Psychopharmacology for the Clinician
Psychopharmacologie pratique

To submit questions for this regular feature, please send them to the editors-in-chief at jpn@cma.ca. Please include details of any relevant case and your name, address, telephone and fax numbers, as well as your email address.

Treatment guidelines for mania

The treatment of bipolar disorder is complex and should involve a multidimensional approach, including psychopharmacology, psychoeducation and psychotherapy. This discussion of the optimal treatment for mania follows the steps that are outlined in the Canadian Network for Mood and Anxiety Treatments guidelines (*Bipolar Disord* 2005;7[Suppl 3]:5-69).

Mrs. S is a 43-year-old married mother of 2 preteen children, who recently lost a high-profile job: "I thought I was very productive and they fired me." At the initial assessment, her husband confirmed a history dating back several years of depressive episodes, as well as "periods of recklessness and surges of creativity." Upon assessment, Mrs. S presented with expansive mood and other manic symptoms. She had been treated with venlafaxine, 225 mg daily, for the past 5 months.

Step 1: Review general principles and assess medication status. Assessment of safety (risk to self and others), physical examination and laboratory investigations (if the patient is cooperative), and a decision about ambulatory or inpatient care are priorities. Screening for substance misuse and strong encouragement to discontinue stimulants, including caffeine, alcohol or other substances, are recommended. In general, antidepressants should be discontinued. In this case, an accelerated tapering of venlafaxine was initiated. The switch rate into mania with venlafaxine appears to be higher than with selective serotonin reuptake inhibitors or bupropion (Vieta et al, *J Clin Psychiatry* 2002;63:508-12; Post et al, *Acta Psychiatr Scand* 2004;110[Suppl 423]:32).

Step 2: Initiate or optimize antimanic therapy. Lithium, divalproex and several atypical antipsychotics (olanzapine, risperidone, quetiapine) are first-line antimanic agents. Because the atypical antipsychotics are commonly administered in the emergency department to manage the acutely agitated state, it may be logical to continue their use as antimanic agents and ultimately as mood stabilizers. Benzodiazepines are useful adjuncts to provide sedation but should not be used alone. Because Mrs. S had received no prior antimanic/mood-stabilizing treatment, treatment with lithium was initiated with clonazepam on an as-needed basis.

For the patient who presents with a break-through manic episode during ongoing treatment with a mood stabilizer, the first step is to check compliance, including serum levels for lithium or anticonvulsant agents. In the noncompliant patient, restoration of adequate dosing is required. If the patient appears to have been compliant, combination treatment is the next logical step. There is most evidence to recommend the use of lithium or divalproex in combination with olanzapine, quetiapine or risperidone.

Step 3: Add on or switch within first-line therapies. Patients should be given at least 2 weeks' treatment at adequate dose/serum levels before adding or switching agents. When a change is required, consider an alternative monotherapy or combination from first-line treatments. Mrs. S was unable to tolerate lithium because of severe nausea and tremors. She was switched to olanzapine, 10 mg daily, and responded favourably. However, after 6 weeks, she had gained 7 kg and discontinued this treatment. A decision was made to switch to divalproex. Mrs. S then experienced break-through manic symptoms during treatment with divalproex. Quetiapine, 100 mg at bedtime, was initiated and increased to 300 mg daily; Mrs. S responded well to the combination of quetiapine and divalproex. Had she not responded to treatment, 2 further treatment steps could have been considered.

Step 4: Add on or switch to second- or third-line therapies. This often includes the use of conventional antipsychotics, clozapine or carbamazepine with a first-line agent. Concern that patients with bipolar disorder have an increased proclivity to experience extrapyramidal symptoms has tended to limit the use of conventional antipsychotic medications such as haloperidol or perphenazine. Although electroconvulsive therapy has also been advocated in the treatment of mania, the evidence is mainly anecdotal.

Step 5: Add on novel or experimental therapies. Other novel (levetiracetam) and established (phenytoin) anticonvulsant drugs show some evidence of antimanic efficacy. There are also preliminary reports of potential antimanic efficacy for tamoxifen, mexiletine, omega-3 fatty acids and calcitonin, but these should only be considered after failure to achieve control with established therapeutic strategies.

Three anticonvulsant mood stabilizers have not been recommended in the treatment of acute mania, but they may be potentially beneficial in combination with established treatments. Although gabapentin and topiramate failed to demonstrate antimanic superiority over placebo, the former may reduce comorbid anxiety and substance abuse, whereas the latter may attenuate the weight gain associated with atypical antipsychotic agents. Although lamotrigine was not as effective as lithium in preventing manic recurrences, it was more effective than lithium as prophylaxis against depression and may be combined with effective antimanic therapies.

Mrs. S's condition has remained stable on the combination of quetiapine and divalproex for more than a year, and she is now managing several business projects.

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The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided.