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IN THIS ISSUE

Focus of the Month:
The Neuroscience of Psychotherapy

Learning objectives for this issue:
1. Describe the presumed neurobiological effects of psychotherapy and medication in the treatment of depression, OCD, and social phobia. **2.** Explain neuroplasticity and how psychotherapy may change the brain. **3.** Understand the most current findings in the literature regarding psychiatric treatment.

How Do Psychotherapy and Medication Change the Brain?

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

We know that for many conditions, both medications and psychotherapy work about equally well. Common sense would dictate that there is some final common pathway of neuropsychiatric change underlying the symptomatic improvements we see. But identifying what is happening in a living human brain is extremely tricky. Recently, a number of articles have reviewed this topic, focusing on functional neuroimaging techniques such as positron emission tomography (PET), single-photon emission computerized tomography (SPECT), and functional MRI.

In this article, I will give a simplified rendition of what we currently know about this topic. I emphasize "simplified" because this literature is about as complex and jargon-ridden as I've experienced in my seven years at the helm of this newsletter. I apologize in advance if I have oversimplified some findings in the service of translation to the clinician's language.

Depression

While both cognitive behavioral therapy (CBT) and medications are effective for depression, it turns out that each treatment may be doing something quite distinct in the brain. Perhaps this should not surprise us, because we know that CBT differs clinically from medication in that it does a better job of suppressing future episodes of depression.

In one study, for example, depressed outpatients were randomly assigned to antidepressants or CBT. After 16 weeks, the response rates were nearly identical: 57.5% for meds and 58.3% for CBT. Next, the medication responders were randomly assigned to either medication continuation or switch to placebo, while all CBT responders stopped psychotherapy. One year later, medication patients who were switched to placebo (n=35) had a 76% relapse rate, patients who continued medication (n=34) had a 47% relapse rate, and CBT-only patients who stopped therapy (n=35) had only a 31% relapse rate. These results imply that a four-month

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course of weekly CBT prevents future depression recurrence better than a four-month course of meds (Hollon SD et al., *Arch Gen Psychiatry* 2005;62(4):417–422).

CBT probably exerts this long lasting effect by giving patients coping skills that they can deploy over the years to control their moods. "Give a man a fish and you feed him for a day; teach a man to fish and you feed him for a lifetime." This much seems clear—but what about the underlying neurobiology of CBT's effects? Researchers have focused on two main regions of interest: the prefrontal cortex (in charge of planning and executive functioning, and therefore presumably the portal through which CBT would exert its effects) and the limbic system (generally speaking, the emotional brain, encompassing the amygdala, the hippocampus, the cingulate gyrus, parts of the basal ganglia—and many other regions, as the official boundaries of the limbic system are often revised).

The first widely disseminated study to compare brain changes in CBT vs. meds focused on 13 depressed patients who responded to CBT versus nine patients who responded to paroxetine (Paxil). Patients who got better from CBT showed decreased metabolism in the frontal cortex and increased metabolism in limbic regions. On the other hand, patients who improved with paroxetine showed essentially the opposite pattern—increases in the prefrontal lobe and decreases in the limbic system (Goldapple K et al. *Arch Gen Psychiatry* 2004;61(1):34–41).

The researchers believed that this data implied that depression is partly a problem with an excessively reactive limbic system, which gets too riled up in response to stress. Most studies have shown that depression correlates with hyperactivity in various limbic components, such as the amygdala, the hippocampus, and the cingulate gyrus. In normal people (according to one theory), the prefrontal cortex dampens down limbic hyperactivity, but in depression it does not do its job properly. Perhaps the frontal cortex has become waylaid into one of several cognitive distortions, such as "catastrophizing," meaning overinterpreting the significance of stressful events. In order to treat this, you have to calm the cortex down and teach it to function more rationally. CBT is the preeminent method for directly achieving this. Therefore, it makes sense, as shown in the Goldapple article, that CBT would lead to lower metabolic activity of the frontal cortex, ie, less ruminating and less catastrophizing. This has been called the "top-down" solution to depression—that is, if you start by fixing your patient's cortex, these changes will gradually work their way down to the limbic system.

On the other hand, it is presumed that SSRIs initially act directly in the serotonin-rich areas of the limbic system, where they calm down the limbic "storm" that correlates with depression. (Thus, paroxetine decreased activity in the limbic system in this study.) Since there is thought to be an inhibitory circuit between the limbic system and the frontal cortex, paroxetine's calming of the limbic system disinhibits the frontal lobe, causing it to "wake up." This is known as the "bottom-up" theory of how antidepressants work.

This all *sort of* makes sense—that is, until you read another study from the same research group published three years later. In this study, responders to CBT were compared with responders to venlafaxine (Effexor). This time, *both* CBT and medication appeared to calm the frontal lobe. The researchers opined that this seemingly inconsistent result was due to the fact that this time they used venlafaxine (which inhibits the reuptake of norepinephrine in addition to serotonin), and that the length of medication treatment was longer (16 weeks vs. six weeks in the paroxetine study) (Kennedy SH et al., 2007 *Am J Psychiatry*;164(5):778–788).

So maybe if you treat with medications long enough, the brain ends up looking like it has undergone CBT? It doesn't sound extremely convincing, but it certainly sounds better in the discussion section than saying that they could not replicate their previous results, which would cast doubt on the validity of the initial findings.

Then, to make matters more complicated, another group of researchers interpreted these finding completely differently. Making a heroic attempt to synthesize a plethora of conflicting neuroimaging findings, they came up with the following idea (DeRubeis RJ et al., *Nature Reviews Neuroscience* 2008;9(10):788–796).

1. Depression is a disease of limbic hyperactivity leading to inefficient frontal lobe functioning. (In plain language, feeling depressed makes it hard to think clearly.)

2. CBT acts by increasing frontal lobe functioning. (While the studies I just described contradict this, the authors cited their own unpublished data in support of this statement.)

3. The fact that some studies show *decreased* frontal lobe activity after CBT treatment means that the lobe has been appropriately "reset" to give it greater reserve capacity to engage the newly learned cognitive skills in case they are needed to combat depression in the future. (This is presumably the reason why CBT is so good at preventing depression recurrence over the long term.)

Is *your* frontal lobe spinning? In another recent review of the literature on neuroimaging and depression, some Stanford researchers acknowledged that "these results…do not cohere to tell as clear a story as we would like" (Gotlib IH et al., *Current Directions in Psychol Sci* 2008;17(2):159–163). Basically, we are witnessing the growing pains of a field of research still in its infancy. As with any new science, there are many pieces of seemingly contradictory data, and there will be many efforts to reconcile the inconsistencies.

One particular brain region deserves further mention here, because it has helped to put deep brain stimulation (DBS) on the map in psychiatry. The subgenual cingulate gyrus, also known as

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Brodmann area 25, or BA 25, is a little nubbin of brain tissue on the lowest part of the frontal lobe. In most functional neuroimaging studies, it is hypermetabolic in depressed patients and calms in response to medication. Its true claim to fame is that it may be a crucial target in the treatment of refractory depression. In 2005, Helen Mayberg and colleagues reported "striking and sustained remission" in four of six patients with refractory depression, all of whom were implanted with electrodes to modulate BA 25 (Mayberg HS et al., *Neuron* 2005;45(5): 651–660).

Paradoxically, when a DBS electrode stimulates tissue next to the hyperactive BA 25, the effect is to calm, or "modulate" it. In the dramatic initial reports, awake patients under local anesthesia in the operating room reported an immediate "lifting of the void" and a resolution of dread when BA 25 was stimulated. So far, a total of 20 patients with refractory depression have received this treatment, with a 60% response rate at six months (Lozano AM et al., *Biol Psychiatry* 2008 64(6):461–467). Placebo-controlled trials are apparently underway.

Obsessive Compulsive Disorder (OCD)

Thankfully, functional neuroimaging studies of OCD have been much more consistent in their results than those of depression. OCD is thought to be associated with hyperactivity of a neural circuit that comprises the orbital frontal cortex, the caudate, the thalamus, and the anterior cingulate cortex—meaning, essentially, that there is way too much communication between an over-worried frontal lobe and an over-active limbic system. In a landmark study (the first ever to use functional neuroimaging in a comparison of medication with therapy), Baxter et al randomly assigned nine OCD patients to fluoxetine (Prozac) and nine patients to behavioral therapy. In the responders (six of nine patients in each group), both treatments led to similar PET scan findings: decreased metabolic activity of the anterior cingulate, the thalamus, and the caudate. Furthermore, the degree of reduced activity in the caudate was correlated with the degree of response (Baxter LR et al., *Arch Gen Psychiatry* 1992;49 (9):681–689). Subsequent studies, while sparse, have been consistent with these findings (Frewen PA et al., *Clin Psychol Rev* 2008;28(2):228– 246).

