Guidelines for the Safety Monitoring of Patients With Bipolar Disorder

By Valerie Taylor, MD, PhD, FRCPC, and Ayal Schaffer, MD, FRCPC

All patients undergoing treatment for bipolar disorder (BD) require some form of medical safety monitoring. The type and frequency of monitoring depends not only on the specific medication prescribed, but also on the specific patient profile and treatment setting. Ensuring adequate safety monitoring for patients with serious mental illnesses such as BD is a major clinical challenge for clinicians. A number of different safety monitoring guidelines have been published in recent years; however, clinicians may find it difficult to identify a general consensus across guidelines, limiting the integration of these guidelines into practice. Recently, the International Society for Bipolar Disorders (ISBD) launched an effort to develop consensus guidelines for safety monitoring of BD treatments, incorporating the most up-to-date information available. These guidelines were published in early 2009 and serve as a valuable framework to assist clinicians in approaching the safety monitoring of treatments for BD. This issue of Mood and Anxiety Disorders Rounds summarizes the salient points from these guidelines, and provides additional case examples and discussions.

General monitoring for all patients with BD

No medications used for treating BD are free from side effects; the considerable benefits of treatment must always be balanced by respect for adverse consequences. A key suggestion in the ISBD guidelines is that every patient with BD should receive “basic safety monitoring” at the outset of treatment. This includes a focussed medical history, a complete physical examination, and laboratory investigations (Table 1). The specific goals of this basic safety monitoring are the following:

- Establish a baseline prior to treatment
- Identify any abnormalities that would influence selection of medication
- Screen for medical comorbidities known to be associated with BD

In addition to completing the basic safety monitoring for all patients, the ISBD guidelines outline additional monitoring for medication-specific adverse drug reactions (ADRs). Overall, the approach is a “basic plus add-on” system, with the “add-on” monitoring dependent on the patient profile (eg, >40 years old; women of childbearing age, etc.), and the specific medication prescribed.

Case #1

John is a 36-year-old patient with BD type I. Since his illness onset 2 years ago, he has been treated successfully with lithium, and is maintained in the therapeutic range. Blood monitoring every 6 months is limited to 12-hour serum lithium levels, thyroid stimulating hormone, blood urea nitrogen, and creatinine levels. No abnormalities have emerged.

After complaints of fatigue for the past few months, routine blood work reveals a microcytic anemia (hemoglobin 105 g/L) and an elevated fasting glucose (7.0 mmol/L). His last annual physical exam was completed by his family physician 4 years ago, with no abnormalities found. For the first time, John mentions a family history of cardiovascular disease (CVD). The results are discussed with John, and his family physician agrees to pursue further investigations and management.

Available online at www.moodandanxietyrounds.ca
**Table 1: International Society for Bipolar Disorders (ISBD) guidelines: recommended baseline parameters to monitor safety in patients with bipolar disorder**

<table>
<thead>
<tr>
<th>Patient history</th>
<th>Medical</th>
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<tbody>
<tr>
<td></td>
<td>Smoking status and alcohol intake</td>
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<td></td>
<td>Potential of pregnancy in women of childbearing age (pregnancy test if clinically indicated)</td>
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<tr>
<th>Family</th>
<th>Cardiovascular / cerebrovascular disease</th>
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<tr>
<td></td>
<td>Hypertension</td>
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<td>Dyslipidemia</td>
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<td>Diabetes mellitus</td>
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<table>
<thead>
<tr>
<th>Physical examination</th>
<th>Waist circumference (Figure 1) and/or body-mass index (BMI)</th>
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<td></td>
<td>Blood pressure</td>
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<tr>
<th>Investigations</th>
<th>Complete blood count (CBC)</th>
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<tr>
<td></td>
<td>Hemoglobin</td>
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<td>Platelets</td>
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<td>White blood cell count</td>
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<td></td>
<td>Electrolytes, urea, and creatinine</td>
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<td></td>
<td>Liver function tests</td>
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<tr>
<td></td>
<td>Fasting glucose and lipid levels*</td>
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<tr>
<td></td>
<td>Total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol, and triglycerides</td>
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</tbody>
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*Nonfasting glucose and total and HDL cholesterol levels may be more practical in some patients; eg, if patient is unlikely to follow fasting instructions or attend for the sole purpose of blood testing.

This case illustrates the potential benefits of using a baseline monitoring approach for all patients. While John was monitored appropriately for lithium treatment, his family history of CVD was not previously identified. As well, it is unclear how long he has had anemia and elevated glucose. This case also raises the issue of who is responsible for ensuring appropriate medical monitoring for patients with mental illness treated by a psychiatrist. While there is no uniquely effective model, collaboration between primary-care physicians and treating psychiatrists is essential to ensure that these patients do not “fall through the cracks.” As trained physicians, most psychiatrists can expect to be involved either directly or indirectly in the medical monitoring of their patients, particularly when pharmacotherapy is a component of treatment.

