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BIPOLAR DISORDERS

Guidelines

The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments

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Objectives: Safety monitoring is an important aspect of bipolar disorder treatment, as mood-stabilising medications have potentially serious side effects, some of which may also aggravate existing medical comorbidities. This paper sets out the International Society for Bipolar Disorders (ISBD) guidelines for the safety monitoring of widely used agents in the treatment of bipolar disorder. These guidelines aim to provide recommendations that take into consideration the balance between safety and cost-effectiveness, to highlight iatrogenic and preventive clinical issues, and to facilitate the broad implementation of therapeutic safety monitoring as a standard component of treatment for bipolar disorder.

Methods: These guidelines were developed by an ISBD workgroup, headed by the senior author (MB), through an iterative process of serial consensus-based revisions. After this, feedback from a multidisciplinary group of health professionals on the applicability of these guidelines was sought to develop the final recommendations.

Results: General safety monitoring recommendations for all bipolar disorder patients receiving treatment and specific monitoring recommendations for individual agents are outlined.

Conclusions: These guidelines are derived from evolving and often indirect data, with minimal empirical cost-effectiveness data available to provide guidance. These guidelines will therefore need to be modified to adapt to different clinical settings and health resources. Clinical acumen and vigilance remain critical ingredients for safe treatment practice.

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Introduction

Medical comorbidities are pertinent to the management of bipolar disorder by virtue of their prevalence, relationship to psychotropic medications, and association with worse clinical outcomes and greater functional impairment (1, 2). Conditions such as obesity, cardiovascular disease, and diabetes mellitus are especially common in those with bipolar disorder, and this association may in part be explained by the prevalence of known risk factors such as smoking and physical inactivity, the effects of psychotropic medications, and perhaps shared aetiological factors (1). Safety monitoring in bipolar disorder may therefore have the dual

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benefit of detecting prevalent medical comorbidities and of minimising the morbidity and mortality that result from adverse drug reactions (ADRs). The availability of effective preventive measures and treatments for most common medical comorbidities additionally highlights the advantages of safety monitoring. However, a recent audit of therapeutic drug level and cardiovascular risk monitoring in bipolar disorder found that only about half of the patients were receiving monitoring according to the minimal recommendations of the US guidelines (3). Poor adherence to guideline recommendations is not unique to bipolar disorder or psychiatry (4), but specific barriers to safety monitoring in bipolar disorder may include the paucity of guidelines focussing on safety monitoring, problems with insight or adherence on the part of the patient, and the segregation of psychiatric care from other medical care in the clinical setting (5).

To the best of our knowledge, there have been no published guidelines exclusively focussing on the monitoring of serious ADRs in bipolar disorder, although such guidelines have been developed for schizophrenia (6), individual classes of medications such as the atypical antipsychotics (7, 8), and some individual medications (9). The American Psychiatric Association practice guidelines (10), the Child and Adolescent Bipolar Foundation treatment guidelines (11), the National Institute for Health and Clinical Excellence (NICE) guidelines (12), and the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines on bipolar disorder (13, 14) have addressed aspects of safety monitoring, but their primary focus has been on symptomatic treatment for bipolar disorder. In order to address this deficiency, the International Society for Bipolar Disorders (ISBD) commissioned a workgroup, headed by the senior author (MB), to develop a set of practical guidelines for the monitoring of serious ADRs that may be associated with the main pharmacological agents used to treat bipolar disorder. The main objectives of these guidelines were, first, to provide safety monitoring recommendations that balance safety and cost-effectiveness; second, to highlight the occurrence of medication-induced side effects and the desirability of their prevention; and third, to facilitate the international implementation of therapeutic safety monitoring as a standard component of bipolar disorder treatment.

These guidelines, being oriented toward safety concerns, focus on the assessment and prevention of serious medical disorders that may be caused or aggravated by medications used to treat bipolar disorder. They do not intend to address ADRs that may be prevalent and/or bothersome but are not serious threats to health (e.g., antipsychotic-induced Parkinsonian tremor). Similarly, these guidelines only address drug interactions that have the potential to cause serious adverse events (e.g., lithium and nonsteroidal anti-inflammatory drugs, lamotrigine and valproate). This document is not a review of bipolar disorder treatments, their ADR profiles, or management, even though an overview of selected ADRs for each medication group has been included to provide background for the monitoring recommendations. Furthermore, these guidelines are limited to medications that have established mood-stabilising properties and are commonly used to treat bipolar disorder, which include lithium, valproate, carbamazepine, lamotrigine, and the atypical antipsychotics. Although various other biological therapies (e.g., antidepressants, benzodiazepines, anticonvulsants with limited evidence of efficacy as mood stabilisers, and electroconvulsive therapy) are also used in the treatment of bipolar disorder, the ISBD workgroup has not included these treatments in these guidelines because they either do not have similar safety monitoring requirements, or are not mainstay therapy. By defining the scope of these guidelines in this manner, the ISBD workgroup hopes to provide clinicians with a concise document on safety monitoring for potentially serious health problems associated with the most widely used treatments for bipolar disorder.

The ISBD workgroup developed these guidelines by first examining the relevant literature and existing guidelines on safety monitoring in bipolar disorder, followed by the drafting of provisional guidelines for internal review. The latter was an iterative undertaking that continued until consensus within the workgroup was reached. The guidelines drafted by the workgroup were then distributed to a multidisciplinary group of health professionals in Canada, The Netherlands, the United Kingdom, and Australia for feedback, especially in relation to their applicability to clinical practice. This group was comprised mainly of psychiatrists, but also included geriatricians, pharmacists, and a pharmacoepidemiologist. Of the psychiatrists, all worked in clinical settings and had diverse expertise, including child and adolescent psychiatry and geriatric psychiatry. Comments that enhanced the guidelines were incorporated.

Following cost-benefit principles, the safety parameters that are suggested for monitoring are either common and medically significant, or rare but potentially serious. The recommendations in these guidelines are a consensus statement on safety monitoring based on the current state of

knowledge, and not a set of definitive clinical care directives. Having been developed by consensus and from indirect and often low-level evidence, with minimal guidance from empirical data on the cost-benefit ratio of safety monitoring in bipolar disorder treatment, these proposed guidelines need to be interpreted with these limitations in mind and to be flexibly and contextually applied in clinical practice. These guidelines are not expected to be universally applicable, as guideline recommendations are influenced by sociocultural factors, such as local healthcare needs, priorities, infrastructure, and resources, as well as evolving knowledge and expert opinions. Nevertheless, where not directly applicable, these guidelines may hopefully still serve as a reference and an impetus to develop locally relevant guidelines.

Format of the ISBD guidelines

The safety monitoring of patients with bipolar disorder needs to take into account the presence of any pre-existing medical conditions, risk factors for adverse effects, concurrent medications, the ADR profiles of the mood-stabilising medication(s) selected, and clinical factors such as likely adherence to treatment and follow-up. In these guidelines, we have proposed a set of basic monitoring parameters for all patients with bipolar disorder, based on a consideration of the prevalent nonpsychiatric comorbidities associated with bipolar disorder, and ADRs shared by multiple classes of mood-stabilising agents. These basic monitoring parameters are described in Basic Safety Monitoring in Bipolar Disorder. In addition to these basic measures, we have separately proposed additional parameters to be monitored specific to individual medications. These 'add-on' monitoring parameters are described in Additional Monitoring for Adverse Drug Effects. This 'basic plus add-on' approach to safety monitoring, summarised in Fig. 1, hopefully provides a simple, practical, and reasonably cost-effective clinical aid. The Special Populations section addresses safety monitoring of treatment in certain special populations, namely, children and adolescents, pregnant and breastfeeding women, and the elderly. Practical Considerations addresses some considerations in the implementation of these guidelines in clinical settings. Lastly, limitations are described in Limitations of the ISBD Guidelines.

Basic safety monitoring in bipolar disorder

Patients with bipolar disorder may have additional medical burden for a number of reasons, including physical complications of disordered mental states, detrimental lifestyle factors, comorbid substance use, ADRs associated with psychotropic agents, and barriers to accessing comprehensive health care (1, 5, 15). Medical illnesses may in turn compound the morbidity, mortality, disability, and healthcare costs in bipolar disorder (5). In particular, the high prevalence of cardiovascular disease and its risk factors, namely, obesity, smoking, diabetes mellitus, hypertension, and dyslipidaemias, has been well documented among patients with bipolar disorder (16–18). Bipolar disorder has been associated with a mortality rate more than twice that of the general population, with most excess mortality attributable to natural causes, and the most frequent cause of death being cardiovascular disease (19). Metabolic syndrome, which refers to a cluster of cardiovascular risk factors that include abdominal obesity, atherogenic dyslipidaemia (elevated triglycerides and low high-density lipoproteins), hypertension, and high fasting glucose, is also highly prevalent in the bipolar population (16, 17). The significance of metabolic syndrome lies in its identification as a multiplex risk factor for type 2 diabetes and cardiovascular disease, and varying criteria for this syndrome have been proposed by different workgroups (20). Cardiovascular risk may be ameliorated by the selection of medications associated with less liability for metabolic and cardiovascular ADRs, monitoring for the emergence of these ADRs, and targeted interventions (21, 22). Conversely, psychiatric treatment may also reduce cardiovascular, nonsuicide, and overall mortality in bipolar disorder, suggesting that bipolar treatment may be associated with better general health care (23). These observations communicate a need for the monitoring of physical health parameters to be incorporated into bipolar disorder management.

ISBD monitoring recommendations

We suggest that as a minimum standard of care, the parameters in Table 1 (also shown in Fig. 1) be monitored in every patient at the outset of treatment for bipolar disorder. These basic monitoring parameters, at treatment baseline, include waist circumference and/or body mass index (BMI) [calculated by dividing weight in kilograms by the square of height in metres (kg/m^2)], blood pressure, full blood count (FBC) (i.e., haemoglobin, platelets, and white cell count), electrolytes, urea, and creatinine (EUC), liver function tests (LFTs), fasting glucose and fasting lipid profile [total triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density

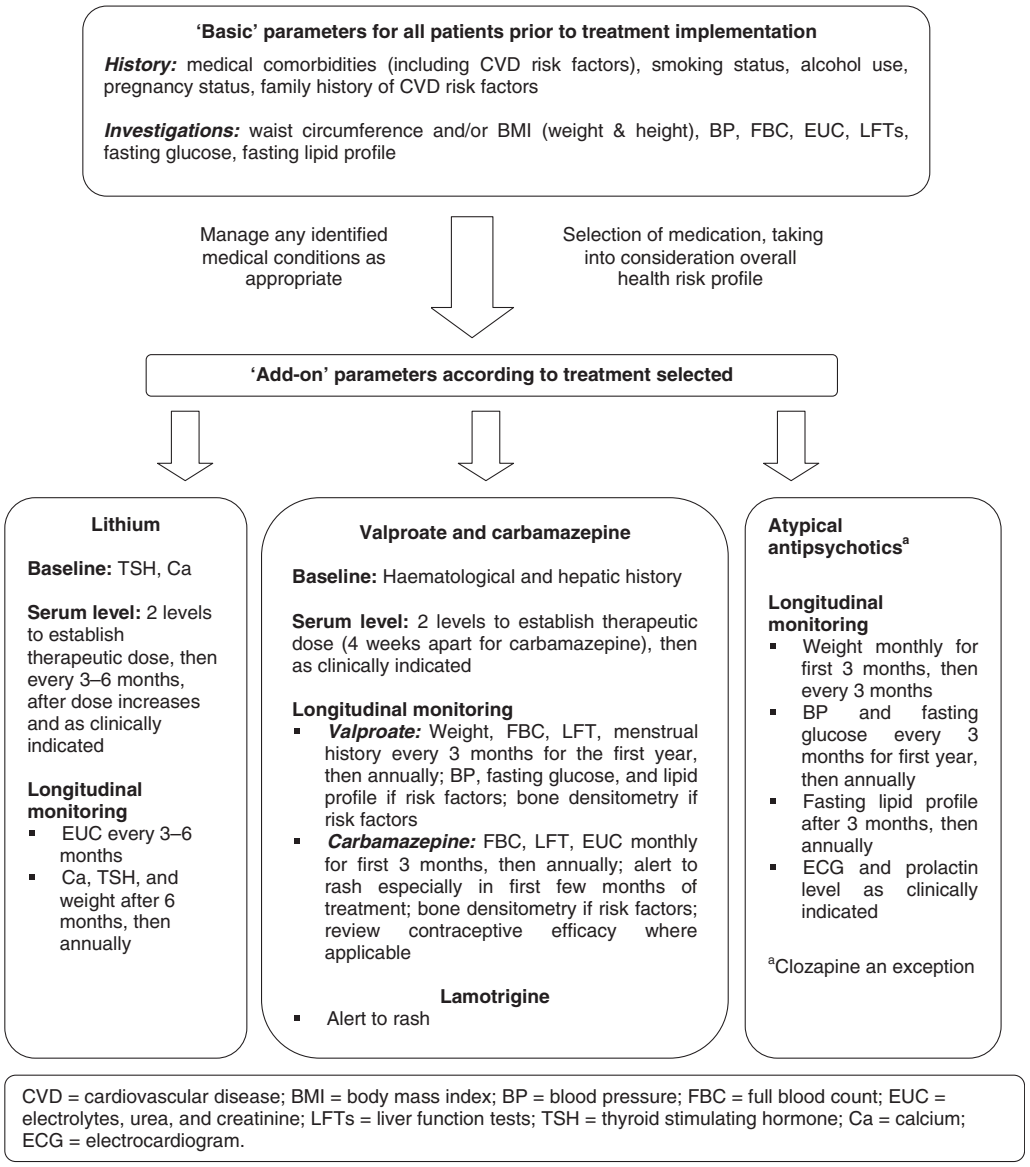

Fig. 1. Algorithm for safety monitoring in bipolar disorder.

lipoprotein (HDL) cholesterol]. In addition, medical history, cigarette smoking status, alcohol intake, and any family history of cardiovascular disease, cerebrovascular disease, hypertension, dyslipidaemia, or diabetes mellitus should be documented. In women of childbearing age, the possibility of pregnancy should be considered, and a pregnancy test performed if clinically indicated. Contraception and pregnancy planning should be discussed with women of childbearing potential in light of the teratogenic effects of some mood stabilisers.

