High-Dose Olanzapine Versus Clozapine

Sir: The article by Meltzer and colleagues[1] suggesting that high-dose olanzapine may be equivalent to clozapine in treatment-resistant schizophrenics warrants some discussion.

The authors' power analysis suggested that 17 patients per group would be sufficient to provide 80% power. However, the power analysis (as is often the case) did not consider dropouts, and this was a particular concern in this study since 6 of 21 patients receiving clozapine dropped out prior to 6 weeks. Early dropouts, prior to the time at which a drug is expected to be effective, reduce power beyond simply reducing the N; since dropouts must generally be included in analyses (i.e., last observation carried forward), and since early dropouts generally do not respond to treatment, they will reduce the mean change. The authors estimated that clozapine would decrease the Brief Psychiatric Rating Scale score by 15 points, but if a third of patients drop out before the medication can be effective, the mean change will be reduced by a third, to only 10 points, even if the remaining patients improve as expected. The authors predicted that patients treated with olanzapine would improve only 5 points, and that the standard deviation would be 10. Thus, the difference between clozapine and olanzapine would be only one half of a standard deviation (5 points) if a third of the patients treated with clozapine drop out early, rather than the full standard deviation (10 points) that the authors used in their power analysis. This change would result in a power of only about 0.35 (rather than 0.80), which means that it is more likely than not that a significant difference between clozapine and olanzapine would *not* be identified in a study this small (an N of 68 would achieve 80% power). More precise calculations, i.e., considering that 6 of 21 is only 28.6% and that 2 patients receiving olanzapine also dropped out early, still yield a power less than 0.50, and power would be reduced further because early dropouts would likely increase the standard deviation.

As Cohen indicates, "If his [an investigator's] power is feeble, he can abandon the research as planned or forearm his ego against the negative results which will probably eventuate and at least warn the scientific community (if he succeeds in getting his results published) that these negative results must be at least partially discounted."[2(p97)]

There was some evidence of clozapine superiority after 6 months (on the Global Assessment of Functioning and the Positive and Negative Syndrome Scale total score). But if clozapine is better than high-dose olanzapine, this study had less than a 50% chance of identifying the difference.

Cohen discusses the rationale for varying p values and power; he states that "generally the consequences of false positive claims are more serious than those of false negative results."[2(p98)] But in this study, funded by Eli Lilly, the "positive" result was no difference; thus, the power should probably have been set even higher than 0.80, to ensure that the study did not erroneously conclude that olanzapine at high dosage is equivalent to clozapine.

Dr. Mattes is currently conducting a depression study funded by Novartis (at one of many research sites).

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Drs. Meltzer and Jayathilake Reply

Sir: Dr. Jeffrey Mattes's criticism of the power analysis in our study is, in part, well taken, if we did not make it sufficiently clear that dropouts were considered in our original power analysis.

We had calculated that it was necessary to recruit 40 subjects per treatment arm in order to achieve 80% power with an expected 25% dropout rate. However, we were unable to recruit more than 21 and 19 patients in the clozapine and olanzapine arms, respectively. Nevertheless, we were able to obtain sufficient data to draw the conclusion we did about the relative efficacy of high-dose olanzapine and clozapine in treatment-resistant schizophrenia, a conclusion we still stand by. The effect of the dropouts was minimized, appropriately in our view, by using a mixed-model repeated-measures analysis of variance (MMRM) rather than last observation carried forward (LOCF), which, as Dr. Mattes points out, would unduly weigh the influence of early dropouts. If the dropouts are independent of response (situation 1), LOCF is a valid approach. However, if the dropouts are dependent only on observations (situation 2), then the MMRM approach is more appropriate, and LOCF is invalid. As suggested by Peter Lane[1] at Research Statistics Unit, GlaxoSmithKline, the MMRM approach is almost always superior to LOCF for either situation listed above.

Recently, 2 studies[2,3] have appeared that provide additional support for the conclusion of our study that high doses of atypical antipsychotic drugs are effective in treatment-resistant patients who fail to respond at conventional doses and that full benefit may take more than 6 weeks to develop. Nevertheless, we reiterate our comments that our results are in need of replication by much larger studies, preferably ones with multiple fixed doses of atypical and typical antipsychotic drugs. The data we have provided will enable these studies to be appropriately powered.

Obtaining precise information about the optimal treatment of patients who fail to respond to antipsychotic drugs within the low end of the dose range that is appropriate for most patients with schizophrenia is a hugely important problem. The value to society of the trials we propose would be tremendous, since inadequate treatment of these patients is an enormous financial burden to the mental health system and devastating to the patients and their families.

