QUESTION-AND-ANSWER SESSION

Q: It was noted that the pooled analyses of the aripiprazole data sets[1] showed minimal or no advantage for drug versus placebo in partially-remitted patients. However, was there not a clinically meaningful advantage among patients who did not benefit from the prospective course of antidepressant?

Dr. Nelson: Yes, that is correct. In the pooled data, ~700 patients were minimal responders (<25% improvement) and ~300 patients were partial responders (25% to 50% change). In patients with minimal improvement, aripiprazole was clearly more effective than placebo and the magnitude of the effect was larger (eg, NNT in minimal responders was 6, versus 12 in partial responders). These results are counterintuitive. Clinical lore has held that we use adjunctive treatments for partial responders, in part to maintain whatever improvement has occurred. However, the question of whether the adjunctive agent was truly not effective in minimal responders has not been addressed. The finding of a larger effect in minimal responders was somewhat of a surprise. In partial responders, aripiprazole was more effective than placebo at most time points except the endpoint. Certainly, aripiprazole appeared to speed up response in this group. These results suggested that patients with partial response to initial treatment continue to show improvement on the original antidepressant and placebo and 31% remitted with an additional 6 weeks of treatment. Alternatively, those with minimal response after 8 weeks of antidepressant treatment did not have much further improvement. Only 12% of those patients remitted with another 6 weeks of antidepressant and placebo.

Q: Should adjunctive treatments be continued with the antidepressant for a full continuation period, or can they be used to jumpstart response and then be withdrawn?

Dr. Thase: Clearly, at this point there are not enough data across multiple agents to determine that. From a clinical viewpoint, it appears that this is one of the central unanswered questions in the adjunctive literature.

Dr. Nelson: If a patient has had minimal response to an antidepressant and then responds to the combination with asecond-generation antipsychotic (SGA), which drug should you stop? If a person has had no response to the initial selective serotonin reuptake inhibitor (SSRI), a strong argument could be made to continue the drug that seemed to make the difference. Another important observation is the rapid effect seen with the addition of an SGA. This was demonstrated in the first controlled olanzapine study.[2]

Dr. Thase: Every study that had olanzapine added to fluoxetine showed a rapidity effect.[3] However, there was not always a statistically significant advantage after 6 or 8 weeks of treatment. If you now look across the studies that have been done with the four different SGAs, including risperidone (which is not approved), there is fairly clear evidence of an acceleration of benefit. Less consistently, albeit the majority of the evidence, you will see sustained benefit across 6 or 8 weeks of treatment. Although it is good that the value of these strategies have been tested and demonstrated for difficult-to-treat patients, there is an important, and almost urgent, need to sort out the question of how long to continue an SGA that works as an adjunctive therapy. Is 12 weeks enough, 16 weeks, 6 months? Or perhaps it should even be maintained as long as preventive pharmacotherapies are recommended.

Dr. Gitlin: Clinically, most psychiatrists and patients err on the side of continuing adjunctive treatments longer. When patients are better, everybody involved in treatment decisions tends to become more conservative about not wanting to mess with the success of the treatment. But given potential long-term side-effect liabilities, this is something that should be considered. Obviously if patients are having distressing side effects, withdrawal of the SGA becomes more significant. Longer-term studies of adjunctive treatments are probably the single greatest need for the next generation of studies that would clinically inform all of us.

Dr. Nelson: Whether one is augmenting a partial response or treating a minimal response could prove to be an important distinction in relation to how long to continue the treatment afterward. While the long-term issue is very important, at the same time, I would not dismiss the apparent rapid effects of adjunctive atypical treatment at the 1- and 2-week time points. For severely depressed patients, more rapid effects can reduce suffering, may reduce the risk of suicide, and may allow hospitalized patients to leave the hospital more quickly. While it is unlikely the Food and Drug Administration would ever approve a drug specifically for rapid effects, I think it is an important clinical advantage. But the clinician must be prepared to withdraw the drug at a later point if the only added value is that more rapid effect.

Dr. Thase: That coincides with your remark about acceleration as opposed to adjunctive paradigms. This is really not being paid attention nowadays, even though there are many reasons to focus on this part of our treatment strategies.

Q: Which study would be most critical from a public health relevant standpoint: SGAs versus lithium or SGAs versus bupropion as the leading adjunctive strategy?

Dr. Gitlin: There is already a strong database of SGAs in terms of the number of good, large, double-blind studies. The greatest knowledge gaps are with the use of a second, pure antidepressant (eg, bupropion) to a first antidepressant (an SSRI). There is also a gap in knowledge about stimulants, which are used in my community a great deal despite virtually no database supporting this approach. I think that is where the clinical experience has outstripped the research evidence, so research in these two areas would be helpful.

Dr. Nelson: I think we need a sequel to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, with two steps: an initial trial as in the aripiprazole and olanzapine trials, followed by either an SGA because of the current evidence; lithium because of its evidence-base and its frequent use as augmentation world-wide; triiodothyronine because it was effective in STAR*D, is easy, and has a good risk-benefit ratio; and bupropion or mirtazapine. Lithium may be the only agent that reduces suicidal behaviors long term. We should look at these various options over the long-term, addressing not only efficacy, but tolerability. I think psychiatry should be prepared to conduct studies like the cardiologists do with anti-arrhythmic drugs in 10,000 patients. We may not be able to have 10,000 patients, but 2,000–3,000 is realistic.

Dr. Thase: I agree. There is public health issue concerning depressive disorders that do not rapidly respond to first-line treatments. Further large studies like STAR*D are needed.

References

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https://doi.org/10.1017/S1092852900027942 Published online by Cambridge University Press