EDITORIAL

Augmenting Obsessive-Compulsive Disorder Treatment
From Brain to Mind

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The article "Cognitive-Behavioral Therapy vs Risperidone for Augmenting Serotonin Reuptake Inhibitors in Obsessive-Compulsive Disorder: A Randomized Clinical Trial" by Simpson et al[1] in this issue reports that exposure/ritual prevention (EX/RP) is without question more effective than risperidone or placebo in augmenting serotonin reuptake inhibitor (SRI) response in an 8-week randomized clinical trial with 100 participants. Simpson et al call for a change in practice, because augmentation for SRI nonresponders with atypical antipsychotics is recommended in the American Psychiatric Association guidelines.[2] This is a well-controlled randomized clinical trial worthy of strong conclusions. Simpson et al have a track record of well-controlled combination studies in obsessive-compulsive disorder (OCD), and the conclusion that EX/RP should be considered first for SRI treatment augmentation is supported by the current data.

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We would like to consider further the implications of these findings and to examine what these data may suggest with regard to mechanism of action of OCD treatment in general. There is no discussion of the mechanisms of action of any of the treatments within the study, neither the monotherapies nor the combined therapies. Simpson et al hypothesized that risperidone and EX/RP would each be equally effective for SRI nonresponders, yet it is difficult to explain no augmentation effects of the risperidone vs placebo based on prior studies. If the prior studies were accurate, then what is unique about the current study that risperidone was not more effective than placebo? Simpson et al note differences between their sample and other studies' samples, including the potentially less refractory nature of the subjects' disease and possible past antipsychotic use; however, there are no clear smoking guns to account for the discrepant findings.

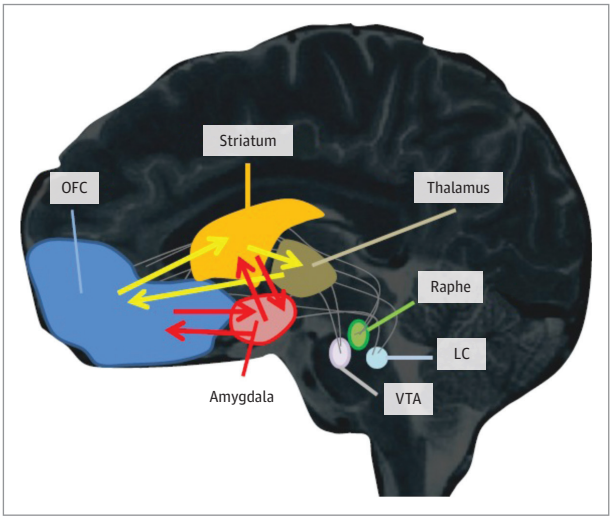
To our knowledge, no study has found that adding medication to EX/RP achieves better outcome than EX/RP alone for OCD.[3] The only exception may be the use of D-cycloserine in addition to EX/RP for OCD.[4,5] This is also true for other anxiety disorders, that, in general, adding other medications, typically SRI antidepressants, to cognitive-behavioral therapy does not seem to afford any benefit over the cognitive-behavioral therapy as a monotherapy, other than with D-cycloserine, which is thought to enhance the *N*-methyl-D-aspartate–dependent emotional learning process.[3] Interestingly, a large randomized clinical trial recently found that risperidone was no more effective than placebo in augmenting SRI nonresponders in posttraumatic stress disorder.[6] Overall, this collection of studies may imply that mechanisms that enhance the process of synaptic plasticity and emotional learning (such as *N*-methyl-D-aspartate–acting agents given only at the time of therapy) may enhance behavioral exposure therapy and possibly other forms of psychotherapy. However, monoaminergic-acting medications, such as SRIs and antipsychotics, may act to primarily dampen symptoms of dysregulated neural circuits but not correct the circuit dysfunction per se. We will examine this idea in more detail later.