In some instances, it may be more practical to substitute fasting with nonfasting levels, for example, if the patient is unlikely to follow instructions for fasting blood tests or to attend for the sole purpose of blood testing. A nonfasting or random blood glucose level greater than 200 mg/dL (11.1 mmol/L) on two separate occasions, or once with 'unequivocal symptoms of hyperglycemia' [i.e., polyuria (large quantities of dilute urine), polydipsia, and unexplained weight loss] is diagnostic of diabetes mellitus (24). Although the routine measurement of haemoglobin A1C levels for diagnostic purposes is not recommended (24), nonfasting haemoglobin A1C levels $\geq 7\%$ are strongly suggestive of diabetes mellitus and levels $\geq 5.8\%$ are an indication for further diagnostic testing (25). Similarly, a nonfasting total cholesterol ≥ 200 mg/dL (5.2 mmol/L) or nonfasting HDL cholesterol < 40 mg/dL (1.0 mmol/L) indicate possible dyslipidaemia and should ideally be

Table 1. ISBD recommended baseline parameters for safety monitoring in all patients with bipolar disorder

	Recommendations
History	■ Medical history ■ Cigarette smoking status and alcohol intake ■ Family history of cardiovascular and cerebrovascular disease, hypertension, dyslipidaemia, and diabetes mellitus ■ Pregnancy and contraception (for women of childbearing age)
Examination	■ Waist circumference and/or body mass index [weight (kg)/height (m)^2] ■ Blood pressure
Investigations	■ Full blood count ■ Electrolytes, urea, creatinine ■ Liver function tests ■ Fasting blood glucose ■ Fasting lipid profile ■ Pregnancy test (if clinically indicated)

confirmed with a fasting lipid profile (26). Nonfasting lipid profiles are unsuitable for assessing triglycerides and LDL cholesterol, as the former is elevated after meals and the latter is indirectly derived by calculations that are unreliable when triglyceride levels are > 400 mg/dL (4.5 mmol/L). However, one can calculate a non-HDL cholesterol (i.e., total cholesterol – HDL cholesterol) from a nonfasting sample: goal values are < 130 mg/dL (3.4 mmol/L) for those with coronary artery disease, < 160 mg/dL (4.1 mmol/L) for those with two or more coronary artery disease risk factors, and < 190 mg/dL (4.9 mmol/L) for all others (26).

The proposed basic parameters can be performed quickly and at relatively low cost, and are relevant for multiple reasons. They are useful as baseline assessments across different medication groups and also serve as clinical screens in a patient population prone to cardiovascular disease, type 2 diabetes, and metabolic syndrome. The latter provides an opportunity for early intervention, and for the considered selection of psychotropic medications that takes into account these cardiovascular risk factors. Although not a part of safety monitoring, advice on and motivational enhancement for smoking and alcohol reduction and/or cessation, as well as exercise and diet, are potentially therapeutic interventions that could readily be incorporated at baseline assessment and as part of ongoing management.

These baseline parameters differ somewhat from existing guidelines. The CANMAT guidelines provide the most comprehensive list of recommended baseline laboratory investigations, which, in addition to our recommended basic monitoring parameters, also include coagulation studies, urinalysis, urine toxicology for substance use, thyroid stimulating hormone (TSH), and prolactin, as well as electrocardiogram and 24-h creatinine clearance under certain conditions (13). Although these investigations are useful in the baseline assessment of bipolar disorder, they are not pertinent to the safety monitoring needs of all bipolar disorder patients, and have therefore not been included in our basic safety monitoring recommendations. The divergence in guideline recommendations reflects the difficulty in determining optimal thresholds for detecting broad adverse effects of varying frequency and severity, balanced against considerations of the likely yields of abnormal findings, cost, complexity, and consequent adherence to guidelines.

Additional monitoring for adverse drug effects

The pharmacological agents in bipolar disorder treatment that require safety monitoring can be grouped as follows: lithium, anticonvulsants (valproate, carbamazepine, lamotrigine), and the atypical antipsychotics.

Lithium

Lithium is a first-line acute and prophylactic treatment option in bipolar disorder (27), and its use has been associated with lower rates of completed suicide (28–30).

Adverse drug reactions

Lithium can cause weight gain and adverse effects in various organ systems, including gastrointestinal (e.g., nausea, vomiting, abdominal pain, loss of appetite, diarrhoea), renal [e.g., nephrogenic diabetes insipidus (NDI), tubulointerstitial renal disease], neurological (e.g., tremors, cognitive dulling, raised intracranial pressure), endocrine (e.g., thyroid and parathyroid dysfunction), cardiac (e.g., benign electrocardiogram changes, conduction abnormalities), dermatological (e.g., acne, psoriasis, hair loss), and haematological (e.g., benign leukocytosis). Below, we discuss serious ADRs associated with lithium. Because of the paucity of well-designed studies, reliable incidence estimates are frequently unavailable. From the safety monitoring viewpoint, lithium toxicity, renal and endocrine adverse effects, and potential drug interactions are the foremost concerns.

Lithium toxicity

Lithium has a narrow therapeutic index, which means that relatively small changes in its serum level

can result in either therapeutic inefficacy or toxicity. Prevention of lithium toxicity is crucial because of the potential for irreversible organ damage and death (31, 32). Lithium toxicity can be associated with more extensive symptoms in the context of chronic toxic exposure (33). The prevention of lithium toxicity is aided by appropriate dosing and educating the patient on preventive measures, such as ensuring adequate hydration and the avoidance of interacting medications. Serum lithium levels, symptomatic response, the emergence and evolution of ADRs, and the recognition of patient risk factors for toxicity are useful elements that can guide dosing. Reduced renal excretion is a risk factor for lithium toxicity, and may result from renal disease (including lithium-induced renal changes), dehydration, and drug interactions (34). The elderly may present increased risks due to medical comorbidities, polypharmacy, and age-related organ changes (35), as may individuals with organic brain syndromes (36). Whenever illness control allows, using lithium doses at the lower end of the therapeutic range may reduce the risk of lithium toxicity. When lithium toxicity occurs, it is important that this is detected as early as possible in order to prevent further progression, irreversible complications, and death. Education of the patient and family can help them to identify early toxicity symptoms, which are often neurological (e.g., coarse tremor, drowsiness, lethargy, weakness, agitation, muscle fasciculation, ataxia, dysarthria), but also commonly include gastrointestinal (e.g., vomiting, diarrhoea), cardiovascular (e.g., dizziness, syncope, arrhythmias), and renal (e.g., polyuria, polydipsia) symptoms (37). Lithium toxicity should be treated as a medical emergency. As symptoms of lithium toxicity may not correlate with lithium levels, and toxicity can occur at levels within the population-derived therapeutic reference ranges (particularly in the elderly), safety monitoring must be primarily guided by symptoms rather than serum lithium levels (35, 38).

Renal ADRs

Lithium-induced renal ADRs include acute lithium intoxication renal effects (such as renal insufficiency and acute renal failure) (32, 39), chronic tubulointerstitial renal disease, and NDI (40, 41). The latter two are discussed here, as these tend to be insidious and are more relevant to safety monitoring, in contrast to the usually acute presentation of lithium toxicity. Renal safety monitoring is additionally important due to the heightened risks of lithium toxicity in the presence of impaired renal function.

Lithium has been associated with chronic renal disease that includes glomerular and tubulointerstitial nephropathy, nephrotic syndrome, and renal failure (41, 42), which may be underestimated in the clinical setting (41–43). Of note, renal disease may continue to progress despite the cessation of lithium (41). However, the majority of patients treated with lithium over long periods do not appear to develop impaired renal function. In a cross-sectional study of 142 patients treated with lithium for over 15 years, 21% had reduced glomerular filtration rates and 44% showed a reduced maximum urinary concentrating capacity (43). In a separate study with a retrospective design, 21% of 114 patients treated with lithium for 4–30 years were classified as renally insufficient, as defined by a blood creatinine level greater or equal to 1.5 mg/dL (132.6 μmol/L) (44). Irreversible renal damage tends to occur at higher creatinine levels, and the generally slow decline of renal function ('creeping creatinine phenomenon') (44) enables safety monitoring to detect progressive renal disease in its earlier stages. Risk factors for lithium-induced chronic renal disease have been debated, but may include longer duration and higher cumulative dose of lithium treatment, hypertension, diabetes mellitus, concomitant use of other nephrotoxic drugs, prior history of lithium toxicity, and NDI (42, 44). Patients with these risk factors would benefit from more cautious renal safety monitoring.

NDI is characterised by impaired renal concentrating capacity due to the insensitivity of the distal nephron tubule to antidiuretic hormone (ADH), and typically manifests with polyuria and polydipsia (45, 46). Lithium causes NDI through multiple urine-concentrating mechanisms, including the inhibition of adenylate cyclase in the collecting duct, and dysregulation of aquaporin-2, urea transporters, epithelial sodium channels, and acid/base transporters in the renal tubules (46, 47). The incidence and prevalence of lithium-induced NDI are not confidently established, but lithium is considered to be the most common cause of acquired NDI (45, 46). A review of studies by Boton et al. (40) suggested impaired renal concentration in 54% of patients and overt polyuria in 19% of patients on long-term lithium. Bendz et al. (43) found NDI in 12% of 142 patients treated with lithium for at least 15 years. Longer duration of lithium treatment and concomitant use of other psychotropic agents are considered to be risk factors for the development of lithium-induced NDI (45, 48, 49). Substantial improvement and even normalisation of the renal concentration deficit in lithium-induced NDI have been reported by studies spanning over periods of up to one year after lithium discontinuation (48, 50, 51), but

persistent deficits have also been documented (48, 52), in some cases over many years after lithium cessation (53). Lithium-induced NDI is generally benign because thirst is preserved, but can become dangerous in fluid depletion (54), and therefore both the presence of NDI and risk of fluid depletion require monitoring. Aside from lithium ADRs, psychogenic polydipsia (55) and medical conditions such as diabetes mellitus and coexisting renal disease should be borne in mind in the assessment of polyuria and renal problems in lithium-treated patients.

Thyroid and parathyroid ADRs

The association between lithium and hypothyroidism has been well documented. In the 20-year longitudinal Whickham Survey conducted in the UK general population, spontaneous hypothyroidism was estimated to have an annual incidence of 0.35% in females and 0.06% in males (56). In comparison, two longitudinal studies of patients on lithium treatment have reported respective annual incidence estimates in females and males to be 2.3% and 0.4% (57), and 2.27% and 0.68% (58). These studies did not share uniform definitions of hypothyroidism, but elevated TSH and thyroid hormone replacement were required in both studies. These studies also supported female gender and pre-existing thyroid auto-antibodies as risk factors for the development of lithium-induced hypothyroidism. However, while increased rates of thyroid auto-antibodies have been reported in bipolar disorder, they are poor candidates for safety monitoring, as they are not clearly linked to lithium exposure (59), and their specificity as predictors for developing lithium-induced hypothyroidism is too low to justify the costs of routine testing. The association between lithium and hyperthyroidism is less clear, as the supporting literature is limited to case reports and the incidence of the condition is too low to demonstrate causality in the extant longitudinal studies (60). Monitoring thyroid function in lithium-treated patients is indicated because of the multisystem effects of hypothyroidism and its adverse impact on mood. It is worth noting that transient minor perturbations of thyroid function tests can occur during an acute affective episode and on initiation of lithium treatment (61–63). Therefore, abnormal thyroid function test results are often best managed by repeating the tests after several weeks to determine whether referral for further thyroid evaluation is indicated.

Lithium is known to cause hyperparathyroidism. Putative mediating mechanisms include the induction of parathyroid hyperplasia and/or adenomas (64, 65), and interference with the negative feedback loop for parathyroid hormone secretion through altering the threshold of calcium-sensing receptors (65, 66) and inhibiting glycogen synthase kinase 3b (67). Secondary and tertiary hyperparathyroidism may also be seen in chronic renal failure, which may result from lithium or from other causes (65). In primary and tertiary hyperparathyroidism, excessive parathyroid hormone leads to increased bone resorption and hypercalcaemia, which may be asymptomatic or may lead to complications such as renal calculi, cardiac arrhythmias, osteopaenia/osteoporosis, and mental state disturbances (67). The prevalence of lithium-induced hyperparathyroidism is not well established, but a point prevalence of 2.7% (7.5% higher than the general population) has been reported in patients treated with lithium for 15 or more years (65). A single elevated calcium level does not imply that investigation for hyperparathyroidism is necessary, and in most cases, it would be more appropriate to first confirm the diagnosis of hypercalcaemia by repeated measurements (68). Although ionised or 'free' calcium assays may be more accurate in the presence of altered blood pH and protein levels, total calcium levels are more convenient to perform, widely available, and are regarded as adequate for screening and diagnostic purposes in hyperparathyroidism (68).

Weight gain

Weight gain due to medications may present an obstacle to the continuation of treatment, as well as generate personal and health concerns. Pooled data from two double-blind, placebo-controlled maintenance studies in bipolar I disorder examined weight changes in patients on lithium (n = 166), lamotrigine (n = 227), and placebo (n = 66) (69). Considering all data from weeks 0–52, weight change was +2.2 kg (+4.9 lb) for lithium, −1.2 kg (–2.7 lb) for lamotrigine, and +0.2 kg (+0.4 lb) for placebo. For those remaining in the study at 52 weeks, mean weight change was +3.8 kg (+8.4 lb) for lithium (n = 29), −1.2 kg (−2.6 lb) for lamotrigine (n = 42), and +2.1 kg (+4.6 lb) for placebo (n = 17). Comparing those who were and were not obese, weight gain was only significant for the obese group treated with lithium (70). This is consistent with clinical studies showing greater weight gain among those already overweight (71, 72).

Drug interactions

Some drugs may increase lithium levels and therefore the risk of lithium toxicity. Lithium levels may increase with the concomitant use of non-steroidal

anti-inflammatory drugs (NSAIDs), including the selective COX-2 inhibitors. This is thought to be mediated by the reduction in renal prostaglandin synthesis by NSAIDs and other as yet unclarified mechanisms (73). Thiazide diuretics and angiotensin converting enzyme (ACE) inhibitors may also increase lithium levels; the former have been cited to occur within days and the latter in weeks (74, 75), although time frames can be influenced by other clinical variables. Because of the potential for a delayed rise in lithium levels, close monitoring for a period of two months has been suggested when lithium is coadministered with ACE inhibitors (74). However, it is probably best practice to be similarly vigilant in situations when thiazide diuretics are used in conjunction with lithium. Loop and potassium-sparing diuretics are considered to have lower likelihoods of increasing lithium levels, but increased monitoring is still recommended.

Safety monitoring recommendations of previous guidelines

The recommendations of some published guidelines for lithium safety monitoring are summarised in Table 2. Some authors have made monitoring recommendations for specific ADRs, such as the inclusion of urinalysis at baseline, routine inquiry about polyuria and nocturia, and creatinine every six months during long-term lithium treatment (76), to identify renal problems. A broad range of baseline thyroid work-up has also been proposed, comprised of TSH, free thyroid hormones, thyroid antibodies, and ultrasound scanning, to be repeated in entirety after one year, followed by annual TSH thereafter (77).

ISBD monitoring recommendations

The ISBD recommends the addition of TSH and calcium to the baseline battery of investigations when treatment with lithium is planned. Further investigations beyond these baseline screens and consultation with the appropriate specialists may be required in patients with known renal, cardiac, or thyroid disease. The inclusion of other thyroid and renal investigations may be useful where indicated on specific clinical grounds, but their yields are likely to be too low to be suitable for routine testing. Treatment with lithium may have to be reconsidered in those with renal impairment at baseline. Lithium levels should be taken at steady state (at least five days after the last dose increase) on initiation of therapy, and repeated until two consecutive levels within the therapeutic range are obtained for the same dosage. Levels are recommended after dose changes, except during treatment initiation and dose titration, when the timing of levels may depend on the dose titration schedule (gradual or rapid dose escalation) chosen to suit the clinical context. Lithium levels are generally taken approximately 12 h after the last dose, to allow the interpretation of values in relation to the standardised reference range. In the long term, lithium levels and renal function (urea and creatinine) should be monitored at 3–6-month intervals, and as clinically indicated (e.g., after initiation of potentially interacting drugs, emergence of ADRs and toxicity symptoms), for the duration of treatment. Repeating serum calcium, TSH, and weight at six months, then annually, is recommended. These recommendations are summarised in Table 3 and illustrated in Fig. 1.

Where hypercalcaemia is identified and confirmed on at least one repeat calcium level, the possibility of hyperparathyroidism should be investigated. A parathyroid hormone level could be obtained, or a referral could be made to an internist or endocrinologist where such resources are available. A diagnosis of hyperparathyroidism would necessitate a review of the lithium therapy and consultation with an endocrinologist. Thyroxine replacement is required in overt hypothyroidism, but should also be considered in subclinical hypothyroid states that persist on repeated testing, particularly in the presence of suboptimal mood control. Inquiry about the emergence of polyuria is a simple but important monitoring strategy. The development of polyuria requires further assessment of renal concentrating capacity, such as corresponding serum and urine sodium and osmolality, and 24-h urine collection. Reduction to the lowest effective dose and switching from multiple to single daily dosing have been suggested as strategies to ameliorate the problem. In the case of persistent polyuria, especially when dose reduction or lithium discontinuation is clinically undesirable, liaison with nephrologists is recommended.

Although important, laboratory tests are most useful when applied in conjunction with clinical monitoring of adverse effects, as illustrated by the example of lithium toxicity developing at levels considered to fall within the therapeutic range. A strong therapeutic alliance and patient education are invaluable to the process of safety monitoring and to the minimisation of ADRs. An example of the latter can be found in the issue of weight gain, where specific advice on the avoidance of high-calorie beverages to alleviate increased thirst associated with lithium-induced polyuria can be especially relevant.

Table 2. Safety monitoring recommendations of previous guidelines for lithium

Guidelines	Recommendations
American Psychiatric Association (APA) practice guidelines (10)	**Baseline** ▪ Medical history and physical examination ▪ Urea, creatinine ▪ Thyroid function ▪ Electrocardiogram if over the age of 40 ▪ Pregnancy test for women of childbearing age **Serum levels** ▪ 5 days after initiating lithium and after each dose adjustment ▪ Minimum every 6 months in stable patients **Longitudinal** ▪ Renal function every 2–3 months for the first 6 months, then every 6–12 months thereafter ▪ Thyroid function once or twice in the first 6 months, then every 6–12 months thereafter
The National Institute for Health and Clinical Excellence (NICE) guidelines (12)	**Baseline** ▪ Height, weight ▪ Urea, electrolytes, creatinine ▪ Thyroid function ▪ Electrocardiogram if cardiovascular disease or risk factors ▪ Full blood count if clinically indicated **Serum levels** ▪ 1 week after initiating lithium and after each dose adjustment ▪ Minimum every 3 months in stable patients **Longitudinal** ▪ Renal and thyroid functions every 6 months ▪ Ongoing monitoring of weight and neurotoxic signs
The Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines (13, 14)	**Baseline**[a] ▪ Complete blood count, platelets ▪ Electrolytes, creatinine ▪ Bilirubin and liver enzymes ▪ Fasting glucose and lipids ▪ Prothrombin time and partial thromboplastin time ▪ Thyroid stimulating hormone ▪ Urinalysis ▪ Urine toxicology for substance use ▪ 24-h creatinine clearance if history of renal disease ▪ Electrocardiogram if over the age of 40 or if indicated ▪ Pregnancy test if relevant ▪ Prolactin **Serum levels** ▪ 5 days after dose titration, establish 2 consecutive serum levels within therapeutic range, and subsequent levels every 3–6 months unless otherwise warranted by the clinical situation **Longitudinal** ▪ Repeat blood count and liver function tests 4 weeks after starting treatment, then every 3–6 months ▪ Thyroid and renal function tests annually

[a]These baseline investigations are recommended for all patients with bipolar disorder, and are not specific for the medications prescribed.

Anticonvulsants

For reasons previously explained, the anticonvulsants considered in these guidelines are valproate, carbamazepine, and lamotrigine.

Adverse drug reactions

These medications have a number of ADRs that are pertinent to safety monitoring. Valproate and carbamazepine may both cause blood dyscrasias, hepatotoxicity, and teratogenicity, the last of which will be discussed in Special Populations, under 'Pregnancy and Breastfeeding'. Carbamazepine has also been linked to hyponatraemia and serious dermatological adverse effects, while valproate has been associated with polycystic ovary syndrome, weight gain, acute pancreatitis, and hyperammonaemic encephalopathy. The severe ADRs associated with lamotrigine are dermatological. Drug interactions such as lamotrigine-valproate and carbamazepine-hormonal contraceptives will also be briefly discussed in the safety monitoring context.

Haematological ADRs

Various blood dyscrasias have been reported with carbamazepine and valproate (78), most notably leukopaenia, agranulocytosis, and aplastic anae-

Table 3. ISBD recommended baseline and longitudinal safety monitoring specific to patients on lithium, in addition to the basic monitoring recommendations

	Recommendations[a]
Baseline	▪ Thyroid stimulating hormone ▪ Serum calcium
Serum levels	▪ Trough levels at steady state (> 5 days) on initiation of therapy, until two consecutive levels within the therapeutic range are established for the same dosage ▪ At steady state after dose changes ▪ Every 3–6 months and as clinically indicated (e.g., after initiation of potentially interacting drugs, emergence of ADRs, and toxicity symptoms) at stable dosages for the duration of treatment
Longitudinal	▪ Urea and creatinine every 3–6 months for the duration of treatment ▪ Serum calcium, thyroid stimulating hormone, and weight at 6 months, then annually

[a]Investigations beyond these recommendations and consultation with the appropriate specialists may be required in patients with known renal, cardiac, or thyroid disease.

mia with carbamazepine, and thrombocytopaenia with valproate.

Carbamazepine. Leukopaenia associated with carbamazepine tends to occur within the first three months of initiating treatment (79, 80), with an estimated incidence rate of 10–20% for this period of time (79), and usually resolves on carbamazepine cessation (80). In a retrospective study of 977 hospitalised psychiatric patients receiving carbamazepine, 2.1% were leukopaenic (cell count $< 4000/mL$), but this was corrected within a mean time frame of 6.5 days [range 2–14 days] after stopping carbamazepine (81). In contrast, agranulocytosis and aplastic anaemia are rare during carbamazepine treatment, but occur in an unpredictable pattern with a more rapid onset. These characteristics limit the usefulness of standard laboratory testing in their detection, which must rely on the clinician's and patient's mindfulness of the possibility of these ADRs when haematological symptoms emerge (80, 82, 83). Case-controlled studies have reported odds ratios of 5.9, 11.0, and 16.9 for carbamazepine-related agranulocytosis (84), in the context of prevalence estimates that lie in the vicinity of 1.6–9.2 per million in Europe and 2.4–15.4 per million in the United States for all drug-induced agranulocytosis (82). Agranulocytosis associated with carbamazepine has been reported to occur after a median duration of 49 days from treatment initiation, and resolved after a median of 6 days following drug cessation (84). For aplastic anaemia, a case–control study in the UK reported an odds ratio of 10.9 (85), and another study using combined data from multiple continents reported a relative risk of 13.0 (86). These figures compare with population estimates for aplastic anaemia of 1–2 per million in Europe and two to three times that in Southeast Asia (83). Interestingly, there have been case reports of the concomitant occurrence of rashes and severe blood dyscrasias (leukopaenia and thrombocytopaenia) attributable to carbamazepine (87), therefore suggesting the clinical prudence of considering severe blood dyscrasias in addition to the rare drug hypersensitivity syndrome (88) in the event of the more readily apparent carbamazepine-induced skin eruptions (87). Only isolated reports of thrombocytopaenia in association with carbamazepine have been published (81, 89).

Valproate. Thrombocytopaenia (platelet count $< 150{,}000/mL$) is the best-documented haematological ADR for valproate. Clinically significant bleeding is generally associated with severe thrombocytopaenia (counts $< 50{,}000$), which is uncommonly observed with valproate treatment (90). In a retrospective cohort study of hospitalised psychiatric patients, 12% had mild to moderate thrombocytopaenia, but none had clinical complications or severe thrombocytopaenia, defined in that study as a platelet count of less than $40{,}000/mL$ (91). In another study, none of 1,251 hospitalised psychiatric patients on valproate had a platelet count below $100{,}000/mL$ (81). In neurological populations, rates of 5–40% have been reported for thrombocytopaenia associated with valproate (90). Thrombocytopaenia seems to occur at higher valproate doses and blood levels (90, 91), develop over months after initiating treatment, and resolve with dose reduction (90). However, there have been case reports of clinically significant coagulopathies that include various combinations of thrombocytopenia, platelet dysfunction, hypofibrinogenaemia, secondary von Willebrand disease, and abnormalities in other clotting factors, but these effects tend to reverse with treatment discontinuation (92). Bone marrow suppression (90) and aplastic anaemia (85) have been reported in association with valproate, but are rare.

Hepatic ADRs

Both carbamazepine and valproate are known to cause elevations in serum liver enzymes, which in themselves do not necessarily indicate serious liver injury (93). However, both agents are also known to be infrequently associated with idiosyncratic hepatitis, but the pathogenic mech-

anism and clinical presentation differ for the two drugs.

Carbamazepine. As a hepatic enzyme inducer, carbamazepine may cause benign increases in gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) (93). It is also associated with asymptomatic and often transient increases of liver enzymes (94), which bear unclear relationships to liver injury. As a guide, other authors have suggested that, in the absence of alternative causes of hepatic dysfunction, alanine aminotransferase (ALT) levels that are greater than 2–3 times above the upper limit of normal be considered a sensitive but nonspecific indicator of drug-induced hepatitis (95, 96). Biochemical liver abnormalities are of greater concern if they occur alongside physical symptoms and other biochemical markers of impaired liver function, such as hyperbilirubinaemia, hypoalbuminaemia, and abnormal coagulation indices (97). However, the precipitous onset of drug-induced hepatitis restricts the usefulness of liver function monitoring, and detection must primarily rely on the recognition of hepatitis symptoms, which may include malaise, anorexia, abdominal discomfort, pruritis, and jaundice. Carbamazepine-induced hepatitis is typically an immune-mediated, hypersensitivity syndrome, and has a mixed hepatitic-cholestatic picture, often associated with fever, rash, and eosinophilia. It tends to occur early (within the first eight weeks) in the course of treatment, resolve on carbamazepine discontinuation (although fatalities have been reported), and recur on rechallenge (95, 98, 99). Carbamazepine-induced hepatitis is uncommon, with one study reporting an incidence of 21.9 per 100,000 in a sample of 1.6 million patients aged between five and 75 (100).

Valproate. Asymptomatic and often dose-related elevations in liver enzymes can commonly occur with valproate (101, 102), but valproate-induced hepatic injury is rare. Combining data from 19 clinical trials, aminotransferase levels were elevated in 11% of 1,197 participants (101). In comparison, the estimated incidence of hepatic injury that resulted in referral to hospital or a specialist was 31.1 per 100,000 patients in a general practice database study (100). In a six-year period from 1987 to 1993, 29 of one million individuals who received new prescriptions for valproate developed fatal liver failure (103). In contrast with carbamazepine, valproate-induced hepatitis is non-immune-mediated (95), and is most likely to occur in the first 3–6 months of treatment, although it has been reported to develop after several years (102). Children under two years of age, particularly those receiving multiple anticonvulsants and those with mental retardation, developmental delay, metabolic disorders, congenital abnormalities, and other neurologic diseases, have been described to be at greater risk of developing valproate-induced hepatitis (98, 103, 104), but patients without these risk factors may also develop this ADR. The mechanism is thought to be unrelated to hypersensitivity, but to reflect mixed idiosyncratic/hepatotoxic effects of valproate and/or its metabolites, which may be enhanced in the presence of other hepatically active drugs (98, 101). In a retrospective study of fatal hepatotoxicity associated with valproate in the US, the most common presenting features included decreased alertness, jaundice, vomiting, haemorrhage, anorexia, and oedema (103).

Dermatological ADRs

Carbamazepine, valproate, and lamotrigine have all been associated with mucocutaneous syndromes. The boundaries separating many of these are indistinct and their classification remains under debate (105). A widely used classification distinguishes between the syndromes of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) with spots and without spots, and SJS/TEN overlap, based on the presence, morphology, and extent of cutaneous and mucosal involvement (106–108). SJS and TEN are more commonly triggered by drugs that include anticonvulsants, whereas EM is mostly triggered by infections (106). To briefly summarise, EM presents with acrally distributed, cutaneous typical target and raised atypical target lesions, involving less than 10% of the body surface area (BSA). There may be mucositis affecting one or rarely two sites, most often the oral mucosa (manifesting with erythematous macules, papules, vesicles, erosions, and ulcers), but any mucosal surface (such as the conjunctivae, respiratory, gastrointestinal, and genitourinary tracts) may be involved. SJS similarly affects less than 10% of the BSA, but differs from EM in the presence of flat atypical target lesions and macules, a more widespread distribution, and prodromal flu-like systemic symptoms. More extensive cutaneous involvement of 10–30% of the BSA is termed the SJS/TEN overlap syndrome. TEN with spots is characterised by epidermal detachment involving over 30% of the BSA in addition to the clinical features of SJS, while TEN without spots describes epidermal detachment involving more than 10% of the BSA without macules or target lesions (106, 108). Mortality rates have been reported to be 3%

(109) and 13% (110) for SJS, and to vary from 3.2% for the least severe TEN to 90% for the most severe cases (108).