The study discussed in this letter was supported in part by an investigator-initiated grant from Eli Lilly, the William K. Warren Foundation, and the Ritter Foundation. Financial disclosure for Drs. Meltzer and Jayathilake appears with the original article [J Clin Psychiatry 2008;69:274–285].

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Depression in Physicians: Hyperfunctioning Depression or Professional Depression?

Sir: In their recent article, Schwenk et al.[1] bring a very important and sensitive issue to light. The authors show a high rate (11.3%) of moderate to severe depression among physicians. However, in the context of the article, they find an even more interesting, yet puzzling issue: the fact that 52.2% of physicians with moderate to severe depression reported that "working hard helps to lessen my depression." An almost equal percentage of the same group reported that "depression has decreased work productivity." Moreover, only 25.2% of those with mild depression reported that working hard helps. So, it appears that physicians with moderate to severe depression are twice as likely to find that working hard helps their depression as compared to physicians with mild depression.

The above finding defies commonly held clinical belief and the available literature,[2–4] as well as DSM-IV criteria in that functional impairment or deterioration is part of the criteria for and clinical assessment of depression. This, however, does not mean that Schwenk and colleagues' finding is incorrect.

According to anecdotes and occasional clinical observations, executives and other professionals may find that escaping in work (or as Schwenk et al. described it, "burying themselves" in work) helps their depression. Furthermore, if (as we believe) these physicians were moderately or severely depressed (with self-diagnosis in this case being as good as it gets), then perhaps there is a subtype of depression in which there is no functional impairment. Whether this subtype is unique to physicians or professionals is an interesting question.

Perhaps Einstein, possibly the most famous professional in the 20th century, was correct to advise his son Eduard, when he started slipping into depression while in medical school, "Life is like riding a bicycle. To keep your balance you must keep moving."[5(p367)]

In summary, this leads us to consider a few important questions: Does functional impairment have to be part of the criteria for diagnosing depression? Do depression with and without impairment represent different subtypes of depression? Are depressed patients without functional impairment a subpopulation that differs from others?

We all know the complexity of diagnosing depression and that there are different subtypes that may be related to different neurotransmitter imbalances. It is well established that depression can present with overeating or undereating, insomnia or hypersomnia, psychomotor retardation or agitation. If it also turns out to be true that there are "hypofunctioning" and "hyperfunctioning" subtypes/symptoms of depression, then the hyperfunctioning subtype has been and could be more prone to be overlooked. The possible existence of these subtypes raises interesting points for future clinical research as well as basic science research for possible correlation to certain neurotransmitters.

Ironically, the question becomes, Would the phenomenon of being a "workaholic" need to be treated as depression or as an addiction?

Dr. Youssef has received honoraria for presentations and is on the speakers panels of AstraZeneca, Bristol-Myers Squibb, and Pfizer and has received research support from Avanir.

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Drs. Schwenk and Leja Reply

Sir: We appreciate the perceptive comments of Dr. Youssef and agree that depressed physicians may have a unique approach to their work when they become depressed. Physicians may use work as a way to cope with their feelings of inadequacy by working harder and longer and becoming even more dedicated and meticulous in their care. However, it is not clear that this type of depression should be labeled as "hyperfunctioning." While these physicians may be working harder, they are almost certainly not experiencing the usual level of work satisfaction.

Depressed physicians may also not be working very productively and may have to work harder or longer just to maintain their usual responsibilities. For example, in our study, nearly 60% of physicians with moderate to severe depression reported that "depression has decreased work productivity," and over 90% reported that "depression has decreased work satisfaction."

Depressed physicians may or may not be impaired, and a determination of impairment would be appropriate, as it would for any medical illness. However, depressed physicians may try to "cure" their depression by working harder, although not necessarily more effectively, which may contribute even further to their sense of inadequacy. These physicians may become more careful and meticulous in their patient care (resulting in decreased work productivity), although they are not necessarily making more mistakes. Patients may actually appreciate the extra attention they receive, and physicians may receive positive feedback for their behavior. However, as we know, depressed patients often have trouble receiving such positive feedback. It certainly does not relieve their depression.

So, we agree with Dr. Youssef that the critical issue here is not the presence or absence of depression but the nature and degree of impairment, just as would be true with any illness or injury. The problem with the stigma of depression in physicians appears to be that diagnosis is equated with impairment. We believe that future work should focus on understanding and

measuring the nature of impairment more accurately. As long as physicians who reveal being depressed are addressed under an "impaired physician policy," as is often the current situation, it is not surprising that physicians are unwilling to admit they are depressed.

