in that (Field T, *J Psychosomatic Obstet Gynaecol* 2004;25(2):115–122).

TCPR: Thank you, Dr. Freeman.

❖ ❖ ❖

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.

GENETICS

Genes Plus Environment in Psychiatry: View Positive Studies Skeptically

Common sense dictates that genetic predispositions probably interact with life stressors to influence our mental health. Plenty of research has been published to evaluate whether this is actually true, but findings have been mixed. The first widely reported positive study, for instance, found that patients who had short alleles (versions) of the serotonin transporter gene (5-HTTLPR) were more likely to suffer depression in response to stressful life events than patients with normal alleles (Caspi A et al, *Science* 2003;301:386–389).

In response to this intriguing finding, a slew of studies tried to replicate this result. One meta-analysis of 14 direct replication studies found no significant link between 5-HTTLPR variation and depressive response to stressors (Risch N et al, *JAMA* 2009;301:2462–2471). But a later meta-analysis cast a wider net, including several indirect replications which used somewhat different measures of stress (such as hip fractures and heart disease) and depression—and it found a strong association between 5-HTTLPR variation, stress and depression (Karg K et al, *Arch Gen Psychiatry* 2011;68:444–454).

The latest study throws a monkey wrench into not only how 5-HTTLPR combines with stress but into *all* gene/environment findings in psychiatry. Researchers examined results from all 103 published studies of gene/environment interactions in psychiatry published from 2000 to 2009. They found that while a whopping 96% of original gene/environment interaction studies were positive, only 27% of replication attempts were successful.

Replication studies with larger sample sizes were unlikely to find significant results, while positive replications usually had smaller sample sizes—implying that the most reliable replications are the most likely to cast the original findings into doubt (Duncan LE et al, *Am J Psychiatry* 2011;168:1041–1049).

TCPR's Take: Dependable findings of gene/environment associations could eventually be helpful in both diagnosis and treatment—but we must await consistent positive replications before jumping on board.

TECHNOLOGY

Can Instant Messaging Enhance Treatment Outcomes?

Whether you see your patients quarterly, monthly, or even weekly, you certainly are not with them as much as their cell phones are. Theoretically (at least, for some types of therapy), we could enhance treatment outcomes by texting patients therapeutic messages on a regular basis.

In a systematic review of research involving the use of cell phones and handheld computers for psychiatric interventions, researchers were able to find eight studies conducted over the past 15 or so years that met their methodological criteria. Three of these studies targeted anxiety, while the remaining five targeted smoking cessation.

In the typical cell-phone based interventions, participants were either texted or called in support of their quitting efforts. The phone-based smoking cessation programs were generally successful; however, the most successful of these were also the most interactive. The participants that received eight sessions of CBT over the phone with a real person were five times more likely to achieve smoking abstinence than a "usual care" group (researchers didn't explain what "usual care" was). While still showing a positive result, a study that examined text message based smoking cessation counseling saw a more modest two to three times greater abstinence rate than the control condition.

The anxiety studies all involved handheld computers that offered learning modules to augment CBT that was performed in the traditional face-to-face manner. Two studies looked at augmentation of CBT for panic disorder with a computer that allowed for self-monitoring of symptoms and additional treatment modules. This intervention was superior to placebo, but CBT alone won out as the best treatment. In the final anxiety trial, people with social anxiety were given 12 weeks of CBT, 12 weeks of CBT plus handheld computer intervention, or waitlist control. The study found no significant differences between the augmentation group and the waitlist control (Ehrenreich B et al, *J Nerv Ment Dis* 2011;199(11):886–891).

TCPR's Take: Judging by this study, it looks like computers aren't going to replace you in treating anxiety. However, suggesting a phone-based intervention to your patients who are trying to quit smoking might be worthwhile. You can learn more about one of the texting interventions studied, STOMP, at http://bit.ly/bbdB3g. Www.smokefree.gov also offers a smoking cessation text messaging program.

❖ ❖ ❖

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 December 31, 2012. 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.

The Clearview CME Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Clearview CME Institute is also approved by the American Psychological Association to sponsor continuing education for psychologists. Clearview CME Institute maintains responsibility for this program and its content. Clearview CME Institute designates this enduring material educational activity for a maximum of one (1) *AMA PRA Category 1 Credit*™ or 1 CE for psychologists. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity.