SJS and TEN are fortunately rare, with one study estimating their combined risk per 10,000 new users to be 2.5 for lamotrigine, 1.4 for carbamazepine, and 0.4 for valproate. Notably, over 90% of these cases occurred within the first 63 days of initiating treatment (111). A case–control study reported the relative risk of developing SJS or TEN to be 11 for carbamazepine and 12 for valproate (112), although the association with valproate became nonsignificant after confounding variables were taken into account (113). For lamotrigine, the risk of 'serious rash' (defined as rash requiring hospitalisation and discontinuation of lamotrigine, SJS, or TEN) was 0.1%, which was calculated from combining data from 12 clinical trials in bipolar disorder and unipolar depression (114, 115). None of the three cases was diagnosed with SJS or TEN, and all resolved on discontinuation of lamotrigine (114). In contrast, benign rash was far more common and developed in 8.3% of those on lamotrigine and in 6.4% of those on placebo in the controlled trial samples (115). A higher risk of 0.3% had previously been reported for SJS and TEN in adults (116). This difference may be attributable to the introduction of cautious titration and monitoring practices for lamotrigine, especially when used with drugs like valproate that inhibit its metabolism (116). Benign and serious dermatological reactions can be difficult to differentiate, and Calabrese et al. have devised a flow chart to assist in this endeavour (115).

Reduced bone density

Reduced bone mineral density (BMD) has been described with valproate and carbamazepine, but this literature is based on anticonvulsant use in epilepsy rather than bipolar disorder (117). The relevance of low BMD is that it underlies osteoporosis, the most common bone disease affecting men and women, and its diagnosis is based on the location of individual BMD measurements within the population distribution (118). Although the association of anticonvulsants with reduced BMD and fractures is well recognised, quantification of BMD reduction for individual anticonvulsants is precluded by methodological constraints such as small sample sizes, lack of controls, variable BMD measurements, differing anticonvulsants, and confounding factors that include fractures attributable to seizures (117). The mechanisms whereby anticonvulsants may cause reduced BMD are not clearly understood, but several mechanisms have been proposed, including accelerated vitamin D metabolism, reduced intestinal calcium absorption, hormonal effects such as secondary hyperparathyroidism and sex hormone changes, induction of a high bone remodelling state, and direct inhibition of osteoblast-like cells (117). These mechanisms require further study, and may differ for individual anticonvulsants. In this context of incomplete understanding of the pathogenesis, risk factors, time course, and extent of bone adverse effects, there is no consensus on the optimal approach to bone safety monitoring during treatment with anticonvulsants. Bone densitometry and measurements of 25-hydroxyvitamin D, parathyroid hormone, serum calcium, and phosphorous have been suggested (117–119). Preventive advice on diet, exercise, adequate sun exposure, smoking cessation, and avoidance of excessive alcohol use may also be helpful (117).

Hyponatraemia

Hyponatraemia, defined as a serum sodium concentration below 135 mmol/L, has been well described in association with carbamazepine, with one study reporting a prevalence of 13.5% (120) and others giving a range of 4.8–40% (121). It is considered mild with levels between 125 and 135 mmol/L, significant with levels between 115 and 125 mmol/L, and serious with levels < 115 mmol/L (122). The clinical features of hyponatraemia depend on its severity and time frame of development. Severe acute-onset (generally when serum sodium falls < 120 mmol/L in < 48 h) hyponatraemia is a medical emergency as it may lead to cerebral oedema, irreversible neurological damage, respiratory arrest, brainstem herniation, and even death (123). In contrast, chronic-onset (> 48 h) hyponatraemia allows homeostatic adjustment, and mild hyponatraemia is usually asymptomatic (123), but the presence of subtle neurocognitive impairments involving attention and gait have been highlighted in seemingly asymptomatic patients (124). Nonspecific symptoms such as lethargy, headaches, and nausea may appear at levels < 120 mmol/L, which may progress to gastrointestinal symptoms, tremors, dysarthria, hemiplegia, psychosis, and seizures at lower levels (123).

Hyponatraemia associated with carbamazepine is usually chronic and 'asymptomatic', and there has been no reported fatality (122). In general, risk factors for hyponatraemia include older age, reproductive age for women, psychogenic polydipsia, renal failure, postoperative state, and concomitant use of medications that may also cause hyponatraemia (122). Although the syndrome of inappropriate ADH secretion (SIADH) has often been regarded as the main cause, the mechanisms underlying carbamazepine-induced hyponatraemia have not been

fully clarified, and may involve altered sensitivity or set-point of hypothalamic osmoreceptors to serum osmolality, increased renal tubular sensitivity to ADH, and SIADH (121, 125, 126). Even though the continuation of carbamazepine is often recommended for asymptomatic hyponatraemia (122), its detection and monitoring are useful as hyponatraemia may progress from asymptomatic to symptomatic, especially in the presence of conditions such as polydipsia, postoperative states, and polypharmacy (122, 126). Chronic hyponatraemia needs to be gradually corrected, as aggressive treatment carries the risk of osmotic demyelination due to rapid fluid shift (123).

Weight gain

Valproate and, to a lesser extent, carbamazepine are associated with weight gain, while lamotrigine is considered to be weight neutral (127). Among more recent literature, a 24-week, randomised, comparative monotherapy trial in epilepsy found valproate to be associated with a mean weight gain of 3.8 kg, whereas carbamazepine and lamotrigine were not associated with weight gain, although the mean ages differed for the groups (128). Other trials have likewise shown higher rates and magnitude of weight gain in association with valproate relative to carbamazepine [12% versus 2% gaining weight; +2.0 kg (+2.8%) versus −0.1 kg (−0.1%) mean weight change] (129) and to lamotrigine (38% versus 8% gaining ≥ 10% total body weight; 5.8 kg versus 0.6 kg mean weight gain over 32 weeks) (130). In the psychiatric literature, weight gain has been more frequently associated with valproate compared to lithium and placebo in a 52-week trial (21% versus 13% versus 7%) (131), but lamotrigine has not been associated with weight gain (70). In comparison with olanzapine, a lower frequency and lesser extent of weight gain have been reported in association with valproate in the short term (10% versus 25% and 2.5 kg versus 4.0 kg weight gain in valproate and olanzapine groups, respectively, over 12 weeks) (132), and in the longer term (11.9% versus 24.8% and 1.22 kg versus 2.79 kg in valproate and olanzapine groups, respectively, over 47 weeks) (133). However, there were no significant differences between the valproate and olanzapine groups in weight gain from baseline from weeks 19–47 in the maintenance study (133). For valproate, weight gain has been reported to be associated with serum levels greater than 125 μg/mL (131).

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) has been associated with valproate. PCOS may be considered to be an endocrine disorder of excessive androgen secretion or activity. It is common among women of reproductive age, but its diagnostic criteria, classification, and epidemiology remain under debate (134). It is believed to be heterogeneous, with interacting genetic and environmental causative factors that may involve pathogenic mechanisms such as defective ovarian steroidogenesis, abnormal hypothalamic-pituitary axis, and insulin resistance (135). The key clinical features of PCOS are hyperandrogenism (hirsutism, acne, androgenic alopecia, biochemical hyperandrogenaemia), chronic anovulation (oligomenorrhoea, amenorrhoea, anovulatory cycles), and polycystic ovaries on ultrasonography (134). However, the diagnosis of PCOS requires the exclusion of alternative causes of these clinical features, such as hyperprolactinaemia, thyroid dysfunction, and Cushing's syndrome (135). The salience of PCOS relates not only to cosmetic and related psychological concerns, but also to complications of infertility and metabolic disturbances that include central obesity, hypertension, dyslipidaemia, and diabetes mellitus (134, 135).

In a study of women with bipolar disorder who were aged between 18 and 45 years, the incidence of PCOS (defined as new-onset oligomenorrhoea and hyperandrogenism) was 10.5% for those treated with valproate (n = 86), compared with 1.4% for those on other anticonvulsants or lithium (n = 144), giving a relative risk of 7.5. Furthermore, it was observed that all cases of oligomenorrhoea developed within the first 12 months of initiating valproate, with a median onset time frame of three months (136). In a follow-up study, PCOS continued in the three women who remained on valproate, but resolved in three of the four women who discontinued this treatment (137). Others have similarly reported improvement in the clinical features of PCOS after switching from valproate to lamotrigine (138), although further prospective studies are needed to confirm the reversibility of valproate-related PCOS (137). Increased rates of hyperinsulinaemia and lipid and reproductive hormone abnormalities have also been found in men treated with valproate (139–141).

Acute pancreatitis

There have been multiple case reports and case series of acute pancreatitis occurring in association with valproate use over the last three decades (142, 143). It is considered to be an uncommon idiosyncratic event, but the incidence is difficult to establish due to inconsistent reporting, reliance on case report data, and the presence of confounding aetiological factors in many cases (144). Using data from 34 clinical trials that included 3,007

valproate-treated patients, a study reported an estimated incidence of two per 1,044 patient-years (144). Valproate-related pancreatitis has more commonly been reported in children, but this may be influenced by extraneous factors, and pancreatitis can occur at any age (142). There has been no apparent relationship with gender, duration of treatment, serum valproate level, or the use of concomitant anticonvulsants (142). Acute pancreatitis may be fatal, and the possibility of its occurrence should be borne in mind whenever a patient presents with abdominal pain, abdominal distension, vomiting, or fever during valproate treatment (143).

Hyperammonaemic encephalopathy

Valproate-induced hyperammonaemic encephalopathy (VHE) is an uncommon but potentially fatal condition, the treatment of which hinges on its diagnosis and discontinuation of the drug (145). The pathogenic mechanisms underlying VHE are not fully understood, but hyperammonaemia is believed to be of key importance and results in increased glutamine levels in the brain and cerebral oedema (145). However, the absence of hyperammonaemia has been reported in some cases (146). VHE typically develops within days or weeks of initiating valproate, but may occur after months to years (146). Its development is unrelated to valproate dose or serum level, or the severity of hyperammonaemia (145, 146). Clinically, VHE may manifest with different symptoms of acute or subacute onset, including confusion, reduced conscious state, cognitive impairment, neurological signs, irritability, agitation, vomiting, lethargy, and seizures (145, 146), some of which may resemble symptoms of the underlying psychiatric disorder. Other authors have recommended that serum ammonia be measured if neurological symptoms emerge in patients taking valproate (145, 146).

Drug interactions

Of all drug interactions involving carbamazepine, valproate, and lamotrigine, the interaction between lamotrigine and valproate and between carbamazepine and hormonal contraceptives are highlighted in these guidelines due to their potential serious consequences and likelihood of being concurrently prescribed in the bipolar treatment setting. Valproate can increase lamotrigine levels via inhibiting its hepatic glucuronidation, thereby increasing the risk of SJS (114, 116). It should be noted that valproate reduces lamotrigine clearance and increases its half-life even in the presence of hepatic enzyme-inducers such as carbamazepine (114). The use of half the usual dosages for lamotrigine initiation and target stabilisation is recommended when valproate is also prescribed (114). The interaction between carbamazepine and hormonal contraceptives is emphasised because of the risk of contraceptive failure that is compounded by the known teratogenic risks of carbamazepine (described below in 'Pregnancy and Breastfeeding'). This arises from hepatic P450 enzyme induction by carbamazepine, and the efficacy of combined oral contraceptive pills, combined contraceptive patches, the progestogen only pill, progestogen implant, and postcoital contraception ('morning after pill') can all be reduced. Medroxyprogesterone acetate depot injections (Depo-Provera), hormone-releasing intrauterine system, and copper-containing intrauterine contraceptive devices, in addition to barrier methods, are contraceptives that are not affected by carbamazepine. These methods are preferred when enzyme-inducing anticonvulsants are used. If they are not suitable, however, higher doses of oral hormonal contraceptives and using combined oral contraceptive pills in a tricycling regime (three continuous cycles of hormonal contraceptives followed by four pill-free days) have been suggested as alternative options (147), although these strategies have not yet been demonstrated to be efficacious in conjunction with carbamazepine (148).

Safety monitoring recommendations of previous guidelines

Currently existing monitoring guidelines give varying but overlapping recommendations, which are summarised in Table 4. In addition to these safety monitoring recommendations, the NICE guidelines advocate the avoidance of valproate use in women under the age of 18, due to concerns about PCOS and the heightened risk of unplanned pregnancies in this age group. These guidelines also discourage the routine prescription of valproate for women of childbearing potential, and emphasise the risks associated with its use during pregnancy and the need for adequate contraception (12). Although teratogenicity and fertility considerations are important, they must be weighed against the reality that of the limited number of efficacious pharmacological treatments available, none is free from potentially serious ADRs. Besides official guidelines, individual authors have also proposed safety monitoring recommendations. In her review on anticonvulsant safety monitoring, Harden (79) has recommended baseline FBC, LFTs, electrolytes, and renal function for all anticonvulsants; FBC and LFTs several times within the first six months of

Table 4. Safety monitoring recommendations of previous guidelines for anticonvulsants

Guidelines	Recommendations
American Psychiatric Association (APA) practice guidelines (10)	**Baseline** ▪ Valproate and carbamazepine: history of hepatic and haematological (including coagulation) problems, full blood count, and liver function tests ▪ Carbamazepine: electrolytes and renal function **Serum levels** ▪ Carbamazepine: steady state level ▪ Valproate: as clinically indicated **Longitudinal** ▪ Carbamazepine: full blood count and liver function tests every 2 weeks for the first 2 months, then reduce to every 3 months for the duration of treatment ▪ Valproate: full blood count and liver function tests every 6 months
The National Institute for Health and Clinical Excellence (NICE) guidelines (12)	**Baseline** ▪ Valproate and carbamazepine: height, weight, full blood count, and liver function tests **Serum levels** ▪ Carbamazepine: every 6 months ▪ Valproate: routine levels not recommended **Longitudinal** ▪ Valproate and carbamazepine: full blood count and liver function tests after 6 months, weight monitoring for those with weight gain ▪ Carbamazepine: electrolytes and urea every 6 months
The Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines (13, 14)	**Baseline** ▪ General baseline investigations as listed in Table 1 **Serum levels** ▪ Valproate: establish level of 400–700 mmol/L on 2 consecutive occasions, then every 3–6 months thereafter (more frequent for patients on concurrent hepatic enzyme-inducing medications) **Longitudinal** ▪ Full blood count and liver function tests after 4 weeks, then at intervals of 3–6 months ▪ Closer monitoring is advised in children under 10 years of age, the elderly, medically ill patients, and those on multiple medications

initiating valproate; FBC, LFTs, and serum chemistry at least once after initiating carbamazepine; FBC annually for both valproate and carbamazepine; and vigilance for skin rash within the first two months of initiating lamotrigine. Furthermore, this author has suggested a cautious approach to bone density monitoring, consisting of preventive advice on calcium intake and exercise, bone densitometry, and urine N-telopeptide levels (as a measure of bone turnover) in perimenopausal women.