**Additional monitoring for patients with BD: the Canadian perspective**

In addition to the ISBD monitoring parameters outlined earlier, other guidelines such as the Canadian Network for Mood and Anxiety Treatments (CANMAT) Bipolar Disorder Guidelines have recommended further basic monitoring be completed when clinically indicated, for example:

- Coagulation studies (prothrombin time [PT] and partial thromboplastin time [PTT])
- Estimated glomerular filtration rate (eGFR)
- 24-hour creatinine clearance (if history of renal disease)
- Urinalysis
- Urine toxicology for substance use
- Thyroid stimulating hormone (TSH)
- Prolactin
- Electrocardiogram (>40 years old or if indicated)

Furthermore, given the high rates of problematic alcohol use, smoking, and poor diet among BD patients, physicians are also encouraged to take an active role in addressing these issues with their patients. Providing specific advice at baseline and throughout the course of treatment on smoking cessation, alcohol reduction and/or cessation, as well as bolstering exercise and healthy dietary habits can be effective therapeutic interventions.

**Monitoring for patients with BD on lithium**

Lithium therapy in patients with BD may be associated with a number of potentially adverse effects and complications. Common side effects such as polyuria and polydipsia, gastrointestinal changes, tremor, cognitive dulling, acne, and weight gain should be clinically monitored. For medical safety patients should be monitored to assess lithium toxicity, renal impairment, and thyroid/parathyroid abnormalities. Specific recommendations for monitoring of patients on lithium therapy are outlined in Table 2.

Accidental lithium toxicity is a dangerous but generally preventable event. In addition to appropriate dosing and monitoring of serum lithium levels, psychoeducation on preventive measures is paramount. Patients should be made aware of the effects of dehydration in elevating lithium levels (inadequate hydration, significant alcohol use, etc). Concomitant use of interacting medications such as non-steroidal anti-inflammatory drugs (NSAIDs), thiazide diuretics, or angiotensin-converting enzyme (ACE) inhibitors may interfere with lithium elimination increasing the risk of lithium toxicity.

Lithium therapy has also been associated with clinical or subclinical hypothyroidism, hyperparathyroidism, and renal impairment. While the precise risk of these lithium-related complications is unknown, there is sufficient concern to warrant monitoring, as outlined in Table 2.

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Monitoring for patients with BD on valproic acid or carbamazepine

All anticonvulsant medications used in the treatment of BD require some form of monitoring, but in this case the focus is exclusively on valproic acid and carbamazepine; both of these commonly used agents require considerable routine safety monitoring. Table 2 outlines the ISBD safety monitoring recommendations for these medications.

Valproic acid treatment is associated with a number of biochemical disturbances. Thrombocytopenia and liver enzyme elevation are the most common ADRs; both are more likely to occur early in treatment, but are generally of mild severity. Patients with associated clinical manifestations or indications of greater severity require urgent assessment and management. Less common but potentially more severe ADRs include acute hepatitis, acute pancreatitis, and hyperammonemic encephalopathy. The value of universal screening for these dangerous reactions may be limited because clinical manifestations and biochemical disturbances can occur rapidly without the presence of prior abnormalities. Weight gain, increased risk of polycystic ovary syndrome (PCOS) and reduced bone density have also been associated with the use of valproic acid, and should be considered in all patients, especially those at greater risk for these conditions (eg, children and adolescents). The ISBD recommends that monitoring should occur every 6 months instead of annually in this population, and an endocrinologist should be consulted if other factors that impact bone growth or reduced bone mineral density co-occur with medication use.

Abnormalities identified in thyroid levels, calcium levels, or renal functioning would generally require additional investigations by the treating physician or consulting specialist.

In using lithium with special populations, it is important to recognize that this medication has a shorter half-life in children. This can result in the need for higher dosages and can be inadvertently mistaken for treatment nonadherence. A “start low, go slow” titration regimen is recommended to minimize ADRs. Changes in physiology also impact monitoring guidelines with respect to lithium during pregnancy. The ISBD guidelines recommend that maternal lithium levels be monitored at minimum every trimester, balancing the probable need for higher dosages with the need to minimize exposure by ensuring symptom control is achieved with the lowest possible level of medication. To further minimize risk of maternal and neonatal toxicity, withholding lithium 24-48 hours prior to planned deliveries or at the onset of labour is also recommended. Exposure to the drug via breast milk is lower than neonatal exposure and decisions regarding breast-feeding should be made on an individual basis, weighing the benefits against the risks of drug exposure.

The elderly are especially vulnerable to ADRs because they are more likely to have problems with compliance, polypharmacy exposure that can impact lithium levels, and possibly more problems with dehydration. Since toxicity can occur within the therapeutic range, it is important to monitor levels and be aware of the clinical presentation of lithium toxicity. In this population, as well, sinus-node dysfunction is an important diagnostic entity to consider if new-onset syncope occurs.

<table>
<thead>
<tr>
<th>Table 2: ISBD guidelines: recommended medication-specific safety monitoring beyond general baseline parameters</th>
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<tbody>
<tr>
<td><strong>Baseline</strong></td>
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<tr>
<td><strong>TSH</strong></td>
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<tr>
<td><strong>Serum calcium</strong></td>
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<tr>
<td><strong>Serum drug levels</strong></td>
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<tr>
<td><strong>Longitudinal</strong></td>
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<tr>
<td><strong>Levels every 6 months in children and adolescents</strong></td>
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<tr>
<td><strong>Inquire about menstrual changes (for women of reproductive age)</strong></td>
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<tr>
<td><strong>Advice on bone health (dietary calcium intake, safe sun exposure, regular exercise)</strong></td>
</tr>
</tbody>
</table>

TSH = thyroid-stimulating hormone
The use of valproic acid during pregnancy also requires the implementation of additional monitoring parameters. Preconceptional counselling about the risk of neural-tube defects and folic acid supplementation is recommended. Since many pregnancies are unplanned, early obstetrical identification and close monitoring of the pregnancy, as well as the appropriate use of investigations to identify malformations are recommended. Breastfeeding instructions should be given on an individual case basis, weighing costs and benefits.

Valproic acid is generally well tolerated in the elderly, but changes in physiology with this population suggest that clinical status and not serum levels should dictate dosage. Coagulation parameters should be monitored when concomitantly administered with acetylsalicylic acid or an anticoagulant, and dietary and lifestyle advice to promote bone health is recommended. Bone densitometry and vitamin D screening should also be considered.

**Case #2**

Mary, a 27-year-old patient with BD type I, was admitted to hospital 6 months ago for a manic relapse after a period of nonadherence to divalproex sodium. She stopped the medication due to her unhappiness with weight gain and alopecia, but has been successfully maintained on carbamazepine monotherapy since her hospitalization. Mary arrives at her appointment distraught because she has had a miscarriage, and she is wondering how she became pregnant while she was using an oral contraceptive.

This case illustrates the clinically important pharmacokinetic interactions that can occur between carbamazepine and other medications, including oral contraceptives. Carbamazepine is a potent inducer of oral contraceptive metabolism, resulting in lower hormonal levels that may reduce efficacy. Mary’s case reinforces the importance of making patients (and other treating physicians) aware of this interaction, and suggesting additional contraceptive measures (eg, higher doses of oral contraceptives or alternative contraceptive strategies).

Carbamazepine is associated with a number of potential ADRs, the most common of which include leukopenia, increased liver enzymes, and hypotension. These disturbances can range in intensity from mild and transient to severe and dangerous, requiring regular monitoring and clinical vigilance (Table 2). Less common complications include agranulocytosis, aplastic anemia, acute hepatitis, and mucocutaneous syndromes (Stevens-Johnson syndrome, toxic epidermal necrolysis); these should be immediately addressed upon clinical or biochemical identification. In the elderly, prescribers need to be aware of issues related to sedation, cognitive impairment, cardiac problems, and bone health. As with valproic acid, patients receiving long-term therapy should receive education on bone health, with a focus on exercise, vitamin D and calcium intake; as well, the use of bone densitometry and vitamin D screening should be considered. This should also be implemented when using carbamazepine in children and adolescents.

Monitoring recommendations for pregnancy and breastfeeding are similar to those identified for valproic acid and include preconceptional counselling regarding the risk of neural-tube defects, folic acid supplementation, early obstetrical identification, and close monitoring. The decision to breastfeed should be based on individual preferences and weighing the outcomes.

**Monitoring patients receiving atypical antipsychotics**

Numerous guidelines exist for monitoring metabolic changes associated with the use of atypical antipsychotics; however, adherence to guideline recommendations is not common practice. This issue must be addressed, since the physical comorbidities that can accompany the use of atypical antipsychotics have a potential impact on both physical and psychological outcomes.

**Case #3**

Catherine is a 42-year-old woman with type 1 BD. It has taken her 15 years, a battle with substance abuse, and 3 hospital admissions – all due to medication noncompliance – to achieve mood stability. She is currently well and takes a combination of lithium, an atypical antipsychotic, and selective serotonin reuptake inhibitor therapy. She initially received bupropion, but because of agitation she switched first to paroxetine and then to escitalopram. During those 15 years, Catherine gained 17 kg, and her body-mass index (BMI) increased from 29.1 kg/m² to 35.4 kg/m². She has developed dyslipidemia and, with a fasting blood glucose level of 6.3 mmol/L, Catherine is considered prediabetic. Catherine believes that her weight has had a negative impact on both her physical and psychological health, and she desires some treatment options.