The principal brain regions implicated in OCD include the cortical-striatal-thalamic-cortical circuit that regulates motor control caudally and emotional/cognitive control more rostrally (**Figure**).[7] Interestingly, these frontostriatal circuitry connections were recognized more than 20 years ago,[8] although at that time, the primary focus was on the striatum. Increased orbitofrontal cortex activity in OCD had previously been identified with positron emission tomography. These findings have since been augmented with a greater understanding of orbitofrontal cortex function and an increased appreciation that other brain areas that regulate emotion exert control within these pathways, particularly the amygdala. Recent work has replicated these early findings that pathophysiological pathways among orbitofrontal-striatal regions may be common to all forms of OCD.[9]

The efficacy of SRIs for OCD was identified serendipitously initially, in part because of the dearth of effective pharmacotherapeutics for OCD. However, dense serotonergic projections from the dorsal raphe to the orbitofrontal cortex and striatum have led to hypotheses that serotonergic manipulations may have direct effects on the disrupted circuit functioning underlying OCD. The observation that OCD tends to require higher doses of SRIs than depression treatment is consistent with potentially different circuit targets of action. However, as discussed by Simpson et al,[1] and well recognized in the field, SRIs are only effective in treating a subset of patients with OCD. Therapeutic strategies for the many patients who do not benefit from SRI treatment are critical for progress.

Antipsychotic agents were also applied empirically, initially, as with other psychiatric agents, in the attempt to extend available drugs to refractory OCD. However, these agents were never as effective as SRIs and the rationale followed the lines of targeting the "psychosis-like" symptoms of severe obsessions and ruminations. Subsequently, the subset of patients with tic-like OCD appear to have responded to antidopaminergic antipsychotic therapy, as do

Figure. Neural Circuitry Associated With Obsessive-Compulsive Disorder (OCD)



For more than 20 years, cortical-striatal-thalamic-cortical (yellow arrows) dysfunction has been associated with OCD symptoms, with the orbitofrontal cortex (OFC) being most directly implicated. Multiple regions within this behavioral circuit, in particular the striatum and OFC, are heavily innervated and modulated by the amygdala in response to emotional stimuli (red arrows). Functional imaging studies have suggested dysfunction within these pathways and abnormal circuit regulation correlating with OCD symptoms. These cortical and subcortical regions are regulated by the 3 monoamine systems that are targeted by current psychiatric medications, serotonin from the raphe nuclei, dopamine from the ventral tegmental area (VTA) and substantia nigra, and norepinephrine from the locus coeruleus (LC). Selective serotonin reuptake inhibitors and antipsychotics are thought to act primarily by altering serotonin and dopamine synapse functioning, respectively, thus altering monoaminergic regulation as their mechanism of symptom reduction. In contrast, exposure and ritual prevention is thought to directly alter the connectivity in the cortical-striatal-thalamic-cortical–amygdala circuits via emotional learning processes.

patients with tic disorders such as Tourette syndrome. In contrast, it has remained unclear how effective they would be in other forms of OCD. Several differences between the 3 small studies demonstrating efficacy with risperidone augmentation to SRIs and the current one are discussed by Simpson et al.[1] One possibility not examined by Simpson et al is the particular combined serotonergic-dopaminergic pattern of risperidone's activity. Perhaps, in this subset of patients, any benefit to be obtained from modulating this cluster of monoamines was already maximized with the ongoing SRI treatment. Whether that would be the case with a different antipsychotic without as much serotonin receptor 2A potency as risperidone remains to be seen. Further, as in all cases of early findings with small studies, one must be vigilant about possible "file-drawer" effects in the literature masking possible negative unpublished studies.

Perhaps a more fruitful area to examine is the potential shared vs unique mechanisms of EX/RP and any monaminergic therapy. Linden[10] reviewed functional neuroimaging studies in OCD following cognitive-behavioral therapy or selective SRI treatment. They found that studies of successful intervention in OCD were consistent in showing decreased metabolism in the right caudate nucleus of the striatum with both cognitive-behavioral therapy and selective SRIs, suggesting common brain effects of treatment in OCD. Alternatively, it may imply a similar neural signal following decreased symptoms when a successful treatment has occurred, regardless of mechanism.

