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IN THIS ISSUE

Focus of the Month:
Treatment of Depression

Alternative Treatments for Depression

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Dr. Borresen and Dr. Shah have disclosed that they have no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

No clinician wants to be a "pill-pusher," and most of our patients do not want that kind of treatment. So what can we offer our depressed patients beyond medications? In this article, we'll review the literature on nonpharmacological strategies, including dietary supplements, food recommendations, light therapy, yoga and mindfulness meditation, and exercise. (See Dr. Spielmans' article, "Psychotherapy for Depression: What's Best?" in this issue for a review of psychotherapy, and the October 2009 issue of *TCPR* for a review of medication options for depression.)

Dietary Supplements

Omega-3 Fatty Acids. While omega-3 FAs are likely effective in the treatment of heart disease, the results of clinical trials for mood disorders have been mixed and generally disappointing (Roth EM et al., *Curr Atheroscler Rep* 2010;12(1):66–72). (For a review, see the February 2010 issue of *TCPR.*)

Thus far, the FDA has approved only one omega-3 FA preparation, Lovaza, for the treatment of elevated triglyceride levels. It is not approved for any psychiatric indication, but it is being heavily marketed to psychiatrists, presumably in the hopes that they will prescribe it off-label for mood disorders (or perhaps to treat the increase in triglycerides that some of our medications cause). Each gram of Lovaza contains 375 mg DHA (docosahexaenoic acid) and 465 mg EPA (eicosapentaenoic acid). Most over-the-counter preparations of omega-3 FAs contain similar amounts of DHA and EPA, but are much cheaper. The dosage approved to lower triglycerides is four grams of total omega-3 per day, whereas the dosage examined in most psychiatric trials is one to two grams per day.

Is there any reason to prescribe Lovaza to patients rather than recommending an OTC from a reputable manufacturer, such as Nordic Naturals or Nature's Way? Paradoxically, for some patients Lovaza may be cheaper—that is, if their insurance companies cover most of the cost. However, insurance companies are unlikely to pay for Lovaza unless you are prescribing it for the specific FDA indication of hypertriglyceridemia.

TCPR's Take: Omega-3 FA supplementation has been shown to be effective for heart health but there is still no convincing evidence that it is effective for mood disorders.

Folic Acid. The relationship between low folate levels and depression is still unclear. There is some support and little risk for recommending folic acid supplementation (400 micrograms/day). However, there is no evidence, other than theoretical, that Deplin (L-methylfolate, an expensive product that is marketed by Pamlab LLC) is more effective than regular folic acid. (For more information, see *TCPR's* thorough review of this topic in the

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Learning objectives for this issue: 1. Counsel your patients on alternatives to medication for the treatment of depression. **2.** Describe the advantages of various types of psychotherapy and behavioral interventions for the treatment of depression. **3.** Explain the relationship between inflammation and depression. **4.** Understand the most current findings in the literature regarding psychiatric treatment. This CME/CE activity is intended for psychiatrists, psychiatric nurses, psychologists and other health care professionals with an interest in the diagnosis and treatment of psychiatric disorders.

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June 2009 issue.)

TCPR's Take: Folate may be an effective adjunctive treatment for depression. We recommend the cheap stuff, meaning basic folic acid that is available for about $3 a month. A list of folate rich foods, which include green leafy vegetables and enriched grains, is available at www.wheatfoods.org. This might be an even better approach for patients.

Vitamin D. A recent epidemiological study suggests that vitamin D deficiency is a risk factor for the development of depression in older persons (Milaneschi Y et al., *J of Clinical Endocrinology and Metabolism* 2010; online ahead of print). It is also clear that many people are deficient in vitamin D, a deficiency which has been linked to several chronic medical problems (see for example the entire issue of *Endocrinol Metab Clin North Am* 2010;39(2)). However, there have been no double-blind placebo controlled studies testing vitamin D specifically for depression treatment or prevention.

The Food and Nutrition Board of the National Institutes of Health recommends 200 IU of Vitamin D as a standard "adequate intake" for adults ages 19 to 50, and 400 IU for those 51 to 70. However, recent reports have increased this recommendation to around 1000 IU (Milaneschi Y et al).

Patients should know that some research suggests that excessive vitamin D intake can lead to hypercalcemia and other conditions. This is a controversial topic, but general agreement is that the risk of toxicity is quite low and requires more research (Cranney A et al., *Evid Rep Technol Assess* 2007;158:1–235). The best natural sources of vitamin D are salmon, tuna, mackerel, and cod liver oil. D3 (cholecalciferol) is the supplemental form of vitamin D currently recommended.

TCPR's Take: Given the clear general health benefits and the possible mental health benefits of adequate vitamin D, we recommend at least informing patients that there is some evidence that many people are vitamin D deficient. Whether it is cost-effective to actually order a 25-hydroxyvitamin D level in depressed patients is unclear, and will require more research in order to determine the sensitivity and specificity of such testing. Vitamin D has been in the news lately, and many patients are asking whether they should take it. A reasonable response would be to recommend the moderate supplementation amounts noted previously, and to direct patients to bring the topic up with their primary care doctors, who are likely to be more current on guidelines. Treatment dosage recommendations depend on severity of deficiency, time of year, skin type, and level of sun exposure—factors which most psychiatrists would be unlikely to invest the time into learning. Nonetheless, for a good review of the current guidelines and issues, see http://bit.ly/arDPOu.

Foods for Mood

Does eating "junk food" cause or worsen depression? Conversely, is there any evidence that we should be prescribing our depressed patients specific diets?

One meta-analysis of 15 studies found that people with obesity had a 55 percent increased risk of developing depression over time, and that depressed people had a 58 percent increased risk of becoming obese (Luppino FS et al., *Arch Gen Psych* 2010;67(3):220–229). This finding raises the possibility of a two-way causal link between obesity and depression—with depressive symptoms leading to lifestyle changes that promote obesity, and with obesity leading to self-esteem and health issues that might cause depression.

Two recent studies have suggested that "whole" foods may be protective against depression and anxiety. One of these studies included women only, and found that a diet rich in fruits, vegetables, whole grains, meat, and fish was associated with a reduced risk of depression, anxiety, and dysthymia (Jacka FN et al., *Am J Psychiatry* 2010;167(3):244–247). Another large study of both men and women found an association between less healthy "processed foods" and depression over a five year period (Akbaraly TN et al., *Brit J Psychiatry* 2009;195(5):408–413). Both of these studies adjusted for possible confounding variables, such as socioeconomic status and age.