Weight gain is perhaps the most common metabolic parameter altered by atypical antipsychotic treatment, and is often identified as a reason for medication noncompliance in patients with BD; in turn, medication noncompliance is the most frequent cause of bipolar illness recurrence. In patients who are treatment compliant, concurrent weight gain impacts outcome, therefore clinicians must be familiar with medical categorization of weight gain to know how much is too much (Table 3). Weight should be measured monthly for the first 3 months and then at

![Mood and Anxiety Disorders Rounds](image-url)
3-month intervals for the duration of treatment. Routine monitoring of weight-related comorbidities is also recommended; a fasting lipid profile should be measured at baseline and then annually, while fasting glucose and blood pressure measurements are recommended at baseline and at 3-month intervals for the first year, with subsequent yearly follow-up. If glucose levels indicate an actual diagnosis of diabetes, glycated hemoglobin (HbA1c) should be monitored as well. The amount of weight gain in patients with a mood disorder may not be the only factor linked to an increase in morbidity from obesity-related diseases; another factor may be the location, i.e., an increased amount of centrally deposited adipose tissue. Visceral fat predicts CVD risk better than total body fat volume and a measure of visceral fat, waist circumference, is positively associated with abnormalities in lipids, blood pressure, and glucose. Weight change should therefore be monitored both by BMI and waist measurements (Figure 1).19-21

To address weight gain in patients receiving atypical antipsychotics requires judicious use of “rational” pharmacotherapy. The use of a medication least likely to exacerbate current comorbidities is always preferred, but this is based on a prior knowledge of a patient’s medical history. Personal or family history of cardiac problems as well as an electrocardiogram or prolactin levels should be obtained where clinically indicated;22,23 in addition, adherence to hematological monitoring is required for clozapine.24,25

Catherine’s case illustrates the possible end result when these types of monitoring protocols are not followed. It is now a challenge to ensure that she continues to adhere to the treatment protocol that helped her get well, while simultaneously arranging for follow-up of the other chronic medical conditions she has developed and attempting to implement strategies to reduce her weight.26 Disease prevention is often much easier than disease management.

In recent months, the focus has increased on the use of atypical antipsychotics in children and adolescents27 because these medications are increasingly prescribed to children and adolescents as first-line treatment for BD.28 Results suggest that this population is at the very least as vulnerable as adults to the cardiometabolic risks associated with this class of medication, and may be at greater risk.29 As a result, for this population, 6-month monitoring should be added to the baseline and annual adult monitoring protocol.

### Table 3: Risk profile associated with weight gain

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Waist circumference</th>
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<tbody>
<tr>
<td>&lt;18.5</td>
<td>Underweight</td>
</tr>
<tr>
<td>18.5 – 24.9</td>
<td>Normal weight</td>
</tr>
<tr>
<td>25 – 29.9</td>
<td>Overweight</td>
</tr>
<tr>
<td>≥ 30</td>
<td>Obese</td>
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### Figure 2: Safety monitoring of lithium, valproic acid, carbamazepine, and atypical antipsychotics in all patients being treated for BD

Even fewer data are available regarding the use of atypical antipsychotics during pregnancy and breastfeeding; as a result, a watchful-waiting stance is advocated for this population, highlighting clinical monitoring of the infant for side effects, especially when the infant is premature.30

Increased vigilance for ADRs is also recommended when using atypical antipsychotics with the elderly because they may have increased risk for sedation, dizziness, hypotension, QTc prolongation or anti-cholinergic effects.14 As with valproic acid and carbamazepine, bone health should also be monitored.

### Conclusions

No medications are available to treat BD without side effects; therefore, to ensure the best possible physical and psychological outcome requires that both patient and healthcare provider be informed and educated. The ISBD guidelines have been designed to promote this education. While they do not address issues related to polypharmacy or comment on every possible potential ADR, the guidelines summarize the current state of the literature with respect to monitoring patients receiving approved medications for common and problematic side effects (Figure 2). This focus on safe, effective treatment in patients with BD will help improve care.

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References


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17-19 March 2010
4th Biennial Conference of the International Society for Bipolar Disorders
Sao Paulo, Brazil
CONTACT: Tel.: +55 11 3682 0244
Fax: +55 11 3682 0288
Email: isbd2010@icms.com.br

16-19 April 2010
5th Biennial Conference of the International Society for Affective Disorders (ISAD)
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Email: k.webster@elsevier.com
Tel: +44 (0) 1865 843211
Fax: +44 (0) 1865 843958

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