Discussion

Mechanisms of Action of Drugs That May Limit Suicide

Dr. Baldessarini: How valuable are comparative pharmacologic studies across drugs that clearly may or may not influence behavior in bipolar illness? Lithium and valproate are probably the 2 best candidates for mood stabilizing action. Would carbamazepine and phenytoin and other compounds be of interest for contrast in such a study?

Dr. Lenox: Basic science researchers are at the mercy of the state of clinical data. When a comparative laboratory study with lithium, valproate, and carbamazepine is done, the research is often based on the assumption that these drugs are equally effective in the treatment of this disorder. There are inherent problems with that assumption based on accumulating clinical data. We may use formulations in pharmacologic investigations whose efficacy may not have been well demonstrated in clinical practice. We have more marginal studies available with carbamazepine than we have with valproate, especially since the manufacturer of valproate pursued an indication for acute mania. We know that carbamazepine does work sometimes, so we need to be cautious. It is important to have a comparative strategy, but the best clinical studies tell us which medications are the best to compare.

Dr. Manji: The comparative pharmacologic study adds some credence to our biochemical marker or measure when we find common targets. When such structurally dissimilar drugs start to affect common structures, the effect hardly seems coincidental. But a lack of common effect should not be discouraging. Some patients respond to some drugs, and others respond to different agents; they do not all work the same way. Still, I think the pharmacological strategy is one of the best ones we have at the moment.

Dr. Baldessarini: Have you done any studies with negative controls, e.g., using drugs such as carbamazepine and phenytoin that may or may not work?

Dr. Manji: My colleagues and I have studied carbamazepine. This drug affects the adenylate cyclate system, but the measures I have indicated show no effects with carbamazepine, D-amphetamine or chlordiazepoxide. We are starting to look at lamotrigine and some of the newer drugs.

Dr. Goodwin: Five direct comparison studies *[Placidi GF, Lenzi A, Lazzerini F, et al. J Clin Psychiatry 1986; 47:490–494; Watkins SE, Callender K, Thomas DR, et al. Br J Psychiatry 1987;150:180–182; Lusznat RM, Murphy DP, Nunn CM. Br J Psychiatry 1988;153:198–204; Bellaire W, Demisch K, Stoll K. Psychopharmacology (Berl) 1988;96(suppl):287; Coxhead N, Silverstone T, Cookson J. Acta Psychiatr Scand 1992;85:114–118]* suggest that carbamazepine is not as effective as lithium. This may be related to the observation that the effectiveness of carbamazepine decreases over time *[Frankenburg FR, Tohen M, Cohen BM, et al. J Clin Psychopharmacol 1988; 8:130–132]*. But today the most important issue facing clinicians is whether valproate is as effective as lithium. There are few solid longitudinal data with valproate. The study by Bowden and colleagues was a 1-year trial that, unfortunately, was unable to separate either lithium or valproate from placebo on the primary outcome measures. There are acute data, though, in the Bowden et al. acute mania study *[Bowden CL, Brugger AM, Swann AC, et al. JAMA 1994;271:918–924]*. In this study, the patients who had responded earlier to lithium responded to divalproex at a rate of only 27%, not much greater than the placebo response rate, whereas patients who had previously failed to respond to lithium had a better response to valproate. This point has been overlooked in much of the discussion of valproate. The promotional literature implies that valproate is now the treatment of first choice for bipolar disorder. This claim is being made on the basis of differential side effects coming out of a prophylactic study in which the lithium blood levels were maintained in a relatively high range. There might be some public health significance in focusing now on the differences, particularly long-term differences, between lithium and valproate. If the Bowden et al. acute mania data are accurate, and antimanic responses predict prophylactic responses, there may be 2 different subtypes of patients here. Valproate and lithium may not be effective in the same patients. It would be useful to obtain some basic science data that might support this hypothesis.

Dr. Manji: I agree entirely. We have tended to focus on common effects, but there are some dissimilar effects. While lithium and valproate in our hands affect a number of the protein kinase C pathways in concert, the mechanism seems to be different. The effects of lithium are inositol dependent; the effects of valproate are not, so valproate appears to affect protein kinase C pathways by a different route. We are using a number of different strategies to identify the therapeutically relevant biochemical pathways affected by these two agents. In addition, we are using yeast genetics to identify genes that appear to confer resistance or sensitivity to lithium's effects, and attempting to identify the human homologues of these genes in patients with bipolar disorder.

Dr. Goodwin: Are there any data that bear on valproate's long-term effects?

Dr. Manji: Much of the valproate work until recently has been in acutely ill patients, and the epilepsy researchers have focused on valproate's acute effects on targets

such as sodium channels and excitatory or inhibitory amino acids. So the chronic effects of valproate on the serotonergic system have not been as well documented.

Dr. Baldessarini: One encouraging aspect of much of this work is that it has a certain heuristic value in terms of trying to predict targets that might be logical for drug development for innovative therapeutics. Another is that the we can pose metabolic predictions that can then be tested. These developments will be exciting to watch over the next few years.