TCPR's Take: While the evidence is preliminary, these studies suggest that a diet high in processed foods, fried foods, and sugar may lead to a higher risk of depression and anxiety. Therefore, we recommend that you take a basic dietary history, weigh your patients (or determine their weights from self reports), and use weight and height to calculate the Body Mass Index (BMI). (You can use a free BMI calculator at www.nhlbisupport.com/ bmi.) Encourage your patients to eat more whole foods like fruits, vegetables, and whole grains. Informational handouts and informed advice on a healthy whole food diet can help patients decide what to eat. The American Heart Association's Nutrition Center is a great resource for patients and providers. (It can be found at www.heart.org.) The Physicians Committee for Responsible Medicine offers excellent information at www.nutritionMD.org, and free online nutrition CME for physicians and other health care providers is available at www.nutritionCME.org.

It is possible, of course, that the association is not causal, and that people who eat wholesome diets are less likely to get depressed for other reasons—for example, that they are wealthier, or have higher self esteems. However, it certainly can't hurt to eat a healthier diet.

Light Therapy

Light therapy is clearly effective for seasonal affective disorder (SAD), defined as depression that follows a predictable pattern of starting in the fall or winter and remitting in the spring (Rosenthal NE et al., *Arch Gen Psych* 1984;41(1):72–80). Is this treatment effective for non-seasonal depression as well? It's unclear, since the largest recent meta-analysis of light therapy for this indication was inconclusive (Tuunainen A et al., *Light therapy for non-seasonal depression.* Cochrane Database of Systematic Reviews 2004, Issue 2).

Meanwhile, light therapy has been tested for myriad other disorders, such as treatment resistant depression, bipolar depression, ADHD, and dementia. One review of this literature found some positive results, but sample sizes were small and it was not clear how well the studies maintained the double blind (Terman, *Sleep Med Rev* 2007;11:497–507).

An intriguing off-shoot of light therapy is called "triple chronotherapeutic intervention" and is a combination of light therapy, partial sleep deprivation (so-called "wake therapy"), and sleep phase advance therapy (a process of resetting a patient's sleep and wake times progressively over many days). For more information about this method,

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see the website for the Center for Environmental Therapeutics at www.chronotherapeutics.org. This is a nonprofit center founded by prominent researchers in the field, and the website offers free downloads of many relevant articles.

In a personal communication with us, Dr. Norman Rosenthal, considered by many to be the "father" of light therapy (see his book *Winter Blues: Everything You Need to Know to Beat Seasonal Affective Disorder* rev 2006; Guilford Publications, Inc: New York, NY), said that in his practice he has had success with light therapy for the common situation of patients who have nonseasonal depression, successfully treated with medication, but whose symptoms nonetheless worsen in the winter or during a period of dark weather.

Broad spectrum white fluorescent light has been used in light therapy studies for almost three decades and is considered effective and relatively safe. Dr. Rosenthal tells us that he personally recommends Verilux Happy Light, Day Light by Uplift, and SunBox, all of which are convenient for most patients and are comparatively priced. (Dr. Rosenthal has no financial relationships with any light box company.) Light boxes are not regulated by the FDA, so efficacy and safety may vary depending on the product. (See the October 2006 issue of *TCPR* for our test drives of some popular light boxes.)

While light-emitting diode (LED) and blue light therapy were found to be effective for SAD when compared to red light in three studies, there have been no studies comparing LED or blue light therapy with white light (Desan PH, *BMC Psychiatry* 2007;7(38):883–889; Glickman G et al., *Biol Psychiatry* 2006;59(6):502–507; Strong, RE et al., *Depression Anxiety* 2009; 26(3):273–278).

We recommend that most patients with SAD start light therapy toward the end of August or early September, which is when those most sensitive to light will notice shorter days. Most light boxes are 10,000 lux and patients should sit in front of them immediately after awakening for 30 minutes. The length of exposure can be titrated up or down according to response. Dr. Rosenthal cautions that bipolar depressed patients should be started at much lower durations (eg, five to ten minutes) to minimize risk of a switch into mania. Potential side effects of light therapy include headache, nausea, eyestrain, irritability, fatigue, and insomnia.

TCPR's Take: Prescribe light therapy for patients with SAD as a matter of course, since it has established efficacy and the side effects are minimal. Consider the treatment (noting the smaller evidence base) in the following situations, as well: 1) As an adjunct for nonseasonal depression that worsens during the winter, and 2) As an adjunct for either drug- or ECT-resistant depression, regardless of seasonality of mood.

Exercise

Everybody loves exercise; everybody hates exercise. We all know it's good for us and we should do more of it, but should we be prescribing it for patients to treat their depression? Epidemiological studies show a negative association between depression and exercise (Goodwin, *Prev Med* 2003;36:698–703), but such studies do little to clarify the issue, since this may mean either that exercise cures depression or simply that people who are already depressed lack the motivation to exercise.

Fortunately, there are a growing number of clinical trials in which depressed patients are randomly assigned to exercise versus a wait list or treatment as usual. A recent Cochrane meta-analysis of 23 such randomized controlled trials (including a total of 907 subjects) indicated a large clinical effect for prescribed exercise treatment compared with no treatment or another controlled intervention. However, you might imagine that research on exercise has some methodological challenges, such as adequately blinding the patients and researchers to the nature of the treatment. In fact, the Cochrane authors deemed that only three of the trials had adequate blinding (of the raters only, as it is nearly impossible to blind participants to exercise), and other aspects of methodology, and limiting the analysis to these three studies yielded a much more modest effect size (Mead GE et al., *Exercise for depression.* Cochrane Database of Systematic Reviews 2009, Issue 3). Other meta-analyses with less strict criteria have also shown impressive benefits of exercise therapy for clinically depressed patients (Craft et al., *Prim Care Companion J Clin Psychiatry* 2004;6(3):104–111).