Social Phobia

Thus far, only one neuroimaging study has compared psychotherapy treatment with medication for social phobia. In this nicely designed study, 18 patients with social phobia were randomly assigned to cognitive behavioral group therapy (CBGT), citalopram (Celexa), or wait list control (six patients to each arm). All patients had pre- and post-treatment PET scans, and they actually had to deliver a speech to six observers while they were in the scanner. Both the CBGT group and the citalopram group responded equally in terms of anxiety scores, whereas the wait list group showed no improvement. PET scans showed that, regardless of treatment, improvement in social anxiety was associated with significant reduction of activity in the amygdala-hippocampal regions—which was a nifty finding, since the amygdala is thought to be the region in which we evaluate the emotional significance of situations, and the hippocampus is our memory center (Furmark T et al., *Arch Gen Psychiatry* 2002;59(5):425−433). Presumably, the successfully treated social phobics were no longer interpreting public speaking as scary, and were no longer retaining memories of panic. Rarely do neuroimaging results fit so neatly with our hypotheses of brain function.

TCPR'S VERDICT: ***We have a long way to go before we understand the neurobiology of psychiatric disorders, but functional neuroimaging is at least making it clear that psychotherapy is as much a "neurological" treatment as a "psychosocial" treatment.***

Some Neurobiological Effects of Psychiatric Treatment: Therapy vs. Medication/Devices

	Treatment	Effect
MAJOR DEPRESSIVE DISORDER	Cognitive behavioral therapy	Decreased activity in frontal cortex and increase in limbic region (Goldapple et al.; Kennedy et al.)
	Paroxetine (Paxil)	Increased activity in frontal cortex and decrease in limbic region (Goldapple et al.)
	Venlafaxine (Effexor)	Decreased activity in frontal lobe and variable in limbic region (Kennedy et al.)
	Deep brain stimulation	Decreased activity in Brodman Area 25 (subgenual cingulate gyrus) (Lozano et al.)
OBSESSIVE COMPULSIVE DISORDER	Fluoxetine (Prozac)	Decreased activity in anterior cingulate, thalamus, and caudate (Baxter et al.)
	Behavioral therapy	Same as above
SOCIAL PHOBIA	Cognitive behavioral group therapy	Decreased activity in amygdala-hippocampal regions (Furmark et al.)
	Citalopram (Celexa)	Same as above

See text for full references

Q&A With the Expert

This Month's Expert

The Neuroscience of Psychotherapy

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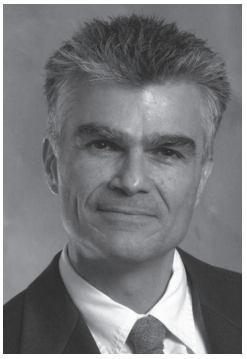
Author, The Neuroscience of Psychotherapy: Healing the Social Brain
2nd Edition, W.W. Norton & Company, Inc., 2010

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



TCPR: Dr. Cozolino, what got you interested in the neuroscience of psychotherapy?

Dr. Cozolino: About 20 years ago, I was very interested in working with adults who suffered trauma as children, especially those from cult situations or with sadistic parents. From there I became interested in memory and how the brain organizes information.

TCPR: How do you actually use your knowledge of neuroscience to help your psychotherapy patients?

Dr. Cozolino: I've found it useful to have a scientifically based, if not totally correct, explanation for what I think is happening in my clients' brains. These explanations are all still at the level of hypotheses, but they allow clients to have nonshaming explanations for what is going on with them.

TCPR: You discuss "enhancing neuroplasticity" in your book. What is neuroplasticity?

Dr. Cozolino: Neuroplasticity refers to the brain's ability to change its functional architecture by creating new neurons (neurogenesis) or making new neural connections. Neuroplasticity is the hub of the integration of psychotherapy and neuroscience.

TCPR: You talk about psychotherapy as "rebuilding the brain." What do you mean by that?

Dr. Cozolino: The brain is an organ of adaptation. The brains of primates, especially humans, have an extended period of post-natal development, unlike the brain of a giraffe, for example. The giraffe is ready to join the herd 10 minutes after birth. A human's immature brain adapts to the early social environment of the family. This is good news if the social environment is functional and adaptive; then the brain that is built in childhood continues to adapt to the environment over time. It is bad news when the family creates traumatic experiences that may not be typical of the environment that we move into later in life.

TCPR: And this inability to adapt causes what kinds of problems?

Dr. Cozolino: A person comes to therapy because life isn't working for some reason. Often, the reason is that the brain adapted to an environment that is not like the life he or she wants. For example, if a person is used to experiencing trauma and doesn't have it, he may recreate it because that is where he feels most comfortable. So we use plasticity in therapy to remodel the brain to get the person to where he wants to be instead of continuing to live in the past.

TCPR: Can you describe a clinical example?

Dr. Cozolino: A typical example from my practice is the young woman in her late 20s or early 30s who can't maintain a relationship. After about three or four months with someone, something goes wrong and she gets out. So we talk about her early life and her history of relationships, and we typically find that she enters relationships with optimism, joy, and attraction, but at some point she realizes the attraction is gone, so she finds a reason to end the relationship. This can go on for 10 or 15 years before she realizes the only thing that's the same in all of these relationships is her, and maybe it's *her* problem and not the boyfriends'.

TCPR: This certainly describes several patients I've seen. What is the neurocircuitry hypothetically underlying this behavior pattern?

Dr. Cozolino: Somewhere early in life there has been the experience of intimacy and dependency that was then lost. A parent may have died, or left the family, or become emotionally unavailable for some reason. In the brain, the amygdala's job is to remember these emotional experiences. We believe that the key circuit for attachment is between the amygdala and the orbital-medial prefrontal cortex. When a child is born, the amygdala is fully developed, but it takes years for that child to learn to build the cortical processes that inhibit and regulate fear. This is why children depend on parents to soothe and regulate them. In the case of our hypothetical patient, the amygdala paired intimacy with the expectation of abandonment, loss, and pain. So her strategy is to "do unto others before they do unto her." She is not aware of the underlying emotional process, but she finds a way to escape relationships.

TCPR: So what do you do in therapy in order to help her?

Dr. Cozolino: In therapy, I work with her to deconstruct that period of time when she shifts from attraction to repulsion. Assuming that she has a good partner and not someone who is abusive, we think together in terms of where she checked out of the present and where the past started to take over.

TCPR: So the theory is that her maladaptive relationship pattern developed because the circuit between her amygdala and prefrontal cortex developed abnormally. But how could a psychotherapist presume that simply through a series of one-hour sessions once a week, which would amount to a very small part of this person's life, she could actually change the way the neurons connect to one another?

Dr. Cozolino: Because, while it's true that our attachment circuitry is developed early on in life, we also know that this circuitry remains plastic. We continue to be able to form very strong attachments even late in life—ask any grandparents how they feel about their grandchildren, and you know that you are never too old to fall in love. In my opinion, the emergence of psychotherapy is related to this process. Psychotherapy didn't just come out of nowhere. It came out of a tradition of priests, rabbis, shamans, and wise men and wise women in the tribe. Our brains are biologically social organs, and we evolved to learn from such caring others. Cortical learning—the type of learning that is flexible and can occur in psychotherapy—depends on the plasticity of frontal neurons, and requires moderate states of anxiety.

TCPR: Effective psychotherapy actually *requires* some degree of anxiety in patients?

Dr. Cozolino: Yes. The basic psychological research on this phenomena is about 100 years old, when researchers gave varying amounts of stress to rats and saw how it affected their abilities to learn how to negotiate a maze to receive food. Over time, they found that at low levels or high levels of arousal or stress, the rats didn't learn; but at *moderate* levels of arousal they did (Yerkes R M & Dodson JD, *J Compar Neurol Psychol* 1908;18:459–482). There is this bell-shaped curve (termed the Yerkes-Dobson curve), that is the sweet spot of learning, which means there is this sweet spot of neuroplasticity, too.

TCPR: And to apply this idea to therapy, we want to somehow get our patients into the sweet spot of stress in order to help them to make progress?

Dr. Cozolino: Right, and a good therapist uses the therapeutic relationship to regulate that level of arousal. Fritz Perls called psychotherapy "a safe emergency." There is this dichotomy that you are stressing or challenging someone, but you are holding them at the same time. We see this process in most schools of therapy. Cognitive behavioral therapy and the use of systematic desensitization is a perfect example. You teach people how to relax; but simultaneously you expose them to the things they are afraid of. You regulate them; you keep monitoring their internal states to make sure that they are not at too high a level of stress.

TCPR: Going back to the woman with the series of failed relationships, what can we do to enhance her neuroplasticity in a beneficial way?