The authors report no financial or other relationship relevant to the subject of this letter.

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ECT Not Proven for Atypical Depression

Sir: Data might speak for themselves, but the interpretation of Husain and colleagues[1] that electroconvulsive therapy (ECT) treats atypical depression is not justified. Here is a restatement of the conclusions that is more consistent with the methods and measurements:

> Patients with atypical depression subjectively felt better in the hospital 24 to 48 hours after completing a course of bitemporal ECT. It was unknown how the patients felt after returning home to the environment in which they had felt the problematic reactive distress and rejection sensitivity that led to hospitalization. In atypical depression, no specific psychopathology is observable by clinicians, unlike most disorders treated by ECT.

Individuals with atypical depression typically have comorbid anxiety disorders and personality disorders.[2,3] Because anxiety disorders were not evaluated or treated, their effects on the results are not known. The phenomena noted as "psychotic" in these patients might have been dissociative symptoms of an undiagnosed anxiety disorder, i.e., pseudopsychotic.[4]

The temporary amnestic side effects of bitemporal ECT are expected to mitigate atypical depression and anxiety disorders. They are expected to interrupt the psychological symptoms of dissatisfaction, worrying, obsessions, and recurrent unpleasant memories. The calming somatic effects of ECT are expected to diminish somatic tension, including agitation, edginess, and neediness to ventilate. These effects are expected to decrease the rated severity of atypical depression. However, these effects are nonspecific and generally do not persist beyond a month and so should not be counted as therapeutic.

The study as reported was open and uncontrolled. The comparison with other depression does not replace the necessity for placebo control in studying treatment of atypical depression, in view of its responses to placebo and psychological therapy.[5] Here, the placebo should have been sham ECT. In this study, placebo improvement would be expected to follow both removal from a stressful environment and the suggestive power of receiving a treatment (ECT) well known as beneficial for depression that is "no fault" of the patient.

The Hamilton Rating Scale for Depression (HAM-D) employed was designed for melancholia, not atypical depression; these are mutually exclusive conditions. The decreased HAM-D score suggests that patients felt better but does not specifically reflect on the severity of atypical depression. Because atypical depression represents a new and different application for ECT, study of the stability of therapeutic response for several weeks to months after discharge is needed before ECT can be recommended for treating it. Thus, the authors' recommendation of ECT for atypical depression is premature.

Dr. Swartz is director of Somatics, LLC.

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Dr. McClintock and Colleagues Reply

Sir: We appreciate the comments made by Dr. Swartz on our recent report of electroconvulsive therapy (ECT) in the treatment of atypical depression.[1] We agree that our study was limited due to the lack of a placebo control group and to the use of the 24-item Hamilton Rating Scale for Depression (HAM-D-24).[2] Without a placebo control, we cannot be certain that ECT was beneficial in treating severely depressed patients with atypical features in the acute phase (i.e., spontaneous improvement could have occurred). In view of the importance of long-term outcome, we are currently analyzing data collected from patients who met criteria for remission and were randomly assigned to receive continuation ECT or pharmacotherapy over a 6-month period.[3]

While the HAM-D-24 is not the ideal measure of atypical depressive symptom features as it lacks atypical symptom items, the shorter 21-item HAM-D was previously found to have change results similar to both clinician-report and self-report versions of the 30-item Inventory of Depressive Symptomatology (IDS-C-30, IDS-SR-30),[4] severity measures that do include atypical depressive items.[5] We enhanced the administration of the HAM-D-24 by utilizing 2 independent, certified clinical raters or psychiatrists in all clinical ratings (baseline and end of treatment). All diagnoses were based on research diagnostic criteria with the Structured Clinical Interview for the DSM-IV (SCID-I).[6]

We agree that anxiety and rejection sensitivity are important variables to examine in future studies. While a placebo-controlled trial is ideal for evaluating the efficacy of ECT in these patients, feasibility may be limiting. One solution might be to compare ECT with a monoamine oxidase inhibitor

(MAOI) given the demonstrated efficacy of MAOIs as compared to placebo.[7]

After a hiatus of more than 40 years, this study addressed the usefulness of ECT for severely depressed patients with atypical features.[8] The paucity of published information in regard to treatment regimens for atypical depression has left clinicians with few evidence-based interventions for such patients. Overall, we conclude that the acute use of ECT for treating severe depression with atypical features may be beneficial for inpatient populations, particularly if they have failed multiple medication treatment trials.[9] Future studies are warranted regarding this treatment modality in both the acute and continuation therapeutic phases.

Financial disclosures accompany the original article discussed in this letter.

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