See article by Zhou et al

Antidepressant Augmentation: Good News, Limitations, and Stumbling Blocks

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Dr Zhou and colleagues[1] have done an excellent job of reviewing and analyzing the world's literature on the efficacy and tolerability of pharmacologic agents used to augment antidepressants in treatment-resistant unipolar major depression. It seems we have some good news, but a lot remains to be accomplished. The good news is that several agents were found to have significant efficacy in terms of response (4 agents) and remission (6 agents) in comparison to placebo. Noteworthy among the failures having at least 1 adequately powered trial were buspirone, bupropion, and methylphenidate. Not surprisingly, several active agents were also found to be less well tolerated in terms of side effects. The analysis is restricted to pharmacologic approaches and does not deal with psychotherapy or neuromodulation options for augmentation. Unfortunately, there are many limitations to this work and many stumbling blocks in the potential translation of the results to clinical practice.

Important factors that may influence the outcome of antidepressant augmentation include whether the previous antidepressant trial yielded nonresponse versus partial response and the number and type of previous antidepressant trials failed. Expert consensus guidelines developed in the 1990s, such as the Texas Medication Algorithm Project,[2] recommended augmentation with a second agent for partial responders and switching to a new antidepressant for nonresponders. Importantly, these recommendations were based on expert consensus and not on empirical evidence. Subsequently, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[3,4] provided some indirect empirical support for these recommendations. Nonremitters to citalopram in phase I of STAR*D were more likely to choose a switch of medication if they were either intolerant or less responsive, whereas those who had some improvement in phase I were more likely to choose to be randomized to augmentation. Unfortunately, these decisions were based on equipoise randomization (patient choice) and were not blinded or randomized, so they did not provide a true prospective test of the validity of the recommendations. Nonetheless, studies containing large proportions of nonresponders versus partial responders or nonresponders to multiple drug trials could be expected to lead to worse results for the augmentation strategy under study, an important methodological consideration.

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Strikingly, it is unclear to me whether any of the 45 studies included in the efficacy analysis of the current article focused on partial responders to an initial agent, which, according to expert consensus, should be the target population for augmentation studies. Using the criteria developed by Thase and Rush[5] for staging treatment resistance in the 48 eligible trials of participants with treatment-resistant depression (TRD), Zhou and colleagues[1] found 35 trials with TRD patients of stage I or greater, 12 trials of stage II or greater, and 1 trial of stage III or greater. No mention is made of response rates or odds ratios based on the TRD staging. As stated by the authors, "further research is needed on homogeneous samples of patients within the same TRD stage."[1(p)]

The Problem of Differential Moderators of Response

Now we come to the big important question for clinicians treating depressed patients. Are there any guidelines, either expert or empirically based, to guide clinicians about which agent to choose for augmentation in a given case? The results reported by Zhou et al[1] found least 4 agents based on response rates and 6 agents based on remission rates that had better results than placebo, but they had a lack of data to study potential moderators of response. I absolutely agree with the potential moderators they have identified in the discussion as important—bipolar spectrum disorder, family history of bipolar disorder, rejection sensitivity, nonpsychotic paranoia, and thyroid hormone level in the low-normal range. The Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition,[6] identified other potential moderators, such as anxiety (buspirone) or fatigue and hypersomnolence (modafinil).

To mount a prospective clinical trial to study the value of these and other potential moderators would present a number of enormous challenges. The first challenge would be sufficient sample sizes. The statistical approach to studying moderators involves looking at the significance of the interaction term between the moderator and a given outcome across the randomized treatment groups being compared. In order to do this efficiently, there should be a relatively equal number of matched and mismatched patients either having or not having the putative predictor in each treatment group. For example, if you hypothesize that family history of bipolar disorder predicts response to lithium augmentation, you would need an ample number of subjects with and without the family history in the lithium, comparator, and placebo groups. Typically, sample sizes required to adequately power studies of interactions are much larger than sample sizes required to study main effects. And as stated by Zhou et al, "small sample sizes in

[randomized controlled trials] impede the development of clear conclusions."[1(p?)]

So that leads to the second major challenge: money. To study multiple clinical and potential biological moderators of response to multiple promising agents in patients with TRD will require large numbers of subjects, will require multiple clinical research sites, and will be expensive. Probably the only potential sources of sufficient funding for such an effort would be the NIMH, the pharmaceutical industry, or both. The STAR*D, the only federally funded study that has come close to this topic so far, was a missed opportunity to prospectively study the value of moderators because of the use equipoise rather than true randomization. Individual pharmaceutical companies have done a good job of development of newer atypical antipsychotic agents for the US Food and Drug Administration approval as augmenters of antidepressants, but they have not studied moderators. For example, it is tempting to speculate that high rejection sensitivity and nonpsychotic paranoia would predict good response to atypical antipsychotic augmentation. This is in accord with my own clinical experience, but this has not been shown in a randomized, prospective study design. Ultimately, I would encourage national networks such as the National Network of Depression Centers, pharmaceutical industry partnerships, and federal/industry partnerships to spearhead and invest in the development of more effective and personalized treatment for TRD.

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