Dr. Cozolino: We can help her understand what is going on in her relationships, so that when she begins to have those flight or fear responses, she becomes consciously aware of that and can make decisions about where the fear is coming from. Is this fear due to the present relationship, or is it due to anachronistic memories? And then, of course, she has to be willing to tolerate the anxiety of staying in the situation even though she wants to run. As therapists, we do this by teaching patients how to relax in challenging situations. My clients often tell me something like: "I am in this situation and I hear your voice saying, 'This is just a memory; this isn't real.'" In other words, in therapy we help our clients develop an internal narrative to re-regulate themselves and get back into that sweet spot of arousal. And if our patient can stay in that situation and allow herself to stay exposed, her amygdala can re-learn and begin to pair the experience of an intimate relationship with survival, as opposed to pairing running away with survival.

TCPR: What's the value of talking about the neuroscience of psychotherapy with this patient? Does she really need to know what's going on with her amygdala?

Dr. Cozolino: For some people just using everyday language is enough. But when people feel like they are crazy or have a character flaw and become ashamed of themselves, I say: "Wait a minute; there is a brain that we all share, and here is how it has evolved in ways that make us vulnerable to all kinds of problems." And so I use this language as an anti-shame device. And it also creates a rationale for intellectualized people to understand why they have to feel things that are uncomfortable in order to make progress in therapy.

TCPR: One of the interesting conclusions from your book is that there really isn't as much of a difference between psychopharmacology—often considered a "biological" approach, and psychotherapy—often considered a "psychosocial" approach. Both presumably cause changes in the brain, and yet they go about it in different ways.

Dr. Cozolino: Right. And in fact, one can go further and make the provocative argument that psychotherapy is actually a biological intervention, and that psychopharmacology is largely a social intervention.

TCPR: How so?

Dr. Cozolino: Because we know from the placebo-controlled antidepressant research that in many cases a large part of the therapeutic response to medication is due to placebo factors, and this depends to a large extent on how well the physician connects with the patient. Which parallels the old Rogerian notion about the importance of warmth, caring, and positive regard in psychotherapy.

TCPR: Thank you, Dr. Cozolino.

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.

SUICIDE

Depression and Suicide Attempts Over Time

Suicide remains impossible to predict, though there have been no shortage of retrospective studies attempting to guide us. Risk factors for suicide attempts include being female (being male confers a greater risk of *completed* suicide), a history of a prior attempt, younger age, having major depression, psychotic symptoms, borderline personality disorder, alcoholism, and chronic physical illness. Since so many of our patients qualify for so many of these risk factors, it is hard to find much use for them clinically.

A recent study has added something new to our knowledge of suicide risk by following a group of depressed patients over a five-year period to see whether the course of depression predicts the incidence of suicide attempts. In a medium-sized Finish city, 269 depressed patients were enrolled and completed interviews and several psychiatric rating scales. Follow-up interviews occurred at six months, 18 months, and five years. All psychiatric records during follow-up were also available to researchers.

During the five-year follow-up period, 14.5% of participants attempted suicide at least once—53% of participants who attempted suicide did so more than once. Seventy-three % of attempts occurred during a major depressive episode, 19% during partial remission (one to four depressive symptoms present), and 8% during full remission.

The authors also found that the risk of suicide attempts increased by a factor of 21 during depressed episodes and a factor of four during partial remission, compared to time spent in full remission. While both previous attempts and poor social support also increased risk, the time spent depressed was by far the major risk factor in suicide attempts (Holma KM et al., *Am J Psychiatry* 2010; 167(7):801–808).

TCPR's Take: Depressive symptoms were tracked retrospectively, so it is possible that some patients may have incorrectly assumed they were depressed when they made a suicide attempt many months previously. Treatment received was not systematically tracked, so the degree to which various interventions may affect suicide attempts remains unclear. However, the study suggests that achieving at least partial remission greatly reduces suicide attempts; helping to improve social support for our patients may be a particularly efficient way to accomplish this goal, given that social isolation was an independent risk factor.

BIPOLAR DEPRESSION

Fluoxetine May Prevent Relapse After Bipolar II Depressive Episode

The debate over whether patients with bipolar disorder benefit from antidepressants rages on. Another double-blind, placebo-controlled study has recently been added to the mix, this one examining whether fluoxetine (Prozac) monotherapy after a bipolar II depressive episode was superior to lithium monotherapy or placebo in preventing a depressive relapse.

