12 - Interactions with other drugs7072

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284 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 In contrast with these recommendations, a naturalistic study found that, in patients who had been in remission for at least 2 years and had discontinued lithium very slowly, the recurrence rate was at least three times greater than in patients who continued lithium and that significant survival differences persisted for many years. Patients maintained on high lithium levels before discontinuation were particularly prone to relapse.66 One large US study based on prescription records found that half of those prescribed lithium took almost all of their prescribed doses, a quarter took between 50% and 80% and the remaining quarter took less than 50%. A third of patients took lithium for less than 6 months in total.67 A large audit found that 1 in 10 patients prescribed long-term lithium treatment had a plasma level below the therapeutic range.68 It is clear that suboptimal adherence limits the effectiveness of lithium in clinical practice. One database study suggested the extent to which lithium was taken was directly related to the risk of suicide (more prescriptions were associated with lower suicide rate).69 Less convincing data support the emergence of depressive symptoms in bipolar patients after lithium discontinuation.62 There are few data relating to patients with unipolar depression. Table 2.1 summarises the prescribing and monitoring of lithium. Interactions with other drugs70–72 Because of lithium's relatively narrow therapeutic index, pharmacokinetic interactions with other drugs can precipitate lithium toxicity. Most clinically significant interactions are largely with drugs that alter renal sodium handling. Rarely, neurotoxicity results from co-prescribing lithium and antipsychotics.73,74 ACE inhibitors Angiotensin-converting enzyme (ACE) inhibitors can (i) reduce thirst, which can lead to mild dehydration; and (ii) increase renal sodium loss leading to increased sodium reabsorption by the kidney, resulting in an increase in lithium plasma levels. The magnitude of Table 2.1 Lithium: prescribing and monitoring. Indications Mania, hypomania, prophylaxis of bipolar affective disorder and recurrent depression. Reduces aggression and suicidality. Pre-lithium work-up Estimated glomerular filtration rate (eGFR) and thyroid function tests (TFTs). ECG recommended in patients who have risk factors for, or existing, cardiovascular disease. Baseline measure of weight desirable. U&Es (including calcium). Prescribing Start at 400mg at night (200mg in the elderly). Plasma level after 7 days, then 7 days after every dose change until the desired level is reached (0.4mmol/L

may be effective in unipolar depression, 0.6–1.0mmol/L in bipolar illness, slightly higher levels in this range in difficult to treat mania). Blood should be taken 12 hours after the last dose. Take care when prescribing liquid preparations to clearly specify the strength required. Monitoring Plasma lithium every 6 months (more frequent monitoring is necessary in those prescribed interacting drugs, the elderly and those with established renal impairment or other relevant physical illness). eGFR, U&Es and TFTs every 6 months. Weight (or body mass index) should also be monitored. Stopping Reduce slowly over at least 1 month and preferably 3 months. Avoid reductions in plasma levels of

> 0.2mmol/L at a time (see section on discontinuation).

Bipolar disorder CHAPTER 2 this effect is variable, from no increase to a fourfold increase. The full effect can take several weeks to develop. The risk seems to be increased in patients with heart failure, dehydration and renal impairment (presumably because of changes in fluid balance/handling). In the elderly, ACE inhibitors increase sevenfold the risk of hospitalisation due to lithium toxicity. ACE inhibitors can also precipitate renal failure so, if co-prescribed with lithium, more frequent monitoring of eGFR and plasma lithium is required. The following drugs are ACE inhibitors: captopril, cilazapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril and trandolapril. Care is also required with the angiotensin II receptor antagonists candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan. Diuretics Diuretics can reduce the renal clearance of lithium, the magnitude of this effect being greater with thiazide than with loop diuretics. Lithium levels usually rise within 10 days of a thiazide diuretic being prescribed; the magnitude of the rise is unpredictable and can vary from an increase of 25% to 400%. The following drugs are thiazide (or related) diuretics: bendroflumethiazide, chlortalidone, cyclopenthiazide, indapamide, metolazone and xipamide. Although there are case reports of lithium toxicity induced by loop diuretics, many patients receive this combination of drugs without apparent problems. The risk of an interaction seems to be greatest in the first month after the loop diuretic has been prescribed and additional lithium plasma level monitoring during this time is recommended if these drugs are co-prescribed. Loop diuretics can increase sodium loss and subsequent reabsorption by the kidney. Patients taking loop diuretics may also have been advised to restrict their salt intake; this may contribute to the risk of lithium toxicity in these individuals. The following drugs are loop diuretics: bumetanide, furosemide and torasemide. Non-steroidal anti-inflammatory drugs Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the synthesis of renal prostaglandins, thereby reducing renal blood flow and possibly increasing renal reabsorption of sodium and therefore lithium. The magnitude of the rise in lithium concentration is unpredictable for any given patient; case reports vary from increases of around 10% to over 400%. The onset of effect also seems to be variable, from a few days to several months. Risk appears to be increased in those patients who have impaired renal function, renal artery stenosis or heart failure and who are dehydrated or on a low salt diet. There are a number of case reports of an interaction between lithium and COX-2 inhibitors. NSAIDs do not appear to diminish the therapeutic effects of lithium,75 as has previously been reported. NSAIDs (or COX--2 inhibitors) can be very carefully combined with lithium, but they should be prescribed regularly, not intermittently, and more frequent plasma lithium monitoring is essential. Some NSAIDs can be purchased without a prescription, so it is particularly important that patients are aware of the potential for interaction. The following drugs are NSAIDs or COX-2 inhibitors: aceclofenac,

acemetacin, celecoxib, dexibuprofen, dexketoprofen, diclofenac, diflunisal, etodolac, etoricoxib,

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