ISBD monitoring recommendations

We propose a set of monitoring recommendations for valproate, carbamazepine, and lamotrigine in bipolar disorder treatment that combines elements of the existing guidelines, with modifications considered to more closely approximate an optimal balance between cost and safety (Table 5 and Fig. 1). However, as the most severe ADRs associated with mood-stabilising anticonvulsants (such as serious blood dyscrasias, hepatitis, mucocutaneous syndromes, acute pancreatitis, and VHE) are rare and idiosyncratic, it must be appreciated that these are best monitored with clinical vigilance rather than laboratory investigations, due to the acuity of their onset and unpredictability of their occurrence.

At baseline, no additional investigations beyond the basic battery are required, as weight and waist circumference, FBC, LFTs, and EUC are already included. However, specific history of haematological and hepatic disease should be elicited prior to commencing valproate or carbamazepine, and the suitability of these agents and the need for closer monitoring should be assessed in the presence of such diseases.

In longitudinal monitoring, we suggest that weight, FBC, LFTs, and inquiry of menstrual changes for women of reproductive age be performed every three months for the first year of valproate therapy, and annually thereafter. In women who report oligomenorrhoea or features of hyperandrogenism, a pelvic ultrasound may be indicated, and in those with cardiovascular risk factors, blood pressure, fasting glucose, and lipid profile should be monitored as described below for atypical antipsychotics. For carbamazepine, we recommend monthly FBC, LFTs, and EUC for the first three months, followed by annual repeat testing. Additionally, patients should be alerted to promptly report the emergence of cutaneous

Table 5. ISBD recommended baseline and longitudinal safety monitoring specific to patients on valproate, carbamazepine, and lamotrigine, in addition to the basic monitoring recommendations

	Recommendations
Baseline	▪ **Valproate and carbamazepine:** check for history of haematological or hepatic disease
Serum levels	▪ **Valproate and carbamazepine:** 2 levels to establish therapeutic dose (separated by 4 weeks for carbamazepine), then as clinically indicated
Longitudinal	▪ **Valproate[a]:** weight, full blood count, liver function test and inquiry of menstrual changes (for women of reproductive age) every 3 months for the first year, then annually
	▪ **Carbamazepine:** monthly full blood count, liver function test, and electrolytes, urea, and creatinine for the first 3 months, then annually; review oral contraceptive efficacy
	▪ **Carbamazepine and lamotrigine:** remind patients to promptly withhold medications and seek medical attention within 24 h of emergence of dermatological eruptions
	▪ **Valproate and carbamazepine:** advice on bone health

[a]In those with cardiovascular risk factors, blood pressure, fasting glucose and lipid profile should be monitored in a similar fashion as described for atypical antipsychotics.

and/or mucosal eruptions, which may signal a serious dermatological ADR, especially when occurring within the first few months of treatment. For both valproate and carbamazepine, advice on maintaining bone health (such as dietary calcium intake, safe sun exposure, and regular exercise) is prudent and bone densitometry may be warranted in high-risk patients, e.g., children, perimenopausal women, the elderly, and those with minimal sun exposure. Vitamin D level monitoring may be of value. The risk of bone loss may be heightened when prolactin-elevating atypical antipsychotics, such as risperidone, are concomitantly prescribed.

We recommend performing at least two drug levels in the initiation phase of treatment with valproate or carbamazepine, despite the unclear implications of the anticonvulsant serum levels in the treatment of mood disorders, in order to establish nontoxic and reference levels for the individual patient. Thereafter, repeating drug levels is only recommended to determine treatment adherence or if clinically indicated, usually in the context of dose adjustments, addition of potentially interacting medications, and emergence of toxic side effects. A particular caution with carbamazepine should be kept in mind, in that it is a cytochrome P450 inducer that increases its own metabolism as well as that of other medications, such as oral contraceptives, valproate, lamotrigine, some antidepressants and antipsychotics, and protease inhibitors. The concomitant use of carbamazepine with these agents should therefore be accompanied by the monitoring of clinical status and the need to adjust dosages. In particular, the potential for lowered efficacy of combined oral contraceptive pills, combined contraceptive patches, the progestogen only pill, progestogen implant, and postcoital contraception would necessitate a review of contraceptive management. Due to the auto-induction of its metabolism, it is recommended that the second serum carbamazepine level be performed after an interval of approximately four weeks.

No specific investigations are required for lamotrigine, but patients should be alerted to and periodically reminded of the risk of SJS and TEN, and should be advised to withhold lamotrigine and present for medical evaluation if suspicious symptoms develop. As described above, warning signs of a serious dermatological ADR may include the emergence of cutaneous macules and characteristic lesions with a target-like appearance, mucositis that may involve the conjunctivae, mouth, respiratory, gastrointestinal, and genitourinary tracts, and associated systemic flu-like symptoms. Skin eruptions in association with mucosal involvement and/or systemic symptoms must be medically assessed immediately, but skin rash in the absence of other accompanying features should still be medically assessed within 24 h.

Atypical antipsychotics

These guidelines focus on the atypical antipsychotics aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone, all of which have demonstrated efficacy in randomised controlled trials for bipolar disorder (149, 150). There is as yet insufficient evidence for the efficacy of amisulpride and the risperidone metabolite, paliperidone, in treating bipolar disorder, and clozapine has specific monitoring guidelines and a principal indication in treatment-resistant schizophrenia. In terms of ADRs, the foremost concern with the group of atypical antipsychotics under discussion is the heightened risk of metabolic complications, especially when superimposed on a population already susceptible to these chronic health conditions. Other major ADRs are cardiac effects and hyperprolactinaemia. In keeping with the primary focus of these guidelines, extrapyramidal side effects

(EPS) will only be briefly discussed from the perspective of safety concerns.

Metabolic syndrome

Atypical antipsychotics have known associations with weight gain, dyslipidaemias, and diabetes mellitus, and although hypertension is an uncommon side effect, it can develop in the context of weight gain (151). Metabolic risks may be compounded by antipsychotic polytherapy (152). Data on the metabolic complications of individual atypical antipsychotics are limited by the rarity of long-term, prospective, randomised, comparative studies, and reported risks have been derived from studies with different levels of methodological rigor and producing inconsistent results (153, 154).

Nevertheless, evidence suggests that the risk of weight gain is present with all atypicals. With the exception of clozapine, the likelihood of weight gain is highest with olanzapine, intermediate with risperidone and quetiapine, and lowest with aripiprazole and ziprasidone (155). A meta-analysis of weight gain with short-term (10-week) antipsychotic treatments estimated olanzapine to be associated with greater increase [4.15 kg (9.15 lb) over 10 weeks] than risperidone [2.10 kg (4.63 lb)] and ziprasidone [0.04 kg (0.09 lb)]. In comparison, the corresponding figures were 4.45 kg (9.81 lb) for clozapine, 2.92 kg (6.44 lb) for sertindole, 3.19 kg (7.03 lb) for thioridazine, 2.58 kg (5.69 lb) for chlorpromazine, 1.08 kg (2.38 lb) for haloperidol, 0.43 kg (0.95 lb) for fluphenazine, and 1.33 kg (2.93 lb) for nonpharmacological controls (156). In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study in schizophrenia, the mean weight changes per month of treatment were 0.91 kg (2.0 lb) for olanzapine, 0.23 kg (0.5 lb) for quetiapine, 0.18 kg (0.4 lb) for risperidone, and −0.14 kg (−0.3 lb) for ziprasidone. The respective proportions of patients who gained over 7% of their baseline body weight over the course of the study (up to 18 months) were 30%, 16%, 14%, and 7% (157).

Although dyslipidaemias and diabetes mellitus can occur independently of weight gain, the relative risk profiles for individual atypical agents are somewhat similar for these metabolic conditions (155, 158). Data from the CATIE study showed significant increases in glycosylated haemoglobin (exposure-adjusted mean increase of 0.40%), cholesterol [exposure-adjusted mean increase of 9.4 mg/dL (0.24 mmol/L)] and triglycerides [exposure-adjusted mean increase of 40.5 mg/dL (0.46 mmol/L)] for olanzapine, and in cholesterol [exposure-adjusted mean increase of 6.6 mg/dL (0.17 mmol/L)] and triglycerides [exposure-adjusted mean increase of 21.2 mg/dL (0.24 mmol/L)] for quetiapine. Ziprasidone and risperidone were not associated with increases from baseline on these measures in this study (157). An open-label, randomised study of schizophrenia and bipolar disorder patients up to 12 months similarly demonstrated significantly higher haemoglobin A_{1C} and dyslipidaemia for the olanzapine compared to the risperidone group. Furthermore, the increase in lipids and haemoglobin A_{1C} for the olanzapine group occurred independently of baseline or change in BMI (159). A pharmacoepidemiological study with matched case–control analysis of hyperlipidaemia during antipsychotic treatment compared to no treatment obtained significant odds ratios of 1.56 for olanzapine and 1.40 for ziprasidone, but an insignificant odds ratio for aripiprazole. Odds ratios for clozapine and first-generation antipsychotics were 1.82 and 1.26, respectively (160). For diabetes, a review of 15 retrospective studies found inconsistent results for the risk associated with atypical antipsychotics relative to typical antipsychotics (153). A review of 22 prospective, randomised, controlled trials similarly found no consistent differences in the incidence of glucose abnormalities between patients on various atypical antipsychotics and their comparator drugs (active medications or placebo), although these studies were mostly short term, measured different glucose parameters, and were insufficiently powered to detect glucose differences between antipsychotics (161). Two population-based case control studies using a US medical insurance claims database reported that, compared with patients on typical antipsychotics, those on clozapine, risperidone, olanzapine, and quetiapine had higher hazard ratios for new-onset diabetes, whereas ziprasidone was not associated with significant hazard ratios in either study (162, 163). Atypical antipsychotic treatment has also been associated with diabetic ketoacidosis and hyperglycaemic hyperosmolar states (164), and the occurrence of diabetic ketoacidosis in patients not previously diagnosed with diabetes has been reported during treatment with olanzapine (165), aripiprazole (166, 167), quetiapine, and risperidone (168). Diabetes in the setting of treatment with atypical antipsychotics may involve the uncovering of underlying predisposition, and may be reversible in some, but not all cases (7).

Cardiac ADRs

Cardiac ADRs of the atypical antipsychotics may be divided into conditions associated with myocardial disease and those associated with abnormalities of cardiac repolarisation. Autonomic side effects such as postural hypotension

and tachycardia/bradycardia may also occur (169). Myocarditis and cardiomyopathy are infrequent but potentially fatal ADRs that have been most strongly associated with clozapine (170–173).

For the atypical antipsychotics considered in these guidelines, the most relevant cardiac ADR is prolongation of the rate-corrected QT (QTc) interval on electrocardiography. The QT interval is a marker of ventricular depolarisation and repolarisation, and its prolongation may increase the risk of ventricular tachyarrhythmias, in particular torsades de pointes (TdP). Usually self-limiting, TdP can nevertheless evolve into ventricular fibrillation and cardiac arrest (169, 174, 175). Most medications that prolong the QTc interval mediate this through their action on the I_{Kr} potassium channels, which slow the efflux of potassium and affect the rapid component of the delayed rectifier potassium current (176). It needs to be appreciated that QTc prolongation is only an indirect marker of potential pro-arrhythmic states, and that the extent of QTc prolongation is not directly related to TdP risk (169, 176, 177). Furthermore, there is considerable QTc interval variability in healthy adults due to biological and environmental factors (178, 179), and consensus has not been reached with regard to a normal upper limit for the QTc. Commonly used upper thresholds for prolonged QTc are 450 ms for males and 460 ms for females, based on the 99th percentile figures for population QTc distributions (180, 181). Another approach employs ranges for the QTc (adult males: normal $<$ 430 ms, borderline 431–450 ms, prolonged $>$ 450 ms; adult females: normal $<$ 450 sec, borderline 451–570 ms, prolonged $>$ 470 ms) (182). Although there is no clear lower limit for QTc prolongation below which one is free from pro-arrhythmic risk (178), TdP is considered rare when the QTc interval is less than 500 ms (169).

Other than sertindole, ziprasidone is considered the most likely of the atypicals to cause QTc prolongation (174, 183). Early placebo-controlled trials of ziprasidone reported an increase in the QTc interval of approximately 10 ms at a daily dose of 160 mg, and although two of 2,988 (0.6%) of ziprasidone-treated patients developed QTc intervals of greater than 500 ms, ziprasidone was not unequivocally implicated in either case (184). In a prospective, randomised study of electrocardiograms (ECGs) obtained at maximal blood concentrations and at steady state, ziprasidone (at a daily dose of 160 mg) was associated with a mean QTc increase of 15.9 ms, compared with 5.7 ms for quetiapine (750 mg), 3.9 ms for risperidone (6–8 mg), 3.6 ms for risperidone (16 mg), and 1.7 ms for olanzapine (20 mg) (183). In the same study, QTc did not significantly increase for any agent when cytochrome P450 inhibitors were added to increase drug levels, and no participant recorded a QTc interval greater than 500 ms. Aripiprazole was not included in this study, but has not been found to cause significant QTc prolongation elsewhere (185). The implication of ziprasidone-related QTc prolongation on clinical outcomes was investigated in the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) study (186), in which 18,154 patients with schizophrenia were randomised to open-label ziprasidone or olanzapine treatment. The primary outcome measure of this otherwise naturalistic study was nonsuicide mortality during the year after initiating treatment, which was similar for the two treatment groups (one-year incidence of nonsuicide mortality was 0.91% for ziprasidone and 0.90% for olanzapine), with both yielding a relative risk of 1.01. All-cause and cardiovascular mortality were similar between ziprasidone and olanzapine recipients, although all-cause hospitalisations and treatment dropout at six months were higher for the ziprasidone group (187).

