is an inducer of cytochrome 1A2 and may lead to attenuation of the efficacy of clozapine unless the dose is increased.

References

1. Rodriguez CI, Corcoran C, Simpson HS: Diagnosis and treatment of a patient with psychotic and obsessive-compulsive symptoms. Am J Psychiatry 2010; 167:755–761
2. Devulapalli KK, Welge JA, Nasrallah HA: Temporal sequence of clinical manifestation in schizophrenia with co-morbid OCD: review and meta-analysis. Psychiatry Res 2008; 161:105–108
3. Chetty M, Murray M: CYP-mediated clozapine interactions: How predictable are they? Curr Drug Metab 2007; 8:307–313

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Antidepressant Use in Bipolar Disorder: Continuing an Age-Old Debate

TO THE EDITOR: In their article published in the July 2010 issue of the *Journal*, Jay D. Amsterdam, M.D., and Justine Shults, Ph.D., (1) add more fuel to the three-decades old debate between those who advocate minimal use of antidepressants in the treatment of bipolar disorder and those who favor maximal usage (2). The authors are to be congratulated for addressing critical methodological parameters in their study: adequate duration (50 weeks) and inclusion of efforts to identify subsyndromal hypomania. Their results are nevertheless surprising. For clinicians and patients, the key question remains whether these results are clinically significant.

Eleven of 28 patients (39.2%) in the fluoxetine group had not relapsed at the end of the study. Even if we extrapolate this proportion to all 83 patients in the second phase of the study, the result is that only 21.6% of the original 148 patients would be deemed well at 50 weeks. This is a relapse rate of 78.4%. From the patient's point of view, these are very poor odds and do not represent a viable treatment option. The best evidence to date is that antidepressants have only a limited role in the treatment of bipolar disorder when long-term stability is seen as the goal of treatment (2).

References

1. Amsterdam JD, Shults J: Efficacy and safety of long-term fluoxetine versus lithium monotherapy of bipolar II disorder: a randomized, double-blind, placebo substitution study. Am J Psychiatry 2010; 167:792–800
2. Eppel AB: Antidepressants in the treatment of bipolar disorder: decoding contradictory evidence and opinion. Harv Rev Psychiatry 2008: 16:205–209

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Response to Eppel Letter

TO THE EDITOR: We appreciate Dr. Eppel's thoughtful comments. Our National Institute of Mental Health study was originally designed to compare the safety and efficacy of long-term fluoxetine versus lithium monotherapy versus placebo in preventing relapse and recurrence of bipolar II major depressive episode. We hypothesized that fluoxetine monotherapy would be superior to lithium monotherapy, with a similar hypomanic mood conversion rate. Survival analysis indicated that the mean time to relapse was 249.9 days with fluoxetine (N=28), 156.4 days with lithium (N=26), and 186.9 days with placebo (N=27). The hazard of relapse was significantly lower with fluoxetine versus lithium, with the estimated hazard for lithium being 2.5 times greater than the estimated hazard for fluoxetine.

Dr. Eppel's use of an absolute proportion of patients who remained well at the end of the study appears to combine initial response in study phase I with failure to relapse in phase II. For example, he suggests that the relapse rate, calculated as the proportion of the 148 patients who entered phase I and completed the entire study, is 78.4%. However, we would suggest that the relapse rate should not be calculated among the 148 patients who entered phase I, since patients were depressed (or in a relapsed state) at the start of phase I. Rather, the comparison of relapse rates and time to relapse between treatment groups should begin after the completion of phase I (i.e., at the start of phase II, when the subgroup of patients who responded to initial fluoxetine monotherapy were randomly assigned to treatment in phase II).

Dr. Eppel also notes that only 21.6% of the original 148 patients would be deemed well after 50 weeks (in phase II). However, only 81 of the original 148 patients in phase I were ultimately randomly assigned into phase II and had at least one additional measurement in phase II. If we had wished to base an estimate of the probability of doing well after 50 weeks of treatment in phase II on the original 148 patient sample, we would have needed to follow all 148 patients until the end of the study, since some of the patients who had not responded by the end of phase I could have responded by the end of phase II.

Although our study was not designed to combine the results of phases I and II, we could estimate the following probabilities based on the combined results of both phases: 1) the probability of responding to fluoxetine monotherapy during phase I *and* failing to relapse in phase II during treatment with fluoxetine; 2) the probability of responding to fluoxetine monotherapy during phase I *and* failing to relapse in phase II during treatment with lithium; and 3) the probability of responding to fluoxetine monotherapy during phase I *and* failing to relapse in phase II during treatment with placebo.

We can estimate each of the aforementioned probabilities using conditional probabilities. For example, the probability of responding to fluoxetine monotherapy during phase I and failing to relapse in phase II during treatment with fluoxetine monotherapy can be calculated as the product of two probabilities:

Pr (response to fluoxetine monotherapy during phase I) × Pr (failure to relapse in phase II during treatment with fluoxetine given that the patient responded to treatment with fluoxetine during phase I), where Pr(A) indicates the probability of A.

Only one treatment, fluoxetine, was administered in phase I, and 83 of 148 patients (56.1%) recovered at the end of this phase (although only 81 patients were randomly assigned in phase II and had at least one measurement postbaseline).

