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Minimizing the Side Effects of Mood Stabilizers

William Coryell, MD

Abstract

How does the clinician best manage side effects associated with mood stabilizers used for bipolar affective disorder? Informed management of side effects can improve a drug's tolerability and therefore increase the likelihood that patients will continue to take the drug most effective for their illness. Placebo-controlled studies have supported the prophylactic use of lithium, carbamazepine, valproate, and lamotrigine for bipolar disorder. This review summarizes the case reports and controlled studies pertinent to the management of side effects for each of these agents.

Introduction

While the importance of pharmacotherapy in the management of bipolar affective disorder has been established, all of the useful agents have also been associated with side effects. Side effects may be endured, they may lead to treatment noncompliance, or they may result in the replacement of a drug that is effective in controlling illness symptoms with an alternative that is possibly less so. Any of these possibilities will diminish the patient's quality of life.

In comparison with efforts to demonstrate the efficacy of mood stabilizers in the acute and prophylactic treatment of bipolar affective disorder, the literature concerning the management of side effects is small, largely anecdotal, and rarely reviewed. The following undertakes such a review, with suggestions relevant to each of the mood stabilizers for which placebo-controlled trials have shown efficacy. The side effects discussed are the ones more commonly described and particular emphasis is given to those for which corrective measures other than drug discontinuation have been proposed.

Lithium

Despite recent shifts in prescribing patterns, the efficacy of lithium in bipolar affective disorder is more thoroughly established than the efficacy of any other medication. Because its use was widespread before the advent of most of the other drugs now being prescribed for bipolar affective disorder, lithium's side effects have been more fully characterized and a number of strategies for managing them have emerged.

Dr. Coryell is professor in the Department of Psychiatry at the University of Iowa College of Medicine in Iowa City.

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Nausea

Nausea may be the first side effect encountered when lithium is introduced, particularly when doses are rapidly increased. Because nausea tends to reflect the rapidity with which plasma levels are increasing,[1] loading procedures will increase its likelihood and this may adversely bias the patient's attitude toward lithium therapy. An obvious solution would therefore be a temporary decrease in dose, followed by a more gradual approach to the targeted plasma level range. Also, nausea often improves when lithium is consistently taken with meals. A slow-release preparation may reduce nausea, but may also increase difficulties with diarrhea.[2]

Tremor

A fine tremor, increased by voluntary movement, is often another early development in lithium therapy. It is often tolerated but may be quite distressing for the patient. If the tremor is seen to peak in intensity within several hours of each dose, a sustained-release preparation may be helpful. Also potentially helpful is a reduction in caffeine intake and the elimination of other drugs, such as tricyclic antidepressants, that may produce or worsen tremor. Because maintenance lithium levels at the lower end of the conventional therapeutic range produce less tremor,[3,4] doses should be titrated against symptom control to determine whether lower doses provide relief.

When a distressing tremor persists despite dosing changes, modest doses of a β-blocker are indicated. According to a number of reports, propranolol 30–80 mg/day is often effective.[5-7] β_1 blockers, such as atenolol and metoprolol, have been used for patients at risk for bronchospasm.[7,8]

Polyuria and Polydipsia

Polydipsia is typically nonprogressive[9] but may substantially interfere with sleep, and may lead to significant weight gain if the patient is relieving thirst with sugared drinks. As with tremor, symptoms are more likely at higher doses, and the problem often subsides when careful titration is used to determine the patient's lowest effective dose.

According to several authors, polyuria is less likely with single daily dosing than with multiple-dose schedules.[10-13] At least one study demonstrated that a shift from multiple dosing to single dosing reduced urinary volume,[14] but another applied random assignment to alternate dosing schedules and found no difference in urine volume.[15]

If changes in dose and timing are unhelpful, the addition of a diuretic may produce a paradoxical reduction in urine volume. Hydrochlorothiazide 50 mg/day has been recommended, but amiloride,[16] in doses titrated to 10 mg BID, is less likely to produce hypokalemia.

Weight Gain

Weight gain attributed to lithium can be an important issue for long-term compliance and may lead a clinician to consider alternative mood stabilizers. The results of randomized, prophylactic studies are pertinent. In the only comparison of lithium, valproate, and placebo, patients taking valproate, but not those taking lithium, experienced significantly more weight gain than those taking placebo.[17] A randomized comparison of lithium and carbamazepine, on the other hand, indicated that carbamazepine resulted in significantly less weight gain.[18] Existing evidence does not support a switch from lithium to valproate to limit weight gain.

As an alternative to switching mood stabilizers, clinicians should consider whether coadministered drugs may be contributing to the problem and whether these are necessary. Atypical antipsychotics are often used adjunctively to hasten symptom control in acute mania and then continued out of concern that monotherapy with lithium may be insufficient for prophylaxis. A gradual discontinuation is warranted to determine whether this is so.

Patients should also be asked whether they are drinking high-calorie beverages to relieve thirst or to counteract the metallic taste often experienced with lithium. A regular exercise program should be encouraged as this may enhance the control of both weight and depressive symptoms.[19]

Cognitive Impairment

Goodwin and Jamison[20] found that the most frequently cited reason for lithium noncompliance was "memory problems." Clinicians often attribute complaints of mental sluggishness to residual depressive symptoms. However, placebo-controlled studies have shown that at conventional therapeutic levels, lithium produces similar complaints in normal individuals[21] and that deficits are measurable objectively as a slowing in cognitive performance.[22]

Lithium treatment is well-known to cause hypothyroidism. This is most commonly reflected in elevated thyroid-stimulating hormone (TSH) levels, but approximately 4% of patients on chronic lithium treatment develop abnormally low T_3 and T_4 levels.[23] It is also well-known that depressive symptoms and complaints of sluggishness are typical concomitants of clinical hypothyroidism. Most clinicians who use lithium screen for hypothyroidism routinely and provide thyroid replacement when thyroxin levels are below normal limits.

However, subclinical hypothyroidism may also be a factor in both persistent depression[24-26] and cognitive impairment.[27,28] A trial of thyroid replacement is therefore warranted when either of these coexist with elevated TSH levels. T_4 is commonly given but converging evidence now suggests that T_3 provides more benefit in this role. Patients given T_3 to augment antidepressant treatment in one study had significantly better outcomes than did those randomized to T_4.[29] In another study, those patients undergoing thyroid replacement with T_4, who were randomized to receive part of their replacement as T_3, reported significantly better mood and energy than did those who continued to receive T_4 alone.[30]

Valproate

As with lithium, many of the side effects associated with valproate are dose-dependent and can be reduced through attention to plasma levels. Bowden and colleagues[31] identified 45 mcg/mL as the minimum therapeutic level. Changes in manic symptoms did not correlate with plasma levels above this threshold, but side effects increased markedly when levels exceeded 125 mcg/mL. This increase reflects dose-dependent protein binding and therefore, conditions that affect protein binding conditions may shift the threshold downward. Thus, older patients, especially those with liver disease, and those taking other drugs that compete for protein binding, may experiencea nonlinear increase in side effects beginning at a lower plasma level.

Sedation

Anticonvulsants that increase

γ-aminobutyric acid, as valproate does, tend to cause more sedation than do anticonvulsants, such as lamotrigine, which operate through the modulation of glutamatergic neurotransmission.[32] While sedation offers an advantage in the acute control of manic symptoms, it becomes problematic during prophylaxis. Because this complaint does not seem to correlate with plasma levels within the therapeutic range, dose decreasing is often not helpful. If sedation is a problem during maintenance, the clinician should consider whether concomitant drugs, such as antipsychotics or benzodiazepines, can be eliminated at this stage.

Gastrointestinal Symptoms and Weight Gain

The most frequent side effects encountered by patients taking valproate are gastrointestinal in nature.[33] Such complaints are less likely with divalproex than with valproic acid.[33] If nausea persists with divalproex, a histamine$_2$ blocker may prove helpful.[34]

Weight gain is at least as likely with valproate as with lithium.[17] If weight gain is a prominent concern for a particular patient, the alternative mood stabilizers carbamazepine[18,35] and lamotrigine[36] should be considered. The continuation of any antipsychotics being given concomitantly should be reconsidered. As noted previously,a regular exercise program can have a number of benefits beyond weight control.

Hyperammonemia

Valproate inhibits urea synthesis and the resulting elevations in serum ammonia levels can have clinical consequences varying from mild fatigue to coma.[37] The neurology literature contains many references to this effect, though the psychiatric literature does not. This effect does not appear to be dose dependent and its manifestations—fatigue, cognitive slowing, and sedation—may be misinterpreted as depressive symptoms or even viewed as a positive response.[38] Moreover, the tendency of valproate to increase ammonia levels is probably common rather than idiosyncratic.

Hjelm and colleagues[39] showed that ammonia levels increased by an average of 101% among five healthy subjects given valproate at doses tapered to 1,500 mg/day over 1 week. Thus, an increase in lethargy after the establishment of valproate therapy warrants a check of ammonia levels. Some have suggested the administration of carnitine 1 g BID as a remedy.[40] This may work by altering the effect of valproate on urea synthesis.

Carbamazepine

Carbamazepine was the first anticonvulsant to be widely used in bipolar affective disorder. There have been no direct comparisons of efficacy between carbamazepine and valproate, and little is known regarding which patients can be expected to respond to one rather than the other. This makes the differing side-effect profiles a relatively important factor as clinicians choose among the anticonvulsants.

Blood Dyscrasias

Carbamazepine has a well-known tendency to lower white cell counts. In perhaps the largest survey of this effect,[41] carbamazepine was five times more likely to produce leukopenia than was valproate, though it was not more likely to produce severe leukopenia, defined as a white blood cell (WBC) count <3,000 mm^3. The onset of leukopenia is most likely during the first 30 days of treatment and is unlikely after 60 days. The WBC threshold[42] below which discontinuation is recommended has varied from 3,000 to 4,000 mm^3. Notably, 11 of the cases with moderate leukopenia described by Tohen and colleagues[41] continued on carbamazepine without adverse consequences. Lithium is known to stimulate leukocyte production and may serve to correct the leukopenia induced by carbamazepine.[43] This combination would be particularly appropriate in cases of incomplete clinical response to carbamazepine monotherapy.

Hyponatremia

Hyponatremia is a relatively common side effect of carbamazepine and may be symptomatic.[44] The patient's medical regimen should be reviewed when low sodium values are noted. Discontinuation of carbamazepine may be averted by adjusting or eliminating coadministrated diuretics.

Lamotrigine

Lamotrigine offers advantages over valproate and carbamazepine in terms of such side effects as fatigue, somnolence, and weight gain.[32] Weight, on average, has been shown to remain stable or to decrease during lamotrigine treatment.[45] Although lamotrigine has only recently come into use as a mood stabilizer, it has been widely used as an antiepileptic and more than 583,000 patient-years of experience have accumulated.[46] Lamotrigine also lacks most of the side effects associated with the antidepressants developed for use in major depressive disorder. Several recent placebo-controlled studies have shown lamotrigine to have both acute and prophylactic benefits for bipolar depression,[47,48] suggesting that this agent is an alternative to the more traditional antidepressants in the management of bipolar depression.

The most frequent adverse events leading to discontinuation in controlled trials have been skin rashes. Indeed, reports of toxic epidermal necrolysis or Stevens-Johnson syndrome have made some clinicians reluctant to use lamotrigine. An expert panel estimated that rashes occur in approximately 10% of patients given lamotrigine and that those severe enough to result in hospitalization occur in 0.3% of adults and 1% of children.[46] Established risk factors for lamotrigine-induced rash are use in childhood, use in combination with valproate, and most importantly, a rapid progression in dose. Recognition of this last risk factor led to revisions in the recommended dose-progression.[49] A large-scale comparison of rates before and after the adoption of these revisions shows that the risk for severe rash (associated with systemic disturbances) was seemingly eliminated, though the risk for nonserious rashes remained at 9%.[49]

Conclusion

Only a few medicines have demonstrated effectiveness in the maintenance of bipolar affective disorder. Because of this, and the fact that most patients with bipolar illness require maintenance for an indefinite period, side effects should be managed with particular care to prevent the unnecessary abandonment of a potentially valuable treatment.

Treatment options fall into four categories. The most obvious category is dose adjustment to titrate symptom prophylaxis against side effects within therapeutic plasma level ranges. An often neglected but frequently reward-

ing intervention is the trial elimination of concomitant medications which may no longer be necessary. The optimization of thyroid status may improve cognitive slowing or fatigue, particularly during lithium maintenance. Emphasis on a regular exercise program is often preferable to switching medication in the face of weight gain. Finally, modest doses of adjunctive medication have been reported as useful in the management of certain side effects. Most of these apply to lithium side effects, doubtless because lithium has been in use far longer than the alternatives.

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