Drug-induced TdP usually occurs in conjunction with other risk factors. In a study of 249 cases of TdP associated with noncardiac drugs, virtually all patients had one other pro-arrhythmic risk factor and 71% had two or more, the most common being female gender (188). Other risk factors include structural heart disease, bradycardia and atrioventricular block, prolonged baseline QTc, family history of congenital long QT syndrome, prior history of drug-induced TdP, electrolyte disturbances (e.g., hypokalaemia, hypomagnesaemia, hypocalcaemia), multiple QT-prolonging drugs, high drug dosages or drug interactions that result in increased levels of pro-arrhythmic agents, hepatic impairment, and genetic polymorphisms that involve potassium channels and drug metabolism (e.g., cytochrome P450 enzymes) (175, 176). For safety monitoring considerations, it is preferable to assess the risk of QTc prolongation and avoid, where possible, QT-prolonging medications in patients with significant pro-arrhythmic risk factors. Whilst some clinicians would routinely perform ECGs before and after initiating various noncardiac QT-prolonging drugs, others have questioned the yield of routine ECGs given the rarity of the problem and the greater importance of assessing for proarrhythmic risk factors, and have therefore recommended ECGs only in patients with unmodifiable risk factors who are starting on QT-prolonging drugs (176, 178, 180). However, the QTc interval is only one indicator of risk for cardiotoxicity and TdP, and other

clinical risk factors should not be overlooked (174, 175).

Hyperprolactinaemia

Prolactin is secreted by lactotrophs in the anterior pituitary under the inhibitory control of dopamine via D_2 receptors; therefore, D_2 antagonists, such as most antipsychotics, may cause hyperprolactinaemia. This may be symptomatic with its manifestations possibly reflecting direct effects on breast tissue and/or hypothalamic-pituitary-gonadal axis suppression, such as breast enlargement and galactorrhoea, menstrual irregularities (e.g., amenorrhoea, oligorrhoea) and sexual dysfunction (e.g., loss of libido, impaired orgasm) in women, and gynaecomastia and sexual dysfunction (e.g., loss of libido, impaired orgasm, erectile and ejaculatory dysfunction) in men (189, 190). The long-term effects of sustained hyperprolactinaemia are not yet established, but there is inconclusive evidence that prolonged hyperprolactinaemia may be a risk factor for pituitary tumours and breast cancer (189, 191, 192). Prolonged hyperprolactinaemia, primarily studied in connection with prolactin-secreting tumours, has been correlated with osteopaenia and osteoporosis only when associated with hypogonadism (189, 191). Among the atypical antipsychotics considered in these guidelines, risperidone has the greatest propensity to cause hyperprolactinaemia, which may be comparable or greater than that associated with typical antipsychotics. Olanzapine generally does not increase prolactin, but may cause nonsignificant sustained hyperprolactinaemia at higher doses. Ziprasidone may increase prolactin, but generally only transiently, and neither aripiprazole nor quetiapine has been associated with prolactin elevation (189).

Haematological ADRs

Apart from the established association between clozapine and agranulocytosis (171), the other atypical antipsychotics are generally considered to have a benign haematological profile. There have been isolated reports of neutropaenia and thrombocytopaenia with olanzapine, risperidone, and quetiapine, and neutropaenia with ziprasidone (193). In a large prospective study of hospitalised patients (194), neutropaenia (defined as neutrophil counts < 1500/mL) was definitely or probably caused by atypical antipsychotics other than clozapine in 0.03% of patients, including 0.05% of those treated with olanzapine and 0.01% of those on risperidone. The only case of thrombocytopaenia attributable to a nonclozapine atypical antipsychotic was associated with risperidone. The peak incidence for neutropaenia (except due to clozapine) was between 20 and 30 days after initiating treatment, and stopping the medication generally led to rapid improvement of cell counts, with full recovery reported in all cases.

Extrapyramidal side effects

EPS refer to Parkinsonian tremor, rigidity, bradykinesia, akathisia, dystonia, and tardive dyskinesia, which are not uncommonly associated with atypical antipsychotics, even though they are considered less problematic than typical antipsychotics in this regard (195, 196). The propensity for EPS differentiates among the atypical agents, from the high D_2 binding affinity agents (risperidone, ziprasidone, and aripiprazole) having the greatest liability, low D_2 binding affinity agents (clozapine and quetiapine) having the least, and the middle affinity agent olanzapine having intermediate risk (196). The risk of EPS is also dependent on the rate of dose escalation, target dose, and individual susceptibility factors (197). In spite of the prevalence of EPS and the clinical significance of tardive dyskinesia, the only life-threatening EPS is severe acute dystonia involving the airways, which is a rare phenomenon (198). Most dystonias occur within 24–48 h of initiating the antipsychotic, increasing its dose, or withdrawing anticholinergic prophylaxis, with 95% of cases occurring within 96 h. Treatment is effective with anticholinergics, which may be administered intravenously in life-threatening dystonias (198).

Safety monitoring recommendations of previous guidelines

The most established safety monitoring guidelines for antipsychotics relate to the haematological risks of clozapine, but guidelines on its other associated risks have also been published (9, 199). Comprehensive recommendations for the monitoring of the broad ADRs of antipsychotics have been developed for schizophrenia (6), which are also relevant to bipolar disorder. Consensus guidelines from various countries have been developed to address the issue of metabolic complications from atypical antipsychotic therapy (7, 8, 200–202). Their recommendations are summarised in Table 6. In relation to the risk of QTc prolongation, recommendations generally consist of a careful assessment of cardiac risks, baseline ECG to identify those with existing abnormalities, and ECG monitoring in patients with cardiac risk factors, especially those on ziprasidone (6, 203). Current guidelines recommend measuring prolactin level and intervening for antipsychotic-related hyperprolactinaemia only if symptoms are present (6, 12).

Table 6. Monitoring recommendations of previous guidelines for metabolic effects of atypical antipsychotics

Guidelines	Recommendations
American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity (7)	**Baseline** ▪ Personal and family history of metabolic and cardiovascular disease ▪ Body mass index, waist circumference ▪ Blood pressure ▪ Fasting plasma glucose ▪ Fasting lipid profile **Longitudinal** ▪ Weight: 4, 8, and 12 weeks after initiating treatment, then reduce to quarterly intervals ▪ Blood pressure and fasting glucose: 12 weeks after initiating treatment, then annually ▪ Fasting lipids: 12 weeks after initiating treatment, then every 5 years ▪ Consider switch to another agent if weight gain over 5% of initial body weight, or on development or worsening of diabetes or dyslipidaemia
British expert group 'schizophrenia and diabetes' consensus summary (8)	**Baseline** ▪ Random or fasting plasma glucose ▪ Glycosylated haemoglobin (HbA_{1C}) **Longitudinal** ▪ Repeat random or fasting plasma glucose and HbA_{1C} after 4 months on an antipsychotic ▪ If normal, repeat random or fasting glucose annually ▪ Ask about hyperglycaemia symptoms
Australian consensus working group position statement on diabetes, psychotic disorders and antipsychotic therapy (202)	Detailed history of metabolic and cardiovascular risk factors for every patient, and monitoring as follows if increased risk identified: ▪ Body mass index and waist-hip ratio at every visit or every 3 months ▪ Random or fasting blood glucose level at baseline and ideally monthly for 6 months, then every 3–6 months ▪ Blood pressure and lipid profile every 6 months
Belgian Consensus Group 2005 (200, 201)	**Baseline** ▪ Detailed history for metabolic risks ▪ Body mass index, waist circumference ▪ Blood pressure ▪ In-depth physical examination ▪ Fasting plasma glucose and lipid profile **Longitudinal** ▪ Weight and waist circumference: monthly (weekly in hospital care) ▪ Fasting blood glucose: every 3 months in patients without diabetic risk factors ▪ Fasting lipid profile: every 3 months for first year, then annually ▪ Blood pressure: every 3 months

ISBD monitoring recommendations

With the exception of clozapine, no baseline measures additional to our proposed basic parameters are required for initiating atypical antipsychotics. Clozapine is uncommonly used for the bipolar disorder indication, but in instances where it is prescribed, we recommend adherence to broader monitoring guidelines that encompass cardiac and metabolic complications in addition to mandatory haematological monitoring. Two such comprehensive guidelines have been recently published (9, 199).

For the monitoring of metabolic ADRs associated with atypical antipsychotics, we believe that the US guidelines (7) embody minimum standards. However, we agree with criticisms that the five-year monitoring interval for blood lipids is too lengthy (200), and believe that more vigorous monitoring of blood pressure and glycaemic status is indicated, given the usual insidious nature of hypertension and diabetes.

We therefore propose a set of monitoring recommendations as follows: monthly weight measurements for the first three months, followed by measures every three months for the duration of treatment; blood pressure and fasting glucose at three-month intervals for the first year, then annually; and fasting lipid profile at three months after initiation of atypical antipsychotic therapy, to be repeated at annual intervals thereafter (Table 7 and Fig. 1). We consider HbA1C to be best reserved as a monitoring aid for patients with diabetes rather than as a screening parameter. As these are suggested minimum monitoring standards, those with metabolic or cardiovascular risk factors may require more frequent and broader investigations.

At present, there is no convincing argument for routine cardiac investigations, such as ECG and

Table 7. ISBD recommended baseline and longitudinal safety monitoring specific to patients on atypical antipsychotics[a], in addition to the basic monitoring recommendations

	Recommendations
Baseline	■ Inquire about personal or family history of cardiac problems, including congenital long QT syndrome
Longitudinal[b]	■ Weight: monthly for the first 3 months, then measures every 3 months for the duration of treatment ■ Blood pressure and fasting glucose: every 3 months for the first year, then annually ■ Fasting lipid profile: at 3 months after initiating treatment, then annually ■ Electrocardiogram and prolactin levels where clinically indicated

[a]Patients on clozapine should adhere to specific guidelines for its monitoring.
[b]Those with metabolic or cardiovascular risk factors may require more frequent and broader investigations.

echocardiogram, to be performed for atypical antipsychotics other than clozapine. We recommend using clinical history to assess cardiac status and risk factors, including personal or family history suggestive of congenital long QT syndrome, and the selection of other atypical options over ziprasidone where prolongation of QTc exists (> 450 ms for males and > 460 ms for females). ECG monitoring and appropriate cardiology consultation are recommended in situations where pro-arrhythmic risk factors are present.

Similarly, there is no strong indication for routine prolactin monitoring. However, symptoms of hyperprolactinaemia, such as breast tenderness, gynaecomastia, galactorrhoea, sexual dysfunction, and menstrual irregularity, should be watched for in patients treated with atypical antipsychotics, especially with agents implicated in increasing prolactin such as risperidone. A serum prolactin level should be performed in the presence of such symptoms. If hyperprolactinaemia persists despite dose reduction and/or switching to another agent, or if hyperprolactinaemia is accompanied by neurological features such as visual field defects and headaches, further investigations are required to search for alternative causes such as pituitary tumours, and an endocrinology opinion may be necessary. In situations where continuation of long-term treatment with an agent that induces hyperprolactinaemia is required, consideration should be given to monitoring BMD, and, in women, the adherence to population breast cancer screening programmes.

Special populations

Children and adolescents

The diagnosis and pharmacological treatment of bipolar disorder in children and adolescents are topical issues in psychiatry, but the focus of the discussion in these guidelines is restricted to safety monitoring considerations rather than comments on the validity of paediatric bipolar disorder and its treatment approaches.

Where mood-stabilising medications are used in children, the developmental differences in pharmacokinetics and pharmacodynamics in this group need to be considered as these influence drug effects, dosages, toxicity, and ADRs (204, 205). The age-dependent changes in pharmacodynamics are often not readily distinguished from pharmacogenetic and pharmacokinetic considerations, but it is broadly accepted that the actions of drugs may alter with developmental stages (204). From a pharmacokinetic perspective, the drug absorption, distribution, metabolism, and excretion processes all show age-dependent changes (206). A higher plasma clearance of hepatically metabolised drugs has been consistently observed in children under 10 years of age compared with adults, which may necessitate the use of higher weight-adjusted dosages in children (204, 205). The mechanisms underlying this observation are unclear (204), but may include greater cytochrome P450 activity and higher liver-to-body-weight ratios (205). Children also have comparatively greater total body water, which increases the volume of distribution for water-soluble medications. Lithium's pharmacokinetics in children are similar to those in adults except for a shorter half-life of 18 h (207), which may result from higher weight-adjusted glomerular filtration rates. In children, steady-state blood levels of lithium can therefore be obtained after approximately four days, and higher dosages may be required because of this, and also because of the greater volume of distribution and lower brain-to-serum-lithium ratios (205, 208). The need for higher dosages per unit of body weight in children relative to adults may be mistaken for treatment nonadherence, and vice versa (206). In order to minimise ADRs, the use of low starting dosages and gradual dose titration are recommended for children and adolescents (209). The following suggested dose ranges must be considered to be approximate and rough guides at best: lithium: 10–30 mg/kg/day with serum level 0.6–1.1 mmol/L; valproate: 15–60 mg/kg/day with serum level 50–125 μg/L; carbamazepine: 10–20 mg/kg/day with

serum level 4–14 μg/L; lamotrigine: 75–300 mg/day; risperidone: 0.25–4 mg/day; olanzapine: 2.5–10 mg/day; quetiapine: 100–600 mg/day; aripiprazole: 5–40 mg/day; and ziprasidone: 40–160 mg/day (208).

Safety data for psychotropic medications in children and adolescents are limited (210), but preschool-aged children are at higher risk of ADRs than older children and adolescents (211). A similar range of ADRs is seen in children and adolescents compared with their adult counterparts for lithium, lamotrigine, carbamazepine (208), valproate (212), and atypical antipsychotics (213), but particular considerations in this group relate to cognitive adverse effects and sedation that may affect school performance (206), disturbance of bone growth due to anticonvulsants or hyperprolactinaemia (213), the long-term sequelae of PCOS and the metabolic syndrome in the young, and the unknown potential effects of these medications on physical growth and brain development (210, 214). For lithium, new-onset enuresis has been reported as an ADR unique to children in a randomised, placebo-controlled trial of 91 patients between the ages of five and 13, which together with fatigue, ataxia, vomiting, headache, and stomachache were common ADRs (215). Valproate-induced hepatitis is more common in young children, especially those under two years of age and receiving valproate as part of polytherapy, while developmental delay and coexisting metabolic disorders are also risk factors (103). The risk of skin eruptions and SJS in association with lamotrigine may also be higher in those under 16 years (116, 216). However, this increased risk has not been confirmed, as its estimation was based on only 14 possible cases of SJS or TEN in clinical trials, the diagnosis of which had not been agreed upon by an expert panel of dermatologists. Furthermore, the influences of concomitant valproate use and rapid dose titration were not excluded (216). With atypical antipsychotics, children and adolescents may be more prone to EPS, hyperprolactinaemia, sedation, weight gain, and metabolic effects (213). Unlike adults, however, the usual clinical features of hyperprolactinaemia are not seen in prepubertal children, making detection more difficult, but chronic hyperprolactinaemia may impair bone growth and possibly increase risks of osteoporosis, pituitary tumour, and breast cancer (213).