Another potential piece of evidence for exercise as a mood-booster is in the literature on fibromyalgia treatment. A Cochrane review of 2,276 subjects across 34 trials of exercise showed robust positive effects on well being and physical functioning, with less of a clear benefit for pain and tender points. The evidence was so persuasive that exercise was awarded the rare "gold level" standard of evidence (Busch AJ et al., *Exercise for treating fibromyalgia syndrome.* Cochrane Database of Systematic Reviews 2007, Issue 4). However, the effect of exercise for fibromyalgia may be qualitatively different than it is for depression. Part of the syndrome of fibromylagia (and chronic fatigue) is the central role that inactivity plays in perpetuating the syndrome, and exercise directly counteracts inactivity. Whether exercise works in a similarly indirect fashion in depression, or more directly as an antidepressant, is unknown.

What is the best way to talk with our patients about the benefits of exercise? Keeping in mind there is evidence that "high doses" of exercise (in frequency and intensity) alleviate symptoms better than "low doses" (Dunn et al., *Am J Prev Med* 2005;28(1):1–8; Martin et al., *Arch Intern Med* 2009;169(3):269–278), the goal is often set at about 30 minutes of moderately intense physical activity a day, three to five days a week. Of course this can be a challenging task for many of our patients who struggle with a lack of motivation and physical limitations.

Methods that have been effective in keeping people engaged include starting patients slowly to gradually build their confidence, carefully assessing each patient's personal barriers to exercise, and having patients keep an exercise log and use a step counter. Step counters are now common and inexpensive and patients may ask your advice on how to use one. The goal of "10,000 steps a day" (five miles per day) that is publicized may be too much for many of our patients. Find out your patient's average number of steps per day (it's often around 3,000 steps), and slowly encourage him or her to increase steps by 1,000 to 2,000 per week. For an excellent discussion on this topic and a more detailed discussion of the practical tips listed above, see the Q&A at http://bit.ly/buykck (Otto et al., *Prim Care Companion J Clin Psychiatry* 2007;9(4):287–294).

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For a good handout to give patients on starting exercise, including frequency and intensity, see uptodate.com's public access patient website, www.uptodate.com/patients, keyword: "patient information exercise."

Meditation and Yoga

While relaxation exercises have been a part of some psychiatric practices ever since Herbert Benson wrote *The Relaxation Response* in 1975, lately there has been more of an interest in integrating yoga and meditation with psychiatric care. Many of these techniques have fallen within the broad term "mind/body" techniques, and there appear to be at least as many such techniques as there are mind/body practitioners. So sit down, breathe deeply, and relax—as you read our summary of the more well-researched mind/body methods.

Meditation. For centuries many religious traditions have maintained that meditation can alleviate mental pain and increase well-being. Mental health researchers have been interested in the possibility of an inward contemplative focus to decrease anxiety and improve mood since the 1920s, in part due to the research of Edmund Jacobson and his creation of a relaxation technique known as Progressive Muscle Relaxation (PMR), a technique still often used today in many stress reduction programs.

In the 1970s stress researchers began to study meditation, dividing it into two types: "concentrative" and "non-concentrative." Concentrative meditation directs attention to a single stimulus, such as a chant or your breathing—the most famous example being transcendental meditation (TM). In a flurry of research interest during the 1970s and 1980s TM was shown to reduce anxiety to a degree comparable to other relaxation treatments. For example, one controlled study of 31 subjects diagnosed with a "anxiety neurosis" compared biofeedback, relaxation therapy, and transcendental meditation (twice daily for 20 minutes), and found no significant differences among the three groups (Raskin et al., *Arch Gen Psychiatry* 1980;37(1):93–97).

These days, we are likely to hear more about "mindfulness training" than about TM. Mindfulness differs from TM and some other meditative techniques in that the aim is to maintain a moment-to-moment awareness of all of the contents of your mind, as opposed to just restricting focus to a single mental task, such as repeating a mantra or staring at a candle.

Mindfulness training was popularized and researched extensively by Jon Kabat Zinn at the University of Massachusetts Medical School in a form called mindfulness-based stress reduction (MBSR). MBSR originated as a group-based program to help with chronic pain and stress associated with other medical conditions, and was later studied to treat anxiety disorders (Kabat Zinn, *Am J Psychiatry* 1992;49(7):936–943).

An offshoot of MBSR is Mindfulness Based Cognitive Therapy (MBCT), which combines the principles of mindfulness group meditation with elements of cognitive therapy. Unlike traditional CBT, however, there is little emphasis on challenging the contents of thoughts—instead the patient is taught to become nonjudgmentally aware of his/her thoughts and feelings. The problem, according to MBCT, is that depressed patients try to think their way out of their dysphoric mood, which leads to rumination ("What's wrong with me?" "Why do I always feel overwhelmed?"), and therefore worsens depression. This "doing" mode of mind is second nature to most of us, but it can paradoxically worsen depression. In contrast, mindfulness meditation cultivates a "being" mode, involving watching your feelings drift by like clouds in the sky. By doing so, the meditator begins to notice and to halt the internal triggers that can spiral into hopelessness.

There are several randomized clinical trials demonstrating the effectiveness of MBCT to prevent depressive relapses compared to treatment as usual (TAU) (Teasdale et al., *J Consult Clin Psychol* 2000;68(4):615–623; Bondolfi et al., *J Affect Disord* 2010;122(3):224–231). The Bondolfi study, for example, enrolled 60 unmedicated patients who were in remission from a recurrent depression, and randomly assigned them to either TAU or TAU plus MBCT. Although both groups eventually relapsed at similar rates, the time to relapse was much longer in the combined group (204 days compared to 69 days for the TAU group). For a good book describing the MBCT method for preventing depressive relapse written for clinicians and patients alike see "The Mindful Way through Depression" written by Mark Williams et al., Guilford Press, 2007 (it includes a nice CD to assist with meditation practices as well).

Just to confuse matters even more, there are a growing number of "mainstream" cognitive therapies that now include mindfulness practices, such as Acceptance and Commitment Therapy (ACT). In contrast to MBCT, which is a group treatment built around daily meditation practices, ACT is an individual psychotherapy that uses a variety of cognitive techniques including mindfulness. The idea here is that trying to control uncomfortable feelings and thoughts is not just ineffective but counterproductive. Instead, ACT encourages patients to accept their full range of emotional and cognitive experiences while also identifying key personal values that can be translated into behavioral goals. In a recent meta-analysis of 18 randomized control trials (n=917), ACT was superior to waiting lists and treatment as usual, though not significantly more effective than established treatments, such as CT, CBT, and problem solving (Powers et al., *Psychother Psychosom* 2009;78(2):73–80). For a good introduction on ACT for clinicians and patients, see "The Mindfulness and Acceptance Workbook for Anxiety" by Forsyth and Eifert, Harbinger Press, 2007 (it also includes a CD with meditation instructions).

