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 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. 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.

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. The only exception may be the use of d-cycloserine in addition to EX/RP for OCD. 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. Interestingly, a large randomized clinical trial recently found that risperidone was no more effective than placebo in augmenting SRI nonresponders in posttraumatic stress disorder. 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). Interestingly, these frontostriatal circuitry connections were recognized more than 20 years ago, 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.

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, 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
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all cases of early findings with small studies, one must be

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 aug-

mentation to SRIs and the current one are discussed by

Simpson et al. One possibility not examined by Simpson et

al is the particular combined serotonergic-dopaminergic pat-

tern 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 monamin-

ergic therapy. Linden reviewed functional neuroimaging

studies in OCD following cognitive-behavioral therapy or

selective SRI treatment. They found that studies of success-

ful intervention in OCD were consistent in showing

decreased metabolism in the right caudate nucleus of the

striatum with both cognitive-behavioral therapy and selec-

tive SRIs, suggesting common brain effects of treatment in

OCD. Alternatively, it may imply a similar neural signal fol-

owing 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 symp-

toms of dysregulated circuit functioning (Figure). However,

they do not necessarily target the cause of the disrupted cir-

cuit function. In contrast, EX/RP is thought to induce plastic-

ity leading to changed functional connectivity. The mod-

els vary somewhat. One model holds that EX/RP results in

extinction learning when the fear is cued yet the feared con-

sequences 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 pro-

cesses, essentially retraining the brain’s habit-forming cir-

cuitry so that the circuit “relearns” not to activate the com-

pulsive ritualized habit when an activating cue occurs. These

slightly different models likely represent very similar pro-

cesses of cortical-subcortical plasticity, leading to interfer-

eonce in the cortical-striatal-thalamic-cortical-amygdala

hyperactive circuits that may underlie the stress-driven ritu-

alistic 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 pharmaco-

therapy would be predicted to come from approaches that

enhance emotional learning.5-7

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 medica-
tion, because the American Psychiatric Association guide-

lines 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 mecha-
nisms of action, those receiving EX/RP had considerably

more contact and more focused and structured generaliza-

tion, 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 impor-
tant therapeutically, not to mention the possible self-

selection effects of advertising for a study that used psycho-

therapy, as pointed out by Simpson et al.

As always, more work remains, but the data presented by

Simpson and colleagues are intriguing and thought provok-

ing. They remind us that there are likely unique aspects of brain

function that are differentially targeted by medication and psy-

chotherapeutic approaches. As the neurobiology of OCD and

other disorders are further dissected, we can hope for prog-

ress with targeted combined pharmacotherapy and psycho-

therapy in which rationally designed therapeutics can be fully

derived from our understanding of the brain, its dysfunction,

and mechanisms of recovery.
When Depression Doesn’t Lead With Depression

Michael Craig Miller, MD

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.” This basic (and familiar) information is very useful, but 2 articles in this month’s issue remind us how limited this description of depression is.

Judd et al1 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 al2 suggests a neurobiological basis for the disruptions of emotion regulation that are characteristic of depression. Their study2 also provides us with a way to think about how these faulty processes may be corrected by antidepressant treatment. These studies1-3 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 al2 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 al2 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 al2 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...