Proposed guidelines for safety monitoring in children and adolescents have been published in relation to the treatment of bipolar disorder (209, 217), atypical antipsychotics (213), endocrine and metabolic effects of mood stabilisers (214), and QTc prolongation (218).

ISBD monitoring recommendations

The ISBD supports the judicious and monitored use of mood-stabilising medications in children and adolescents, with a strong emphasis on psychosocial interventions. Where medications are used, agents with relatively more favourable long-term ADR profiles should be preferentially selected, even though this would largely be based on data extrapolated from the adult literature. An open discussion of significant ADRs, placed in the context of the psychiatric indication and efficacy of the treatment, is important in communication with patients and their family/guardians. Education on manifestations of potentially dangerous ADRs, the unpredictable and acute onset of some of the most serious ADRs, and the limitations of routine monitoring measures are particularly pertinent. In addition to the baseline and first-year monitoring recommendations as outlined above for adults, it would be prudent to continue monitoring the listed parameters on a six-month (rather than annual) basis in the long term for children treated with valproate and atypical antipsychotics. For patients on long-term valproate or carbamazepine, precautionary advice should be given for bone density protection, which may include regular exercise and Vitamin D and dietary calcium intake. Consultation with endocrinologists and bone densitometry are suggested if there are additional risk factors for impaired bone growth or reduced BMD. The possibility of hyperprolactinaemia with atypical antipsychotics should be kept in mind, and a serum prolactin level performed if symptoms emerge in adolescents. As many clinical features associated with hyperprolactinaemia, such as breast growth and menstrual irregularities, occur in normal pubertal development, a high proportion of negative results would be anticipated. In prepubertal children, clinical features of hyperprolactinaemia are usually not apparent, which may be an argument for routine prolactin level monitoring. However, given that the long-term sequelae of asymptomatic hyperprolactinaemia remain uncertain, the ISBD is not recommending routine prolactin levels but rather advocates for the selection of medications less likely to cause this ADR.

Pregnancy and breastfeeding

A clinical dilemma unique to the treatment of maternal bipolar disorder in pregnancy is the balance of achieving optimal illness control against the potential iatrogenic risks of medications, which include teratogenicity (morphological and possibly neurobehavioural), neonatal toxicity, and with-

drawal syndromes. Similarly, the desirability of breastfeeding during mood-stabilising treatment is dependent on maternal bipolar illness factors, the overall benefits of breastfeeding (nutritional, psychological and financial), the feasibility of formula feeding, and the potential medication ADRs for the infant. These decisions are therefore highly contextual, and further complicated by the inconclusive safety data for most medications in pregnancy and breastfeeding. The infeasibility of randomised controlled studies in these groups and our dependence on less scientifically rigorous studies for reference have been barriers to more precise characterisation of the medication safety profiles for foetuses and breastfed infants. We summarise below the specific ADRs associated with mood-stabilising medications in pregnancy and breastfeeding prior to discussing the ISBD safety monitoring recommendations.

Lithium

The potential problems for lithium in pregnancy and breastfeeding that require safety monitoring considerations are teratogenicity and neonatal lithium adverse effects, including toxicity syndrome. Lithium was initially considered to be highly teratogenic, especially for the cardiac malformation Ebstein's anomaly, based on data from the Register of Lithium Babies (219). However, the voluntary physician-reporting basis of this register likely led to an overestimation of teratogenicity, and subsequent cohort and case control studies have suggested more temperate risks. The revised risk estimates of Ebstein anomaly are 1–2 per 1,000 births, or 20–40 times higher than the general population rate of one per 20,000 births (220, 221). There are few studies of neurobehavioural teratogenicity, but the limited available data suggest that children exposed to lithium *in utero* do not differ from nonexposed children in this aspect of development (222, 223).

There are case reports of neonatal complications associated with lithium exposure, which include depressed neurological status, feeding difficulties, cardiac dysfunction, bradycardia and arrhythmia, NDI, hypothyroidism, respiratory distress, and macrosomia. Most of these were transient and resolved with excretion of lithium within two weeks (224, 225). Lithium concentrations in maternal and umbilical cord blood were reported as similar (225), but renal immaturity in neonates may compromise their lithium clearance and increase their susceptibility to toxicity (224). Withholding lithium at the onset of labour or 24–48 h before scheduled deliveries has been suggested as a strategy to reduce this risk (225). Lower levels of lithium may be transmitted in breast milk. There are few case reports of neonatal complications from lithium exposure via breast milk. One study estimated neonatal lithium levels to be about 25% of the corresponding maternal levels, with none of the 10 infants showing obvious side effects, although transient increases in blood urea nitrogen, creatinine, and TSH were found in some (226). The monitoring of lithium levels in breast milk and infant blood has been suggested (227). However, the feasibility and utility of this approach remains unclear at this stage.

Valproate and carbamazepine

Both valproate and carbamazepine are associated with increased rates of major malformations, although the association is less strong for carbamazepine (228). Valproate has been associated with malformations such as neural tube defects, midface hypoplasia, and cardiac, limb, and genitourinary defects (229). For valproate monotherapy, rates of major malformations have been estimated to range from 6.2 to 16.1% in different countries, with the higher rates possibly influenced by high-dose treatment (230). A meta-analysis of major malformations in valproate monotherapy has reported relative risks of 3.77 [95% confidence interval (CI): 2.18–6.52] in comparison with healthy controls, and 2.59 (95% CI 2.11–3.17) when compared to monotherapy with other anticonvulsants (231). Neural tube defects associated with maternal valproate treatment have been estimated to occur at rates of 1–5.4%, compared with population base rates of 0.02–0.33% (232), with higher valproate doses and polytherapy both having been linked to especially heightened risks (228, 230). Valproate has also been associated with neurobehavioural sequelae of cognitive impairment (233) and autistic spectrum behaviours (234) in offspring. In comparison, rates of major malformations with carbamazepine have ranged from 2.2 to 6.2% (228), and neural tube defects have been estimated to occur in about 0.5–1% of exposed pregnancies (235, 236). Further work is needed to clarify the cognitive effects of *in utero* exposure to carbamazepine as studies have produced mixed findings (237, 238). Periconceptional folic acid supplementation has been recommended as a means to reduce the risk of neural tube defects, largely based on population data rather than data from women on valproate or carbamazepine, although there is preliminary evidence for prophylactic efficacy in the setting of carbamazepine exposure (239).

There are no well-established risks for valproate during labour, delivery, and the immediate postnatal period (230). Cases of neonatal bleeding in carbamazepine-exposed pregnancies have been reported, which are believed to be due to carbamazepine-induced foetal vitamin K deficiency. Prophylactic administration of antenatal vitamin K to carbamazepine-treated pregnant women has been suggested (240), but there is evidence that contradicts the usefulness of this practice (241). There are limited data on the safety of breastfeeding during treatment with valproate and carbamazepine, but the American Academy of Pediatrics considers them to be compatible with breastfeeding (242). There have been no reported infant side effects from breastfeeding while on valproate (243), except for one case report of thrombocytopaenia (244), which has subsequently been suggested to be unrelated to valproate (245). With regard to carbamazepine, there have been two reported cases of cholestatic jaundice and one case of liver dysfunction in exposed breastfed infants, all of which resolved over time (246), and four reports of poor feeding (243).

Lamotrigine

Prospective registries have reported major malformation rates of 1% (247), 2.9% (248), and 3.2% (249) in association with lamotrigine from respective sample sizes of 98, 414, and 647. The latter study also found a dose-response relationship (249). Oral clefts were observed in 0.89% of exposed pregnancies in the North American registry, compared with 0.25% in five other registries and 0.037% in the control groups (250). However, an association with oral clefts and a dose-response relationship (with daily dosages up to 400 mg) to malformations have not been replicated in the most recent analysis of the drug company registry data (251). A prospective study of possible neurodevelopmental effects of anticonvulsant exposure, including lamotrigine, in the offspring of epileptic mothers is currently under way (252).

Lamotrigine clearance increases as the pregnancy progresses due to induction of hepatic glucuronidation, and clearance precipitously returns to normal within days of delivery. Dosages are therefore likely to be in need of increase during pregnancy to ensure efficacy and reduction after delivery to prevent toxicity (253). To the best of our knowledge, there has only been an isolated case report of neonatal side effect from *in utero* lamotrigine exposure, which was in the nature of elevated gamma-glutamyl transpeptidase that returned to normal over several months (254). There are reports of breastfeeding during lamotrigine treatment without short-term adverse effects on the infant (255), and although there are theoretical concerns over Stevens-Johnson syndrome, there are no reports of this in breastfed infants exposed to lamotrigine to date.

Atypical antipsychotics

There have been few systematic studies on the use of atypical antipsychotics in pregnancy, and the available evidence is limited to case reports, case series (256, 257), and studies that combine different atypical antipsychotics (258). However, no obvious patterns of adverse outcomes for offspring have emerged from the existing data. Differential transplacental passage of several antipsychotics has been demonstrated (259), with olanzapine having the highest transmission ratio, followed by haloperidol, risperidone, and quetiapine, none of which was completely transmitted. Those receiving olanzapine were more likely to have lower birth weight and neonatal intensive care unit admissions, but causality has not been established because of the limited sample size.

Data on infant outcomes with atypical antipsychotic exposure via breastfeeding are likewise limited. These medications are excreted in breast milk, but there have been no reported adverse events that can be attributed to these drugs (260). A subsequent review (261) highlighted the difficulties of determining the safety profiles of atypical antipsychotics in breastfeeding, but recommended the avoidance of breastfeeding during clozapine treatment because of potentially life-threatening adverse effects for the infant, and, to a lesser extent, olanzapine due to reports of EPS. A cautious approach has been advocated in the absence of conclusive data, consisting of clinical monitoring for side effects in the infant, additional precautions in premature infants given the relative immaturity of their drug-metabolising capacity, minimising drug exposure, and monitoring of laboratory parameters (262).

ISBD monitoring recommendations

Given the limitations and the complexity of risk considerations, clinical decisions in relation to the use of medications in pregnancy and breastfeeding need to be made in conjunction with the patient and her family, based on the overall balance of benefits and risks. In evaluating risk-benefit ratios and discussing them with patients, it is useful to note the difference between relative and absolute risks. Since congenital malformations occur at low

rates, the absolute risk for teratogenicity usually remains small even if relative risks are increased. For example, even if the preliminary estimated relative risk of oral clefts with lamotrigine is replicated to be in the vicinity of 32.8, 99.5% of infants exposed to this drug will not have this condition (263). On the other hand, the absolute risk of maternal bipolar relapse associated with treatment discontinuation is substantially higher, despite a seemingly lower relative risk. A prospective observational study of 89 pregnant women with bipolar disorder found that 70.8% had a relapse of illness during pregnancy, but the risk was 2.3 times higher in those who stopped versus those who continued mood stabilisers, with respective relapse rates of 85.5% and 37.0% (264). This study also showed that those who discontinued medications spent more of their pregnancies ill with a mood episode compared with those who continued medications (43.3% versus 8.8% of weeks in pregnancy), and relapsed earlier (median time to relapse of 9 weeks versus > 41 weeks from conception). Such lengths of symptomatic illness likewise pose short- and long-term risks to the offspring.

Pregnancy planning can facilitate the minimising of risks of both maternal bipolar illness destabilisation and drug exposure for the offspring, and is encouraged to be undertaken by clinicians with all female patients with childbearing potential. Where pregnancy is not desired, effective contraception is recommended. Otherwise, pregnancy planning discussions should include: (i) advice on attempting to conceive at a time of mental stability, (ii) the evaluation of the prophylactic benefits of maintenance treatment against the teratogenic risks and ADRs of medications on the offspring, and (iii) the increased monitoring needs over the course of pregnancy and in the postpartum period. In unplanned pregnancies, the inadvertent exposure of the foetus to medications prior to awareness of the pregnancy may alter the risk-benefit considerations. The vigilant clinical monitoring of maternal mental state is imperative if medications are discontinued, but is still required when treatment is maintained. For women taking valproate and (to a lesser extent) carbamazepine, preconceptional counselling about the risk of neural tube defects is indicated. As neural tube defects develop within the first 28 days after conception (265), often prior to the diagnosis of pregnancy, periconceptional folic acid supplementation is recommended. Further strategies to minimise teratogenic risks with valproate include using the lowest effective dose, preferably not greater than 1000 mg per day (230), and avoiding polytherapy. Prenatal diagnosis for neural tube defects should be offered in liaison with obstetricians. In general, early liaison with obstetricians is recommended to ensure close monitoring of the progression of the pregnancy and the appropriate use of investigations to assist in the early detection of malformations. This is particularly relevant for women on lithium, valproate, and carbamazepine due to the increased risks of major malformations.

For mood stabilisers, in particular lithium, the physiological changes during pregnancy that include increased renal clearance can alter drug pharmacokinetics and may result in reduced serum drug levels that can compromise therapeutic control. More frequent monitoring of maternal lithium levels (at a minimum in each trimester) is advised during pregnancy, and dosages should be adjusted accordingly to ensure adequate treatment. Despite the probability of requiring higher lithium dosages, the lowest dosages required for control of the illness (targeting the lower ends of the acute or maintenance reference ranges) should be used to minimise foetal lithium levels and ADR/toxicity risks. Withholding lithium at the onset of labour or 24–48 h before scheduled deliveries is advisable to further reduce neonatal as well as maternal lithium toxicity risks. As maternal renal clearance rapidly returns to normal after delivery, lithium doses need to be brought back to preconceptional doses to avoid maternal lithium toxicity (219, 225).