TCPR's Take: Meditation has become mainstream, and the future is in integrating components of its benefits into psychotherapy.

Yoga. Although the term yoga evokes the image of drawstring-clad practitioners who have formed themselves into improbable postures, the word itself—roughly translated from Sanskrit—means "to unite," and is a general term in Hinduism for the various means by which a person can connect with Brahman, the universal consciousness. The type of yoga most commonly practiced in the U.S. is called Hatha yoga, which focuses on postures (called asanas). Hatha yoga combines meditation, yoga postures and philosophy to promote well-being. There are a confusing number of different yoga practices, ranging from Ashtanga yoga (sometimes called "Power yoga"), a fast-paced intense style of yoga

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that is physically demanding, to Iyengar yoga, which focuses on precise body alignment and holding poses over long periods.

Does research support yoga as a treatment for psychiatric disorders? A 2005 literature review identified five randomized controlled trials, each of which used different types of yoga interventions to treat depression. All of the trials reported positive results but all had methodological shortcomings (Pilkington et al., *Journal of Affect Disord* 2005;89:13–24).

One of the few (and best) randomized trials demonstrating the usefulness of yoga examined a technique called Sudarshan Kriya yoga (SKY). In this study, 45 depressed hospitalized patients were randomized to SKY, imipramine (150 mg–225 mg/day) or ECT for four weeks. Reductions in depression measured by the Beck and Hamilton depression rating scales occurred in all three groups, with imipramine and SKY performing similarly, both inferior to ECT (Janakiramaiah N et al., *J Affect Disord* 2000;57(1–3):255–259). A recent randomized trial of 46 individuals with major depression or dysthymia compared three treatments: yoga with meditation (not SKY), group therapy with hypnosis, and psychoeducation (considered the control group). Significantly more participants in the yoga group experienced a remission than did controls at a nine month follow up. Remission rates in the hypnosis group did not significantly differ from the control group (Butler et al., *Journal of Clinical Psychology* 2008;64(7):806–820).

Yoga is often used to treat anxiety, and a 2005 review located eight studies, all with positive results, but again the authors noted the "poor quality" of most of the studies (Kirkwood et al., *Br J Sports Med* 2005;39(12):88–91). One of the better trials in this review randomized 91 subjects with a DSM-III diagnosis of "anxiety neurosis" to either five days per week of yoga practice or diazepam (no dose or frequency given) for three months. Those assigned to yoga had significantly lower anxiety scores at the end of the trial than patients taking diazepam (Sahasi et al., *J Pers Clin Stud* 1989;5:51–55).

Recent trials have found women in particular may benefit from yoga's anti-anxiety effects. One study showed a significant decrease in anxiety for only the women who were randomized to a twice weekly yoga class for 90 minutes compared with a control group (Javnbakht et al., *Complement Ther Clin Pract* 2009;15(2):102–104). Similarly, another recent trial randomly assigned 98 women with breast cancer to either 60 minutes of yoga once a day or brief supportive therapy and found an overall decrease in several anxiety measures in the yoga group compared to the brief supportive therapy group (Rao et al., *Complement Ther Med* 2009;17(1):1–8).

TCPR's Take: Yoga can be a useful adjunctive treatment for both depressed and anxious patients, and may be particularly helpful for women—but the research is still quite limited.

Psychotherapy for Depression: What's Best?

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

Are all psychotherapies equally effective for the treament of depression? Or do cognitive behavioral techniques clearly rise above the pack, as implied by the amount of media coverage they receive? In this article, we'll take a hard-nosed look at the evidence.

Cognitive therapy (CT). Teaching patients to examine the evidence for their underlying negative thoughts such as "I am a loser," or "I always fail," is key to cognitive therapy, as depression often includes unrealistic negative beliefs. When something goes awry, such patients tend to blame themselves (technically termed "internal negative beliefs"), believe that their flaw is permanent ("stable negative beliefs"), and believe the flaw covers a large swath of their personality ("global negative beliefs"—for example, "I'm a failure," as opposed to, "I made a small mistake"). In therapy, you help your patient to identify negative thoughts and to seek evidence about whether they are true. Homework assignments help patients identify and transform these thoughts in real time as they live their lives.

Behavioral activation therapy (BT). Depressed patients, often driven by their negative thoughts, sometimes call in sick to work, stop attending college classes or engaging in hobbies, and avoid social events. If they felt better, they would engage in these important life functions, but because they are depressed, they just don't feel up to it. The behavioral activation approach says essentially: "Don't wait until you feel better—rather, you'll feel better once you become more active."

Avoiding work, school, and social situations leads to guilt and withdrawal of positive reinforcement. While most people don't love their jobs, they have a certain sense of accomplishment from getting tasks completed on the job. Also, going to work or spending time with friends and family often provides some positive social reinforcement. So by avoiding these important life tasks, depressed people are limiting their chances to improve their moods. If patients change avoidance behavior to allow for more reinforcement from the environment, mood should improve. This is often a gradual process—depressed patients aren't expected to change all of their behavior at once. In a meta-analytic comparison of 11 trials that directly compared behavioral activation therapy to a full package of CBT (both cognitive and behavioral interventions), both treatments yield similar benefits (Cuijpers P et al., *J Consult Clin Psychol* 2008;76:909–922).

Cognitive-Behavioral Therapy. Cognitive-behavioral therapy has earned its reputation as a strongly supported treatment for depression. Dozens of clinical trials clearly show that cognitive and behavioral interventions, alone or in combination, are more effective than no treatment or psychological placebo (Gloaguen V et al., *J Aff Disord* 1998;49(1):59–72; Wampold BE et al., *J Aff Disord* 2002;68:159–

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Q&A With the Expert

This Month's Expert

Inflammation and Depression

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Dr. Raison owns equity in, and serves as chief scientific advisor for, Contemplative Health, an online provider of training in meditation. Dr. Carlat has found no commercial bias in this educational activity.