Researchers treated 148 patients aged 18 and older who were currently in a bipolar II depressive episode with Prozac (20 to 80 mg/day) for 12 weeks. Dosage was determined based on response. At the end of this phase, those who had a Hamilton Depression Rating Scale (HAM-D) score of ≤8 (which indicated recovery from the depressive episode) were randomized to one of three conditions for the next 50 weeks. These included 1) Prozac, 10 to 40 mg/day (n=28), 2) lithium, 300 to 1,200 mg/day (to a serum level of 0.5 to 1.5 mmol/liter) (n=26), or 3) placebo (n=27).

The primary outcome measure in this study was time to relapse or recurrence of a major depressive episode. In the Prozac group, the average time to relapse was 250 days. This is significantly longer than the time to relapse for lithium monotherapy (156 days) and the placebo group (187 days).

Researchers also assessed hypomania among all treatment groups. Ten patients in the study had hypomanic episodes: three in the Prozac group, two in the lithium group, and five in the placebo group. The difference in incidence of hypomanic switching among groups was not statistically significant (Amsterdam JD et al., *Am J Psychiatry* 2010;167(7):792–800).

TCPR's Take: This study scores a point for the antidepressant team in the bipolar debate. Patients on Prozac monotherapy not only went longer without a depressive relapse, they also had no greater risk of a hypomanic switch than those on lithium or placebo. One caveat may be that only 54.7% of patients in the original group responded well enough to the 12-week course of Prozac to enter the randomized phase of the trial. This could lead to questions about the severity of illness among this group, and therefore, how representative they are of most patients with bipolar II disorder.

BIPOLAR DEPRESSION

Depakote for Acute Bipolar Depression? Maybe

Treatments for acute bipolar depression are clearly less than ideal. Antidepressants have often shown little benefit for this indication. Quetiapine (Seroquel) has demonstrated efficacy, though its utility for depression in bipolar II is less impressive and its side effect profile is also concerning. Despite often being recommended, lithium has questionable efficacy in acute bipolar depression (Grandjean EM et al., *CNS Drugs*

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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 August 31, 2011.

As a subscriber to *TCPR,* you already have a username and password to log on 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. In the Goldapple study that compared brain changes from psychotherapy (CBT) vs. paroxetine (Paxil), which of the following was found to be true (Learning Objective #1)?
   [ ] a. Patients who got better from CBT showed decreases in brain activity in both the frontal cortex & the limbic region.
   [ ] b. Patients who got better from CBT showed increases in brain activity in both the frontal cortex & the limbic region.
   [ ] c. Patients who got better from CBT showed decreases in brain activity in the frontal cortex & increases in the limbic region.
   [ ] d. Patients who got better from CBT showed increases in brain activity in the frontal cortex & decreases in the limbic region.

2. Neuroimaging studies have consistently shown that people with obsessive compulsive disorder have decreased activity in a neural circuit that comprises the orbital frontal cortex, the caudate, the thalamus, and the anterior cingulated cortex (L.O. #1).
   [ ] a. True [ ] b. False

3. Neuroplasticity refers to the brain's ability to change its functional architecture by creating new neurons (neurogenesis) or making new neural connections (L.O. #2).
   [ ] a. True [ ] b. False

4. The Holma et al study of suicide and depression found that what percentage of patients with depression attempted suicide at least once over a five-year period (L.O. #3)?
   [ ] a. 2.1%
   [ ] b. 10%
   [ ] c. 14.5%
   [ ] d. 21.5%

5. In the Amsterdam et al study, the average time to depressive relapse for the Prozac group was which of the following (L.O. #3)?
   [ ] a. 250 days
   [ ] b. 187 days
   [ ] c. 156 days
   [ ] d. 84 days

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

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2009; 23(3):225–240) and some studies have shown that lamotrigine (Lamictal) has little efficacy in the short-term (Geddes JR, *Br J Psychiatry* 2009;194 (1):4–9).

A recent meta-analysis examined whether divalproex (Depakote) works for this difficult-to-treat condition. Despite a thorough literature search, only four trials with a total of 142 patients were found. The studies were six to eight weeks in duration. Across three trials, the response rate on Depakote was 39.3% compared to 17.5% in placebo, a significant difference. In four trials, Depakote significantly outperformed placebo in terms of remission rates (40.6% vs. 24.3%). Seven patients would need to be treated with Depakote to generate one additional response or remission that would not have occurred on placebo. Rates of discontinuation due to side effects were not significantly different (4.3% for Depakote and 2.8% for placebo).

TCPR's Take: The data are quite limited, but they suggest that Depakote may be modestly effective for bipolar depression.

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