Therefore, we would suggest using 56.1% (N=83/148) as an estimate of the probability of responding to fluoxetine monotherapy in phase I. According to Table 1 (CONSORT diagram), the number of patients who relapsed in phase II was nine with fluoxetine, 15 with lithium, and 14 with placebo. Therefore, the proportion of patients who had not relapsed at the end of phase II was 67.9% (N=19/28) for fluoxetine, 42.3% (N=11/26) for lithium, and 48.1% (N=13/27) for placebo. We note, however, that there were also patients who were lost to follow-up evaluation during phase II. If we conservatively assume that all patients who were lost to follow-up evaluation relapsed, then the percentage of patients who remained well would be computed as the percentage of patients who completed therapy, or 39.3% (N=11/28) for fluoxetine, 19.2% (N=5/26) for lithium, and 25.9% (N=7/27) for placebo.

However, we note that it is likely that at least some patients who were lost to follow-up evaluation did not relapse prior to the end of phase II. In this case, the proportion of patients who remained well would be higher than the prior estimate. Therefore, the proportion of patients remaining well during phase II would be 39.3%–67.9% for fluoxetine, 19.2%–42.3% for lithium, and 25.9%–48.1% for placebo. As a result, we will base our estimates of the conditional probabilities on these ranges.

The probability of responding to fluoxetine in phase I and remaining well at the end of phase II can then be estimated for each treatment condition as follows: 1) between 0.561×0.393=0.220 and 0.561×0.679=0.381 for fluoxetine; 2) between 0.561×0.192=0.108 and 0.561×0.423=0.237 for lithium; and 3) between 0.561×0.259=0.145 and 0.561×0.481=0.270 for placebo.

Therefore, the probability of responding to fluoxetine monotherapy during phase I and remaining well at the end of phase II ranges from 22.0%–38.1% for fluoxetine; 10.8%–23.7% for lithium; and 14.5%–27.0% for placebo. The estimated probabilities are highest for fluoxetine, although the ranges do overlap.

However, we note that the time to relapse was significantly longer during fluoxetine therapy using survival analysis. The benefit of survival analysis is that it does not only consider whether patients relapse or complete the study; rather, it takes the actual time of relapse or dropout from the study into account. This is important because, even if the relapse rates for two treatments are identical, one treatment might be considered superior from a patient's perspective if it significantly delays the time to relapse. As we have already mentioned, our analysis indicated that there was a clinically meaningful benefit incurred by treatment with fluoxetine in terms of delaying the time until relapse because the mean time to relapse was 249.9 days with fluoxetine (N=28), 156.4 days with lithium (N=26), and 186.9 days with placebo (N=27).

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Lithium Carbonate Maintenance Therapy in a Hemodialysis Patient With End-Stage Renal Disease

TO THE EDITOR: Lithium is generally contraindicated in patients with impaired renal function because of its nephrotoxic effects. However, once end-stage renal disease develops, lithium carbonate can be used in conjunction with hemodialysis for the treatment of patients with bipolar affective disorder, as first reported by Procci in 1977 (1). We report a case of successful lithium carbonate maintenance therapy in a hemodialysis patient, complicated by lithium toxicity.

"Mr. B" was a 68-year-old man with a 30-year history of bipolar affective disorder. In 2001, he was admitted to the hospital for acute renal failure following an alcoholic binge and rhabdomyolysis, and he subsequently developed end-stage renal disease. Hemodialysis was initiated in 2004, and the patient remained anuric.

Over the next several years, the patient failed treatment with a series of different mood stabilizing agents. He experienced drug-induced fever with carbamazepine, decreased mental acuity with olanzapine, worsening of a preexisting tremor with valproic acid, and little therapeutic effect with oxcarbazepine and lamotrigine. In 2008, he refused further treatment with valproic acid and was started on lithium carbonate (600 mg), administered orally following 3-hour dialysis sessions three times per week.

Over the following 2 years, the patient's serum lithium concentrations were maintained in the range of 0.6–0.8 mmol/l. He reported a subjective improvement in his tremor, and his manic symptoms (hypersexuality, yelling, decreased sleep, religious delusions) were generally under much better control, with only two episodes of hypomania and one episode of overt mania occurring over the course of 2 years, a great improvement over his prior course.

In April 2010, Mr. B started to exhibit signs of hypomania, and his lithium dose was increased to 900 mg, with a subsequent serum level of 0.84 mmol/l. One month later, he exhibited somnolence and slurred speech, and laboratory testing revealed a lithium concentration level of 1.42 mmol/l. His subsequent postdialysis lithium concentration level was 0.31 mmol/l. The lithium dose was reduced to 600 mg, but the following predialysis lithium concentration level was once again elevated, at 1.41 mmol/l. This was believed to be as a result of reequilibration from the intracellular space following clearance of the drug from the extracellular space during dialysis (2). After two more dialysis sessions, the patient's serum lithium level stabilized at 0.75 mmol/l, and he exhibited improved mental status.

In conclusion, lithium carbonate maintenance therapy was successfully used in the patient presented in this case, but the experience of lithium toxicity underscores the delicate nature of lithium balance in hemodialysis patients, with particular attention to reequilibration between the intra- and extracellular spaces, and perhaps an increased vulnerability to toxicity, even at levels <1.5 mmol/l.

References

1. Procci WR: Mania during maintenance hemodialysis successfully treated with oral lithium carbonate. J Nerv Ment Dis 1977; 164:355–358
2. Friedberg RC, Spyker DA, Herold DA: Massive overdoses with sustained-release lithium carbonate preparations: pharmaco-