TCPR: Dr. Raison, you are involved in some interesting research about the connections between inflammation and depression. Tell us about it.

Dr Raison: My research focuses on inflammation and the development of depression in response to illness and stress. This is arguably one of the hottest areas of research in mood disorders today.

TCPR: So what have you and others found?

Dr Raison: Many studies show that people with depression have higher measures of various inflammatory markers in the blood than people who are not depressed (Howren MB et al., *Psychosom Med* 2009;71(2):171–186).

TCPR: Can you remind us of how inflammation occurs?

Dr Raison: Inflammation is a very complex set of reactions that traditionally occur when the body's immune system recognizes some sort of foreign invader. White blood cells called macrophages are activated and engulf the invader. This leads to the production of chemicals called cytokines that serve as messengers that travel around the body spreading the word that there is an invader. These cytokines activate various other mediators of the innate immune system. This is how you get things like fever, as well as pain and heat at the site of an injury. The innate immune system also helps activate what is called the adaptive immune system. This gets T-cells and B-cells fired up to kill the invader and help tissue heal. The symptoms of sickness, although uncomfortable, are good things, as they are proof that the cells are attacking and killing the invader—the bacteria or virus, for example. Meanwhile, the cytokines get a lot other cells in the body to start working on fighting the invader, too. So the liver might take a break from its usual job of making albumin and start producing C-reactive protein (CRP), which is a classic marker of inflammation.

TCPR: So what does this have to do with depression?

Dr Raison: Well, what's interesting from a psychiatric point of view is that cytokines are able to signal across the blood brain barrier. Cytokines in the gut can cause the production of cytokines in the brain, and vice versa.

TCPR: How did the discovery of this connection come about?

Dr Raison: It actually started with the discovery that whether an animal was given an injection of bacteria to make it sick, or it was subjected to some sort of psychological stress, you got the same type of symptoms in response. These symptoms include loss of appetite, increased anxiety behavior, decreased sexual activity, and increased body temperature. This led to the idea that maybe there was some tie between sickness and stress-related disorders. The literature in animal and human studies supports the idea that psychological stress activates inflammation (Maier SF et al., *Psychological Review* 1998;105(1):83–107; Steptoe A et al., *Brain, Behav, Immun* 2007;7:901–912; Kiecolt-Glaser JK et al., *P Natl Acad Sci USA* 2003;100(15):9090–9095).

TCPR: So you're saying that psychological stress can cause the body to react in the same way as it would to a foreign invader, like a bacterium or a virus?

Dr Raison: Exactly. It turns out that inflammatory processes that originally evolved to respond to a foreign microorganism can also be activated from perceptual states of the brain. What I mean is that danger, loss, and fear—all the things that indicate that your ability to survive or reproduce might be threatened—can activate the production of cytokines in the same way an infection can.

TCPR: How have you tested this idea?

Dr Raison: In our research, we bring a group of people into the lab in a relaxed state, hook them up and start drawing their blood. Then we bring in a psychosocial stressor by making them perform a stressful task in front of a judgmental panel of experts. If we measure the blood before, during, and after they are stressed, we can see that the cytokines go up in response to the stress (Pace TW et al., *Am J Psychiatry* 2006;163(9):1630–1633; Bierhaus A et al., *P Natl Acad Sci USA* 2003;100(4):1920–1925).

TCPR: And you associate the stress response with depression.

Dr Raison: Stress is known to be one of the major risk factors for depression. Stress causes cytokines to be turned on. Moreover, if you look at the physiology of many people with depression, they look like they are "forever being chased by the tiger" as I like to say, meaning that they exist in states of chronic stress system hyperactivity, as measured by increased sympathetic and decreased parasympathetic activity, as well as resistance to cortisol and activation of inflammatory pathways (Raison CL et al., *Am J Psychiatry* 2003;160:1554–1565;

Raison CL et al., *Trends in Immunology* 2006;27(1):24–31). Given these tendencies in depression, it is perhaps not surprising that on average, people who are depressed have higher levels of cytokines than people who are not depressed. Furthermore, a number of studies have shown that people who are depressed have inflammatory markers that put them at risk for heart disease, diabetes and dementia (Miller AH et al., *Biol Psychiatry* 2009;65(9):732–741). The chronic mild rise in inflammation over time exerts wear and tear on the body.

TCPR: When you say there is inflammation, what specifically is getting inflamed?

Dr Raison: When I say "inflammation," what I mean is that there are increased levels of cytokines in the blood. Evidence suggests that brain levels also rise—especially shown in animal models, where we see that stress activates pro-inflammatory cytokines in the central nervous system. Something as simple as social isolation can cause the cytokine IL-1 beta to suppress the production of an important neural protein called BDNF (brain-derived neurotrophic factor) in the hippocampus (Barrientos RM et al., *Neuroscience* 2003;121(4):847–853; Rachal Pugh C et al., *Neurosci & Biobehav Rev* 2001;25(1):29–41). A deficit of BDNF has been repeatedly implicated in the pathogenesis of depression, so this finding really links inflammatory pathways to other brain systems known to be abnormal in depression (Aguilera M et al., *Psychol Med* 2009;39(9):1425–1432; Schmidt HD et al., *Behav Pharmacol* 2007;18(5–6):391–418; Mossner R et al., *World J Biol Psychiatry* 2007;8(3):141–174). If you block the cytokine in the CNS, you can prevent this whole process.

TCPR: This is all very interesting research, but how do we apply what you've learned to the treatment of our patients with depression?

Dr Raison: Depression is such a nuanced condition that this unfortunately does not translate into a simple answer—give all patients an "anticytokine" medication, for example. The data suggest that inflammatory processes contribute to depression. However, depression comes from a combination of your genes and environmental adversity—all things being equal, if your cytokines run high you are more likely to develop depression than someone whose cytokines run low (Gimeno D et al., *Psychol Med* 2009;39:413–423; van den Biggelaar AHJ et al., *Clin Exp Immunol* 2010;160(1):42–47).

TCPR: So it's not just a matter of stopping the production of cytokines to stop depression.

Dr Raison: No, depression is too multifactorial for that to be likely to fix everyone who suffers from a mood disorder. I can say that research supports the idea that if you can reduce the cytokines of people with depression, they might feel better. Most standard antidepressants lower inflammation in the blood of depressed people (Miller AH, *Biol Psychiatry,* op.cit).

