Introduction

Using the Newer Pharmacotherapeutic Agents as Mood Stabilizers in Bipolar Spectrum Disorders

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Bipolar disorder is an episodic psychiatric illness requiring lifelong treatment. As a group of illnesses, bipolar disorder has a prevalence rate of 1.2% to 3.4%[1] in the general population, a rate that is half as much as type 2 diabetes mellitus, and yet it is the sixth most disabling medical condition.[2] For the fortunate patient with a lithium-responsive biology, life reverts to near normal, but for somewhere between one third to two thirds of bipolar subjects, alternatives to or adjunctive treatment with lithium is needed, especially in the maintenance phase.

In the absence of a definitive etiopathogenesis, it is difficult to consider specific treatments for the maintenance phase of this illness. Even if it does not work for everyone, lithium has been suggested as a specific treatment for bipolar disorder. It is only recently that clues to its molecular mechanisms of action have been reported. One set of molecular actions that lithium shares with certain anticonvulsants is modification of voltage-sensitive sodium and calcium channels. In this supplement, H. Steve White, Ph.D., describes how the regulation of these ion channels by anticonvulsants may stabilize neurotransmitter levels of dopamine, serotonin, norepinephrine, and also γ-aminobutyric acid and thus may provide partial answers to why some anticonvulsant agents seem effective for bipolar illness. Dr. White also considers the kindling and sensitization model as a hypothesis for why certain anticonvulsants may be useful in the maintenance treatment of bipolar illness.

Carbamazepine and divalproex sodium have a fairly long history of use in the maintenance treatment of bipolar disorder, even if controlled maintenance treatment data are less than robust. Nonetheless, in this supplement, A. Eden Evins, M.D., describes the use of the newer anticonvulsants—lamotrigine, gabapentin, topiramate, oxcarbazepine ("new" to the United States, but "old" to Europe), zonisamide, and tiagabine—in bipolar disorder and the evidence that does (or does not) support the use of these agents. The efficacy of the new generation of atypical antipsychotics—clozapine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole—for treating the various phases of bipolar disorder—mania, depression, and maintenance—are then described by Robert M. A. Hirschfeld, M.D. These agents, used as monotherapy or as adjunctive therapy with mood stabilizers, have shown efficacy with differential side effect profiles, thus becoming valuable new resources in the treatment of bipolar disorder.

We then move onto the important patient issue of weight gain, especially in the context of adherence with long-term treatment. Louis J. Aronne, M.D., and Karen R. Segal, Ph.D., describe the frightening epidemic of overweight and obesity unfolding in our society and the implications for our patients and for our practice. They describe the data on weight changes with antipsychotic agents, antidepressants, lithium, and anticonvulsants, since these agents are the "bread and butter" of bipolar disorder treatment. Clinicians and patients alike face a

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difficult choice if efficacy with a specific agent and excessive weight gain go hand in hand. All else being equal, at the initiation of treatment, clinicians may have a choice of deciding which among the different classes of agents (whether monotherapy or, as most commonly practiced, in combination treatment) would least likely cause excessive weight gain or, for that matter, in obese patients may actually cause weight loss. In this context, topiramate appears to stand out as an agent that is associated with weight loss. The results of ongoing controlled clinical trials will inform us regarding the efficacy of topiramate for bipolar disorder and various psychiatric conditions.

Anticonvulsant agents, old and new, have been known to be associated with cognitive effects, in the main, psychomotor slowing, reduced attention, and memory problems. Kimford J. Meador, M.D., cautions the reader to be a discerning clinician, especially as data on this issue are complicated by the study design, whether patients with epilepsy or healthy volunteers were evaluated, whether these studies involved monotherapy or combination therapy, and, importantly, the rate of titration and dosage. Curiously, and interestingly, when the effect size of the cognitive effect is estimated, it appears modest, and selective depending on the measures employed. This is not to say individual patients are not exquisitely sensitive, and the clinician reader already knows this fact. I would fully affirm Dr. Meador that we have to use the most efficacious agents for the disease condition and use our knowledge of the individual patients and medicine to minimize side effects so as to ensure adherence with maintenance treatment recommended for people with bipolar illness.

As is evident at the time of this writing, methodologically and rigorously controlled data are unavailable for the newer anticonvulsants (with the exception of lamotrigine, which has positive data mainly for acute bipolar depression and rapid-cycling bipolar II disorder and the prevention of recurrent depressive episodes), and the data for gabapentin, if anything, are negative. Similarly, methodologically and rigorously controlled data are unavailable for the newer atypical antipsychotics (with the exception of olanzapine, which has U.S. Food and Drug Administration approval for the treatment of acute mania, and risperidone and quetiapine, which have recently been found effective in double-blind, placebo-controlled studies in patients with bipolar disorder). Nevertheless, clinicians are using these agents off-label mainly in patients who are treatment resistant, and, as Gary S. Sachs, M.D., points out, at different decision points in a treatment algorithm. The last thing the authors of this supplement would like to do is burden practitioners with yet another "algorithm"! However, on the basis of the strength of available data (or the lack thereof), Dr. Sachs describes what he would do if a patient presented with a manic, mixed, or depressive episode or even in a euthymic state.

REFERENCES

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2. Murray CL, Lopez AD, eds. The Global Burden of Disease. Boston, Mass: Harvard University Press; 1996