A critical difference between EX/RP and monoamine medication is the underlying nature of the treatment. Both SRI and antipsychotic treatments are targeting the symptoms of dysregulated circuit functioning (Figure). However, they do not necessarily target the cause of the disrupted circuit function. In contrast, EX/RP is thought to induce plasticity leading to changed functional connectivity. The models vary somewhat. One model holds that EX/RP results in extinction learning when the fear is cued yet the feared consequences do not occur and anxiety decreases in the absence of the compulsive behavior. Alternatively, EX/RP can be thought of as inducing new operant learning processes, essentially retraining the brain's habit-forming circuitry so that the circuit "relearns" not to activate the compulsive ritualized habit when an activating cue occurs. These slightly different models likely represent very similar processes of cortical-subcortical plasticity, leading to interference in the cortical-striatal-thalamic-cortical–amygdala hyperactive circuits that may underlie the stress-driven ritualistic behaviors. The critical point of behavior therapy, then, is that it relies on learning processes and retraining the brain, not only on symptom reduction. Progress in this area in terms of facilitating behavioral therapy with pharmacotherapy would be predicted to come from approaches that enhance emotional learning.[4,5]

There are a few minor remaining limitations with the study. The SRI treatment was not part of the experimental design, and thus, this aspect is less well controlled. All patients had to be at least receiving their second SRI medication, because the American Psychiatric Association guidelines call for switching to another SRI if there is no response to the first. There was considerably more therapist contact in the EX/RP condition compared with the medication-only conditions. Notwithstanding the possible biological mechanisms of action, those receiving EX/RP had considerably more contact and more focused and structured generalization, with daily homework, between-session telephone check-ins, and at least 2 sessions occurring outside of the clinic to promote generalization. Thus, it is also plausible that simply having increased clinical interactions was important therapeutically, not to mention the possible self-selection effects of advertising for a study that used psychotherapy, as pointed out by Simpson et al.

As always, more work remains, but the data presented by Simpson and colleagues are intriguing and thought provoking. They remind us that there are likely unique aspects of brain function that are differentially targeted by medication and psychotherapeutic approaches. As the neurobiology of OCD and other disorders are further dissected, we can hope for progress with targeted combined pharmacotherapy and psychotherapy in which rationally designed therapeutics can be fully derived from our understanding of the brain, its dysfunction, and mechanisms of recovery.

ARTICLE INFORMATION

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When Depression Doesn't Lead With Depression

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A layperson looking for information about depression might turn to the excellent website provided by the National Institutes of Health/National Institute of Mental Health. He or she would read that depression is characterized by low mood (beyond sadness or the blues), combined with "symptoms that interfere with a person's ability to work, sleep, study, eat, and enjoy once-pleasurable activities."[1] This basic (and familiar) information is very useful, but 2 articles[2,3] in this month's issue remind us how limited this description of depression is.

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Judd et al[2] examined 31 years of survey data from a National Institute of Mental Health depression study showing the prominence of anger and irritability in depression. All the patients in the cohort had major depressive episodes. More than half of them presented with overt irritability/anger.

A complementary article by Heller et al[3] suggests a neurobiological basis for the disruptions of emotion regulation that are characteristic of depression. Their study[3] also provides us with a way to think about how these faulty processes may be corrected by antidepressant treatment.

These studies[2,3] highlight what experienced clinicians know: depression frequently does not lead with low mood. Irritability, anger, anhedonia, or disruptive behavior may be equally defining of the illness that we call depression. And the trouble with regulating such emotion may be—at least for some—the primary deficit, more apparent than low mood per se.

Judd et al[2] make the important point that our understanding of the relationship between irritability and depression is hampered by imprecise definitions of terms. The authors defined irritability carefully. Participants must have had clinically significant outward manifestations, such as being argumentative, shouting, or obviously losing their temper. Patients presenting with this degree of irritability had a long, severe course of illness. They had more than their share of comorbid substance abuse and anxiety. Their functioning was more impaired, and their quality of life was lower relative to those without significant irritability/anger.

Judd et al[2] suggest the possibility that this group of patients constitutes an important subtype of depression. Somewhat paradoxically, irritability was poorly correlated with criterion symptoms for depression. Because the participants in this study, by definition, did meet criteria for a major depressive episode, Judd et al[2] cannot shed light on angry or irritable individuals who do not meet depression criteria. It is possible that many of those, while deserving treatment for depression, never make it to the doctor's office. Instead, they are viewed merely as men and women behaving badly.

There is practical advice that flows from the study by Judd et al.[2] The authors urge clinicians to identify overt irritability or anger when it is possible to do so. When the symptom reaches the level of clinical significance defined in their study, a difficult course of illness may lie ahead. They recommend making anger a direct focus of treatment.

Emotional dysregulation, the subject studied by Heller et al,[3] subsumes any negative affect, not just irritability. One could