TCPR: Beside the cytokine-lowering effects of regular antidepressants, is there anything else we can try?

Dr Raison: Some data suggest that people who don't respond well to SSRIs have higher cytokine levels (Miller AH, ibid). If you test a patient's blood and find that he or she has a high C-reactive protein (CRP) level—say about four or so—some research shows that adding a Cox-2 inhibitor could improve response (Muller N et al., *Mol Psychiatry* 2006;11(7):680–684). But that's not always the case, and CRP levels do not directly correlate with mood. Anything over about three for CRP is in the high range. However, I could have a CRP of two and be completely miserable and depressed, and you could have a CRP of five and be fine.

TCPR: Any other suggestions?

Dr. Raison: A couple of open trials have examined adding 325 mg of aspirin a day to Prozac nonresponders and have reported a response within about week or two (Brunello N et al., *Int Clin Psychopharmacol* 2006;21(4):219–225; Mendlewicz J et al., *Int Clin Psychopharmacol* 2006;21(4):227–231).

TCPR: To sum up the evidence—cytokines are a part of the inflammatory process. There is some evidence that an increase in cytokines may contribute to the development and maintenance of depression. So in some cases adding an anti-cytokine or anti-inflammatory agent, such as Celebrex or aspirin, may help with depression.

Dr. Raison: All true. There is no magic bullet with depression. This research butts up against our tradition of compartmentalizing depression as a sort of discrete disease state. These systems interact in very complex ways that we are just beginning to understand.

TCPR: Thank You, Dr. Raison.

Correction: It was brought to our attention by reader Dr. Matthew Tessena of the University of Rochester that some of the cross-reactivities listed in the article, "A Primer on Drug Testing," from the May 2010 issue of *TCPR* are no longer relevant with the latest EMIT (enzyme multiplied immunoassay technique) tests. However, we should have noted other cross-reactivities that were not included in the article. In addition, in the chart of Available Drug Tests, the detection window for urine was listed as six to 24 hours. In actuality, the window is closer to three to four days, except for alcohol, which is eight to 12 hours. To read the full list of additional cross-reactivities, visit www.thecarlatreport.com/may-2010-tcpr-correction.

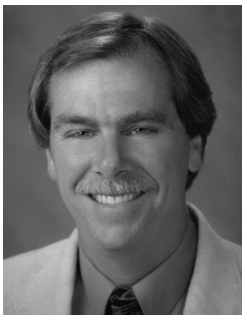
Q&A With the Expert

This Month's Expert

Behavioral Activation for Depression

Steven Hollon, PhD

Professor of Psychology
Vanderbilt University
Nashville, TN



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

TCPR: Dr. Hollon, your work as a psychologist and researcher focuses on the treatment and etiology of depression. What in particular do you study?

Dr. Hollon: I'm interested in how cognitive and behavioral interventions compare to medication in the treatment of depression, and what their enduring effects are.

TCPR: Would some of our patients do better with psychological treatments vs. medication treatments?

Dr. Hollon: Medications work well, are relatively safe, and a lot of people respond to them, so of course they are a popular treatment choice. In terms of what makes patients who respond to therapy different than those who respond to medication, there aren't many clear differences. However, there are differences between the effects of medication and the effects of nonmedication treatment.

TCPR: What are some of the differences?

Dr. Hollon: A main difference is in how enduring the treatment effects are. There is no indication that taking medication for depression protects you from getting depressed again once you stop taking it. It's like taking insulin for diabetes; it is protective when you are taking it, but it doesn't keep working after you are done.

TCPR: How are the effects of therapy different?

Dr. Hollon: Research shows that cognitive and behavioral interventions have lasting effects, even after they are stopped. Actually, it appears that they cut the risk of depression relapse by about half. That is, patients treated to remission with cognitive behavioral therapy are only about half as likely to relapse following treatment termination than patients treated to remission with medications (Dobson et al., *J Consult Clin Psychol* 2008;76(3):468–477; Hollon et al., *Arch Gen Psych* 2005;62(4):417–422).

TCPR: So there appears to be something specific about therapy that appears to provide long-lasting protection. Do you know what that something is?

Dr. Hollon: What it looks like is that people learn skills to help them manage their depression. Studies show that the specific patients who are more successful at learning cognitive and behavioral skills are those who are better protected from relapse. This is true for even short-term therapy—as little as three or four months.

TCPR: How well do patients respond to therapy? Is it comparable to medication?

Dr. Hollon: If you take a fairly short-term course of cognitive therapy, you get about a 60% response rate, or 30% full remission—which is about the same as medication. But once you stop therapy, these people are no more likely to relapse than the ones who stay on medication (DeRubeis RJ et al., *Arch Gen Psych* 2005;62(4):409–416).

TCPR: What specifically are the skills that we should be teaching our patients to help them prevent a depression relapse?

Dr. Hollon: There are a couple things. The first is behavioral activation. This is encouraging people not to wait until they feel like doing something, but just to go ahead and do it. When in doubt, do. Often, it's not that people who are depressed can't *do* things, it's just that they can't *start* things.

TCPR: So you encourage them to become active. What is the second skill?

Dr. Hollon: The second is questioning the accuracy of negative self beliefs. Most of the time people who are depressed are unduly negative. They underestimate what they are capable of doing—like getting a job or having a relationship. So you can teach them to do something anyway—break their tasks down to size and act on them, even if they have negative views of the outcome. So, if you think you can't get a job, well, you should just put in the job application anyway.

TCPR: You've described two main curative principles: behavioral activation and questioning negative beliefs. What kind of research convinces you of their effectiveness?

Dr. Hollon: Among patients who responded to cognitive therapy for depression in a recent outcome trial, those who were able to exhibit those two skills were the least likely to relapse following treatment termination (Strunk DR et al., *J Consult Clin Psychol* 2007;75(4):523–530).

TCPR: But is behavioral activation any different from what most psychiatrists do with many of their patients anyway? I know I am frequently advising patients, "Get out there, get a job, get a relationship," etc.