Even though infant drug exposure via breast milk is believed to be at a lower level compared to *in utero* drug exposure, the decision to breastfeed during maternal treatment with mood-stabilising medications needs to take into consideration the benefits of breastfeeding and the risks of infant drug exposure. The risks may vary with context; in developing countries, for example, the risks of not breastfeeding may outweigh the theoretical risks of drug exposure. Clinical monitoring for infant side effects and development is recommended, and breastfeeding or the medication terminated if adverse effects emerge.

The elderly

A number of factors specific to the elderly need to be considered in relation to safety monitoring practices. The pharmacokinetic and pharmacodynamic differences of drugs in this group, organ system senescence, and likelihood of medical comorbidities and polypharmacy combine to heighten the risk of ADRs (266). The elimination half-life of drugs in the elderly is mainly altered by changes in volume of distribution and drug clearance. Gastrointestinal absorption is generally unal-

tered by aging, as factors that decrease absorption, such as decreased gastrointestinal perfusion and membrane absorption, are counterbalanced by factors that increase absorption, such as longer transit time (267). Reduced lean body mass and total body water in the elderly decrease the volume of distribution of hydrophilic drugs such as lithium, and increase the volume of distribution of lipophilic drugs such as the anticonvulsants (267, 268). Clearance may be further slowed by reduced hepatic and renal blood flow, liver volume, and hepatic metabolism. Phase I metabolism, consisting of oxidation and reduction, is well known to decrease with aging (267), and even Phase II conjugative metabolism has been suggested to undergo some age-related decline (266). For some drugs, such as valproate, altered protein binding capacity in the elderly can increase the ratio of free to bound drugs (269). Pharmacodynamic changes due to aging may increase the likelihood of ADRs at lower doses, possibly due to fewer neurones and receptors (268). Therefore, the elderly may be more prone to developing ADRs such as constipation, urinary retention, delirium, and cognitive dysfunction on medications with anticholinergic properties, sedation on medications with antihistaminergic properties, and postural hypotension on those with α-adrenergic blocking properties (270).

Lithium

The elderly have been shown to require lower dosages than younger patients to achieve similar blood levels, primarily because of normative decrease in volume of distribution and renal clearance (271, 272). Renal clearance may be further compromised, and therefore the risk of lithium toxicity increased, in the presence of hypertension, congestive cardiac failure, renal disease, dehydration, and/or the concurrent use of NSAIDs, ACE inhibitors, or thiazide diuretics, which are not uncommonly encountered in the elderly (273). The risk of lithium toxicity may be compounded by the diminished physiological capacity of the elderly to respond to dehydration. The estimation of renal function in this population cannot be reliably gauged using serum creatinine levels due to reduced muscle mass (274), and may be more accurately estimated using equations such as the Cockcroft-Gault equation {creatinine clearance in mL/min = [(140 − age) × weight (kg) × 0.85 if female]/72 × plasma creatinine (mg/100 mL)}, which takes into account aging-related muscle mass change by factoring in the predictors of age, body weight, and sex (275). The elimination half-life of lithium in the elderly is in the order of 28–36 h, compared to 24 h in younger adults (273), therefore delaying the attainment of steady-state concentrations. It has been suggested that daily dosages of 300–600 mg and not exceeding 900 mg be used for patients aged 65–75 years, and daily dosages of 150–300 mg and not exceeding 450 mg be used for those older and more frail (272).

Aside from pharmacokinetic factors that increase serum lithium levels and pose risks of toxicity if dose adjustments are not made accordingly, the elderly may also be more susceptible than younger adults to developing ADRs and toxic effects at comparable serum levels within the generally accepted therapeutic range (272). Aiming for lower therapeutic ranges has been suggested for the elderly (272), but an optimal therapeutic range that balances efficacy and risks has yet to be established for this group (273). Lithium ADRs in the elderly commonly include sedation, fatigue, neurological effects (cognitive impairment, tremor), polyuria and renal impairment, and gastrointestinal effects (272, 273). Cardiac ADRs are more likely to occur in the elderly, with the best-recognised event being sinus node dysfunction causing bradyarrhythmias (276, 277). This may occur due to a combination of individual cardiac predisposition and the direct effect of lithium, possibly via sodium channel blockade (278). One study found that signs of moderate sinus node dysfunction (heart rate under 50 beats per minute and sinus pause greater than 1.5 s), but not severe dysfunction, occurred more frequently in patients on long-term lithium (n = 45) compared with age-stratified controls (279). It has therefore been suggested that pulse rate and ECG be monitored, especially in older patients and in those with cardiac disease (276, 277).

Anticonvulsants

Clearance of the anticonvulsants carbamazepine, valproate, and lamotrigine tend to show age-related decline (266), and both dose-dependent and drug-specific ADRs are common in the elderly and can occur at lower blood levels than in younger adults (280). For carbamazepine, ADRs such as drowsiness, dizziness, ataxia, and cognitive impairment may be particularly problematic for the elderly, given the risks of falls and confusion (273). The potential for osteopaenia and osteoporosis in association with long-term carbamazepine or valproate (as well as prolactin-elevating atypical antipsychotics) treatment is especially important to consider in the elderly (280). The association of carbamazepine with bradyarrhythmias and atrio-

ventricular conduction delay has also been reported to occur primarily in elderly women, at either therapeutic or modestly elevated serum levels (281). This may be related to composite Class I antiarrhythmic characteristics of carbamazepine (282) or represent the unmasking of latent conduction abnormalities (281). Obtaining an ECG prior to commencing carbamazepine and after the establishment of a therapeutic level has therefore been suggested for elderly individuals (281). A cautious treatment initiation and dose titration regime has been recommended, e.g., starting at a daily dose of 100–200 mg and increasing by 100 mg per day every 3–5 days, with target serum levels generally falling between 4 and 12 μg/L. Typical daily doses are 400–800 mg in the healthy elderly, and 100–200 mg in those who are frail. Because of the auto-induction of carbamazepine, dosages may require increasing over the first few weeks of treatment (273).

Valproate is considered to be generally well tolerated in the elderly, with common ADRs being tremors, sedation, and gastrointestinal symptoms (283). Coagulation parameters should be monitored where valproate is prescribed in conjunction with aspirin and anticoagulants, not only because of the possibility of thrombocytopaenia compounding any bleeding diathesis (266), but also because of the interaction of valproate with aspirin (increase in free fraction serum valproate) and warfarin (increase unbound fraction of warfarin) (273). In addition to reduced clearance, the free fraction of valproate is also higher in the elderly, and the serum level may therefore underestimate the level of active valproate. Dosages should not be determined by serum levels alone, especially in the elderly, and clinical status should remain the main marker of tolerability (273).

Lamotrigine has a relatively favourable profile with regard to ADRs, especially in terms of cognitive side effects (284). In clinical trials involving elderly populations, using the same general dosing schedule as recommended for adults, lamotrigine has been associated with fewer ADRs, rashes, and treatment discontinuations than carbamazepine (285), and fewer treatment discontinuations and an equal number of rashes compared to lithium (284).

Atypical antipsychotics

As mentioned previously, the elderly are more prone to ADRs than younger adults, and may be more likely to experience ADRs such as sedation and anticholinergic side effects with olanzapine, postural hypotension and EPS with risperidone, and sedation, dizziness, and postural hypotension with quetiapine (273). As risk factors for QTc prolongation may be more prevalent among the elderly, increased vigilance for this complication is indicated for this age group when ziprasidone is prescribed.

In elderly patients with dementia, there have been reports suggesting increased risks of cerebrovascular adverse events that include strokes and transient ischaemic attacks with risperidone and olanzapine (286, 287), although the strength of this association and causality relationship are not clear. A meta-analysis of 15 randomised, placebo-controlled trials of risperidone, olanzapine, quetiapine, and aripiprazole also showed increased mortality in those randomised to the atypical agents (3.5% compared to 2.3%, odds ratio 1.54) (288). This relationship with increased mortality is not unique to atypical antipsychotics, and has also been found with conventional antipsychotics in dementia patients (289). The US Food and Drug Administration has therefore issued a warning for the use of atypical antipsychotics in the treatment of behavioural disturbances in dementia (290). These cerebrovascular and mortality risks have not been established for elderly patients without dementia, and need to be considered in light of the risks associated with alternative treatments or uncontrolled symptoms in bipolar disorder.

ISBD monitoring recommendations

In the elderly, we recommend the considered selection of pharmacotherapy that takes into account the patient's medical status and the ADR profiles of medication options, adherence to the 'start low, go slow' adage for drug initiation and dose escalation, and clinical vigilance for ADRs and potential drug interactions. Serum levels remain useful, but ADRs may occur at lower levels compared to younger adults and clinical status is a superior guide to serum levels for dosing purposes.

For lithium, particular attention should be paid to assessing risk factors for toxicity, including adherence not only to prescribed treatment, but also to maintaining adequate hydration, the ability to recognise toxic symptoms, renal impairment, hypertension, cardiac failure, and concurrent use of NSAIDs, thiazide diuretics, and ACE inhibitors. Signs of toxicity can emerge within the therapeutic range, and although regular monitoring of serum levels is important, lithium toxicity is a clinical diagnosis and the threshold for suspicion should be comparatively low in the elderly. The possibility of sinus node dysfunction should be considered when

elderly patients on lithium develop syncopal episodes. Similarly, sinus node dysfunction and atrioventricular block can occur with carbamazepine, and symptomatic patients will require further investigations. For those who receive long-term valproate and carbamazepine, dietary and lifestyle advice to promote bone health is recommended, and bone densitometry and vitamin D screening should be considered. These measures should also be considered for those on prolactin-elevating atypical antipsychotics, even though the impact of chronic hyperprolactinaemia on bone density in postmenopausal females and older males remains unclear.

Practical considerations

A system of care committed to a culture of patient safety is required for the optimal implementation of safety monitoring recommendations, but the constituents of such a system will vary depending on the clinical setting, taking into account such factors as the level of care required, the healthcare model, and local health resources. Although treating clinicians are responsible for communicating treatment rationale and risks to patients and for individualising monitoring recommendations, the use of psychiatrists to coordinate safety monitoring procedures is probably often an inefficient and impractical use of healthcare resources. The configuration of effective safety monitoring arrangements in public psychiatric settings could include junior medical staff, case managers, or general practitioners assuming a coordinating role, whereas general practitioners or private psychiatrists may do so in private-sector psychiatry. Computerised electronic medical records with reminder prompts may also be of assistance in coordinating safety monitoring, as they have been similarly employed in the treatment of conditions such as diabetes and hypertension (291). Because diffusion of responsibility may be an intrinsic sociological characteristic of teams (292), clear lines of responsibility for coordinating monitoring practices and for the interpretation of results need to be established, regardless of the specific personnel arrangements. In the event of emergent ADRs, clinicians should review the risk-benefit balance of the treatment and make appropriate treatment changes and referrals to medical specialists. For example, a step-wise approach to the management of atypical antipsychotic ADRs, grounded in risk prevention and harm minimisation principles, has been proposed with hierarchical steps of abstinence, anticipation, reduction, and treatment (293).

In practice, treatment and safety monitoring may be impeded when treating patients who are nonadherent, hard to engage, disorganised, or itinerant. If obstacles to implementing safety monitoring are encountered, it may be preferable to select, where possible, medications associated with comparatively lower iatrogenic risks and requiring minimal monitoring. In situations where monitoring difficulties chiefly arise from amendable factors, such as disorganisation and passive lack of insight, external structures such as case management, involuntary treatment orders, and the involvement of family and caregivers may assist in overcoming these barriers to safety monitoring (294–296). However, when obstacles cannot be overcome, a pragmatic perspective of the risks and benefits of treatment can assist the clinician in reconciling to the practical limitations, but minimum safety monitoring should nevertheless be attempted as much as the situation permits.

The selection of the safest medication is often complex, and involves the consideration of the differential efficacies of pharmacological options, the incomparability of diverse ADRs, and any restrictions to choice due to prior poor treatment response or nonadherence. The absence of ADR-free medications is a clinical reality, and choosing among imperfect candidates can be aided by the adequate understanding of psychopharmacology and of the patient's mental illness, as well as his or her medical history.

Limitations of the ISBD guidelines

Guidelines are practical clinical tools, derived from existing data that are often awaiting confirmation and the consensus opinion of professional workgroups. These guideline recommendations on safety monitoring are intended to embody an appropriate standard of care, which may need modification according to clinical circumstances and sociocultural contexts, especially given the absence of empirical data on the cost-benefit ratios of the proposed monitoring strategies. They must thus rely on the medical knowledge and acumen of clinicians to be modified for use with individual patients, taking into consideration factors such as comorbidities, polypharmacy, capacity for adherence to monitoring procedures, and local health resources. A corollary is that these guidelines do not represent an absolute minimum standard of care in medico-legal proceedings.

In clinical practice, combination therapy is common in the treatment of bipolar disorder (297). In the interest of clarity and brevity, these

guidelines focus on individual pharmacological groups, and have deliberately avoided making recommendations for pharmacological combinations that may be used in bipolar disorder. Clinicians are encouraged to be cognisant of drug-drug interactions and to adjust the monitoring recommendations for each constituent medication in combination therapy accordingly.

There are currently minimal data on the yield of the suggested safety monitoring investigations, and, as noted above, the specific recommendations in these guidelines are not yet substantiated by empirical research. To our knowledge, only a single pilot study has examined the yield of routine safety monitoring in bipolar disorder, and found a relatively low yield for many such investigations (298). These ISBD recommendations have erred on the side of safety, but will benefit from substantiation and refinement by research on their practical utility and cost-benefit analysis.

It should be emphasised that the strength of these ISBD safety monitoring guidelines, as for all routine monitoring, lies in their ability to increase the likelihood of the early detection of and early intervention for relatively insidious but clinically significant ADRs, such as metabolic syndrome. Their utility in the detection of rare idiosyncratic ADRs is limited, as these are often acute and unpredictable in their onset, and the yield from monitoring is known to be low in other fields of medical practice (102).

Conclusions

These ISBD safety monitoring guidelines have been formulated by expert consensus with the intention of providing recommendations that may be a useful resource for clinicians in their treatment of patients with bipolar disorder. These guidelines will need to be applied flexibly in the context of diverse clinical, healthcare structural, and resource settings, and are likely to evolve with research on treatment and safety monitoring in bipolar disorder. Clinical vigilance and a clearly defined monitoring system are critical ingredients for the safe treatment of bipolar disorder. Psychiatry as a discipline specialises in the management of ambiguous problems, and is accustomed to conceptualisation within both the individual and systemic contexts. The issue of safety monitoring is merely one aspect of care that demands the utilisation of these skills.

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