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 the first of Pamlab's controlled trials of Deplin, by Papacostas et al, which study group showed the best outcomes (Learning Objective #1)?
   - [ ] a. SSRI + Deplin 7.5 mg/d for 30 days, then 15 mg/d for 30 days
   - [ ] b. SSRI + placebo for 30 days, then Deplin 7.5 mg/day for 30 days
   - [ ] c. SSRI + placebo for 60 days
   - [ ] d. There was no statistically significant difference in outcomes among any of the three groups

2. Nuedexta is a combination of what two drugs (LO #2)?
   - [ ] a. fluoxetine and quinidine sulfate
   - [ ] b. dextromethorphan (DM) and quinidine sulfate
   - [ ] c. dextromethorphan (DM) and fluoxetine
   - [ ] d. citalopram and quinidine sulfate

3. Dr. Marlene Freeman recommends what ratio of EPA to DHA in omega-3 supplements (LO #3)?
   - [ ] a. 2:1
   - [ ] b. 1:2
   - [ ] c. 3:4
   - [ ] d. 4:3

4. In the Duncan et al study of gene/environment, what percentage of attempts to replicate past studies were successful (LO #4)?
   - [ ] a. 27%
   - [ ] b. 72%
   - [ ] c. 79%
   - [ ] d. 97%

5. In the Ehrenreich et al study of computers and therapy, the participants that received eight sessions of CBT over the phone with a real person were how many times more likely to achieve smoking abstinence than a treatment-as-usual group?
   - [ ] a. two times
   - [ ] b. five times
   - [ ] c. six times
   - [ ] d. 10 times

PLEASE NOTE: WE CAN AWARD CME CREDIT ONLY TO PAID SUBSCRIBERS

Deplin: Is it Just Folate by Another Name?

Continued from page 2

patients who have a mutation that slows the conversion of folic acid to L-methylfolate. This is called the MTHFR C677T mutation, found in 10% of whites and up to 22% of Hispanics and those of Mediterranean descent (Farah A, *CNS Spectrums* 2009;14(1 supp 2):2–7). Theoretically, if your body is genetically inefficient at converting folate to L-methylfolate, you might make fewer neurotransmitters, and you might be more vulnerable to depression (the tenuous biochemical argument that we reviewed above).

But there are problems with the mutation story, too. In heterozygotes for the mutation, the conversion rate is reduced only a little—to 70%–80% of the normal rate. Even in homozygotes, the conversion rate is reduced to 30%–40%. Given all the uncertainties about the role of L-methylfolate in neurotransmitter synthesis, it is not clear that mutations decreasing its production have any clinical ramifications.

Furthermore, this mutation is more likely to occur in bipolar disorder and schizophrenia than in depression (Gilbody S et al, *Am J Epidem* 2006;165(1):1–13), meaning that these patients may need Deplin more than depressed patients—if you believe Pamlab's biochemical hypothesizing. Should we therefore be "Deplinizing" patients with mood disorders *and* psychosis? Pamlab hasn't weighed in on this one yet.

Finally, there is the possibility that

Continued on page 8

Deplin: Is it Just Folate by Another Name?

Continued from page 7

the folate tail is wagging the homocysteine dog. It turns out that folate deficiency causes an elevation in homocysteine, a nonessential amino acid thought to be involved in thrombosis, cardiovascular disease, stroke, and other morbidities. Homocysteine is itself an NMDA receptor agonist and a pro-oxidant, and elevated homocysteine has been found to be strongly associated with depression in several studies totaling nearly 11,000 individuals (Kronenberg G et al, *Curr Molec Med* 2009;9(3):315–323). This wouldn't argue against using folic acid supplementation, but it does call into question the neat, convenient "trimonoamine modulator" model for Deplin's presumed efficacy.

TCPR'S VERDICT: Folate supplementation may help some depressed patients, but it's hard to say why, and it's even harder to prove that Deplin is more effective than folic acid. Deplin has a nice story, but the threads tying the story together remain weak, the clinical data are unconvincing, and the price tag is just too high.

THE CARLAT REPORT: PSYCHIATRY
P.O. Box 626
Newburyport, MA 01950