Dr. Hollon: You need to tell them how. You need to show them how to break things down into manageable chunks. For example, say your patient wants to get a job. First he needs to find out who is hiring. Then he needs to put together an application. There may be half a dozen steps to get through. It's like trying to get up a slippery hill. You could try to climb up the slope, but it's easier to take the stairs.

For someone who is depressed, a step-by-step approach makes accomplishing things much easier.

TCPR: So literally, you might have a patient bring in the classified section of the newspaper to his appointment?

Dr. Hollon: Absolutely. I will get the process started right in the session, because getting started is really where depressed people have trouble. I might have them look for jobs on the computer in my office or work with them on their resumes during a session. If someone is severely depressed, I might sit down with him and write out a schedule of everything he is going to do between now and our next session. Things as simple as, "stop at Starbucks on the way home," and "fold the laundry at 4 o'clock."

TCPR: So this is like personal coaching.

Dr. Hollon: That's exactly what it is. I might even go with him to Starbucks and encourage him to start a conversation with the barista, for example. Sometimes we have to help structure things for the patient. Because when you're depressed you always have two things to do: you have to decide what to do, and you have to do it. If we can help a depressed patient decide in advance, all he has to do is carry it out.

TCPR: Thank You, Dr. Hollon.

Psychotherapy for Depression: What's Best?

Continued from Page 5

165).

Cognitive and behavioral techniques often go hand-in-hand. You might teach a depressed patient to challenge her negative thoughts and also change her depressive behavior. CBT can be seen as fighting depression on two fronts, though there is actually not much data to suggest that a two-pronged approach works much better than using either cognitive or behavioral tactics alone.

In comparisons with antidepressant medication, CBT fares about as well in the short-term but offers better long-term results after treatment discontinuation. One meta-analysis of six comparisons found that relapse rates at 1 to 2 year follow-up after successful treatment were significantly lower with psychotherapy (27%) than with medication (57%). Nearly all patients described in this report received CBT, so it is tempting to conclude that CBT has demonstrated convincing long-term efficacy relative to medication, but major caveats are in order (de Maat S et al., *Psychother Res* 2006;16:562–572). These comparisons were based on fewer than 300 patients, and the medication arms typically used MAOI or tricyclic medication, so we would need larger studies using modern antidepressants to draw firmer conclusions. Nonetheless, this evidence base provides preliminary support to bolster CBT's case as a very impressive long-term antidepressant.

Interpersonal Therapy (IPT). IPT emphasizes the importance of relationships in depression. In the IPT model, you take a thorough history of your patient's past and present relationships. Depending on your patient's issues, IPT may offer one or more of the following four therapeutic interventions: 1) Helping your patient mourn the loss of somebody; 2) Teaching conflict management skills; 3) Helping patients understand how to navigate shifting roles (eg, from one job to another, or from being married to getting divorced); and 4) Providing social skills training. IPT is designed to be a short-term intervention of 12 to 16 weekly sessions that yields long-term benefits. A meta-analysis of five randomized trials comparing IPT to CBT found that both techniques were effective, with no significant differences between the two in depression outcomes (Cuijpers P et al., *J Consult Clin Psychol* 2008;76:909–922).

Psychodynamic therapy (PT). PT was adapted from traditional Freudian psychoanalysis, a procedure often associated with patients lying on couches, silent analysts, and a relative lack of empirical validation. However, several variants of PT are designed as brief interventions and have solid scientific support. The underlying theory is that all people develop relationship templates (ideas of how relationships tend to work), based upon their experiences. Early relationships with parents may be particularly powerful in shaping these templates. Patients often transfer their experiences with others onto their relationship with the therapist. For example, a patient who had cold, disapproving parents may interpret neutral behavior on the part of the therapist as harsh or rejecting. The psychodynamic therapist discusses transference with the patient, helping the patient to develop insight into what drives his behavior and views of the world. The therapist is finely attuned to behaviors indicating "resistance"—such as frequently showing up late or missing appointments, avoiding discussion of important issues, or ignoring the therapist's suggestions. These generally signal some reluctance to change and should be examined, though the therapist should be tactful and caring when discussing these issues. A very understandable description of many key aspects of PT can be found at: http://bit.ly/bkiS4s.

While PT has not been studied as much as other techniques for the treatment of depression, a recent meta-analysis of four trials found that PT worked significantly better than waiting-list control groups in relieving depressive symptoms with a moderate to large effect size. But in a meta-analysis comparing PT to other interventions, nearly all of which were variants of CBT, PT was less effective by a small but statistically significant margin across 13 studies (Driessen E et al., *Clin Psychol Rev* 2010;30:25–36). This paper had a shortcoming, however: some of the included studies failed to use random assignment to treatment groups. Another meta-analysis that included only randomized comparisons found no statistically significant difference between PT and CBT across seven trials (Cuijpers P et al., *J Consult Clin Psychol* 2008;76:909–922).

Supportive Therapy (ST): Supportive therapy is defined in different ways by various practitioners. Most often, ST has been described by what it does *not* do: it is not psychodynamic, behavioral, or cognitive. What is left is a general focus on reflective listening, encouraging emotional expression, and developing a strong therapeutic relationship. The patient is typically left in charge of directing the topics of treatment sessions. Surprisingly, in a meta-analysis of 18 randomized comparisons between ST and CBT, the two treatments were equally effective (Cuijpers P et al., *J Consult Clin Psychol* 2008;76:909–922).

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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. Please see the study guide listed below to prepare for this month's post–test. Learning objectives are noted on page 1. 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 July 31, 2011.

As a subscriber to *TCPR,* you already have a username and password to log onto www.TheCarlatReport.com. To obtain your username and password, please email CME@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. Preliminary research has hinted that a whole food diet may be protective against depression and anxiety (Learning Objective #1).
   [ ] a. True [ ] b. False

2. Three studies found LED and blue light therapy to be superior to what type of light for the treatment of seasonal affective disorder (L.O.#1)?
   [ ] a. Red light [ ] b. White light
   [ ] c. Green light [ ] d. Black light

3. What type of psychotherapy posits the idea: Don't wait until you feel better to start engaging in life activities (L.O.#2)?
   [ ] a. Interpersonal therapy [ ] b. Psychodynamic therapy
   [ ] c. Supportive therapy [ ] d. Behavioral activation

4. When compared to cognitive behavioral therapy, how do the other types of psychotherapy described in Dr. Spielmans' article perform for the treatment of depression (L.O.#2)?
   [ ] a. Not as well [ ] b. Equally well
   [ ] c. Better [ ] d. They have not been compared to CBT

5. According to Dr. Hollon's research, patients treated to remission with cognitive behavioral therapy are twice as likely to relapse following treatment termination as patients treated to remission with medications (L.O. #2).
   [ ] a. True [ ] b. False

6. According to Dr. Raison, cytokines do what in response to stress (L.O. #3)?
   [ ] a. Decrease [ ] b. Stay the same
   [ ] c. Increase [ ] d. Are destroyed

7. In the Ghaemi study, patients with bipolar disorder who remained on antidepressants went for an average of how long without a depressive relapse (L.O. #4)?
   [ ] a. 12 weeks [ ] b. 39 weeks
   [ ] c. 41 weeks [ ] d. 110 weeks

8. In the Van Ameringen study, olanzapine was more effective than placebo for treating trichotillomania (L.O. #4).
   [ ] a. True [ ] b. False

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

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

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

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

5. How long did it take you to complete this CME/CE activity? ___ hour(s) ___ minutes

6. **Important for our planning:** Please state one or two topics that you would like to see addressed in future issues.

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.

TRICHOTILLOMANIA

Olanzapine Effective for Trichotillomania

Traditional treatment for trichotillomania involves medications used to treat obsessive compulsive disorder. A recent double-blind, placebo-controlled trial examined if a dopaminergic agent—in this case olanzapine (Zyprexa)—would produce positive results.

Researchers funded by Eli Lilly (the manufacturer of olanzapine) randomly assigned 25 patients with trichotillomania to two groups: one group (13 participants) was treated with olanzapine, the other group (12 participants) was treated with placebo. A response was defined by a Clinical Global Impressions-Improvement (CGI-I) score of ≤2. At the end of 12 weeks, 85% (11 of 13 subjects) of those treated with olanzapine responded to treatment, compared to 17% (two of 12) in the placebo group. Significant differences between the groups were evident as early as six weeks into the trial.

Doses of olanzapine ranged from 2.5 to 20.0 mg per day, with an average final dose of 10.8 mg per day. Two of the patients in the olanzapine group achieved total remission, which was defined as a complete stop to hair pulling behavior. As might be predicted, the most significant side effect of olanzapine was weight gain, with those in the olanzapine group gaining an average of 10.1 pounds in 12 weeks vs. a loss of 0.66 pounds in the placebo group (Van Ameringen et al., *J Clin Psychiatry* online ahead of print).

TCPR's Take: This study shows that olanzapine is likely effective for trichotillomania. We would need larger studies to be more confident in these findings, and patients would need to be informed that they might gain as much as one pound per week with this treatment. Although other, less weight-gain inducing antipsychotics have not been tested for trichotillomania, both habit reversal therapy and treatment with the amino acid N-acetylcysteine have, so we would suggest trying these first (Woods DW et al., *Behav Res Ther* 2006;44 (5):639–656; Grant JE et al., *Arch Gen Psychiatry* 2009;66:756–763).

BIPOLAR DISORDER

Antidepressants: Little Long-Term Benefit for Bipolar Disorder

Most people with bipolar disorder are maintained on antidepressants, but the evidence base is rather meager. In a recent trial, researchers recruited 70 patients with bipolar disorder, all of whom had responded to a combination of a mood stabilizer and an antidepressant. These patients were recruited from various community or university clinics, and had been treated with a variety of mood stabilizers—mainly lithium (44%), Lamictal (41%), and Depakote (23%)—and antidepressants—primarily Wellbutrin (22%), Paxil (22%), Celexa (19%), and Effexor XR (19%).

In order to be enrolled in the study, patients had to have been euthymic for two months. They were then randomly assigned to two groups: continue the antidepressant [n=32], or discontinue the antidepressant [n=38]. Both groups continued whatever mood stabilizer they were already taking. These patients were then followed for one year to see how they fared.

At one year follow-up, patients who remained on antidepressants went a little bit longer without a depressive relapse (average of 41 weeks) than those who discontinued them (average of 32 weeks). However, there was no significant advantage for antidepressant continuation on the number of manic, depressive, or mixed episodes, or the percentage of weeks during which patients were depressed or manic. Twenty-four percent of patients were "rapid cyclers" (meaning that they had at least four mood episodes a year). These patients actually did worse on continued antidepressants than patients who discontinued antidepressants (1.29 depressive episodes versus 0.42 depressive episodes) (Ghaemi SN et al., *J Clin Psychiatry* 2010;71:372–380).

TCPR's Take: There are several limitations to the study. It was not double blinded, so both the patients and the researchers knew which patients were taking which drugs. This might lead to raters being biased, since the study was conducted by a group well known for advocating that antidepressants can be dangerous in bipolar disorder (Ghaemi SN et al., *Bipolar Disord* 2003;5(6):421–433). In addition, since the patients used a wide variety of different medications, it is impossible to know if these results generalize to all antidepressants or only certain specific ones. Nonetheless, this appears to be the only randomized trial of modern antidepressant discontinuation in bipolar disorder, and it indicates that we should be particularly cautious prescribing these medications to patients with a rapid cycling pattern.

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Psychotherapy for Depression: What's Best?

Continued from Page 9

Bottom Line: In many clinical trials comparing psychotherapies to each other for the treatment of depression, the only clear trend is for legitimate therapies to perform about as well as each other and for *bona fide* therapies to outperform psychological placebo treatments (eg, prerecorded relaxation instructions, group therapy without clear psychological rationale, etc.). Though CBT is the brand of therapy with the reputation of having the most empirical support, it appears that all legitimate therapies perform about the same in treating depression. CBT has shown better long-term results than medication, but this is quite tentative and sorely in need of more investigation (de Maat S et al., *Psychother Res* 2006;16:562–572). Therapies other than CBT may compare equally well to meds, but the relevant studies have yet to be published.

TCPR'S VERDICT: ***For depression, all psychotherapies probably yield about the same results, though CBT is unique in that in some studies it led to a lower rate of relapse than antidepressant medication.***

Next Month in the *The Carlat Psychiatry Report*: The Neuroscience of Psychotherapy, including an interview with Dr. Louis Cozolino.

This Month's Focus:
Treatment of Depression

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