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AU:6, page 109	"The worry is that they can end up treating conditions like the ones they were given for in the first instance" – 'treating' changed to 'causing'. Please verify.	
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c0007

AU:1

Mood-stabilisers

7

CHAPTER CONTENTS

HISTORY OF MOOD-STABILISATION

There are hints that the Greeks as early as the second century AD recognised that spring waters that were alkaline and as a result perhaps high in lithium salts were calming.[1–3]

Lithium was isolated by August Arfwedson in 1817, from stone – *lithos* being Greek for stone. In the 1850s alkaline compounds such as lithium developed a reputation for treating rheumatic disorders and gout by interfering with the precipitation of uric acid in the blood and joints. Lithium was in fact available in many countries through to the 1970s for the treatment of rheumatism.

In the 1850s, mania and melancholia were viewed by some as part of the same family of diseases as gout. This led to the use of lithium for mania and melancholia and a claim in 1880, by Carl Lange in Copenhagen, that it prevented episodes of periodic depression. At the same time, William Hammond in New York claimed the same thing.

Despite these discoveries, lithium slipped out of use for mood disorders and had to be rediscovered in 1949. Its disappearance was in part because the ideas connecting gout to manic-depressive illness vanished, and in part because of its side effects – increased urine flow, tremor of the hands and difficulties with memory or concentration. Later, in the 1940s, when used as part of a salt restriction diet in the US, lithium was linked to cardiac problems, and it was banned by the Food and Drug Administration.

In 1949, following observations that lithium had a tranquillising effect on laboratory animals, John Cade in Australia gave it to manic, depressive and schizophrenic patients. He noted that it was particularly beneficial in mania. Cade's observations were followed up by Mogens Schou in Denmark, who confirmed in clinical trials that lithium was beneficial in patients with mania. This led to its subsequent spread for use in the treatment of mania.

The adoption of lithium, however, was slow and patchy for several reasons. One is that it can have serious side effects, so that blood lithium levels have to be checked regularly to ensure that its side effects do not outweigh its benefits. Second, lithium as an elemental compound is widely available and therefore no drug company stands to make much money out of it. It has certainly not

been marketed as aggressively as other compounds. For 50 years, awareness of its usefulness depended largely on the efforts of Mogens Schou. Third, even for the treatment of mania, it took second place to the antipsychotics.

p0135 But in the 1960s, studies from the UK and Denmark appeared supporting Lange's 1880 claim that lithium may be useful in the prevention of recurrent episodes of mania or depression. These claims for a prophylactic effect caused a storm of controversy, which, in fact, may have helped market lithium.[4] One of the arguments of critics was that the results that showed people doing well on lithium and poorly off it might simply be the result of a withdrawal syndrome. This argument was dismissed by lithium's supporters at the time, but it now seems that there is indeed a dependence syndrome, although there appears to be benefits from lithium beyond those of avoiding withdrawal.

p0140 Lithium was not available in Japan during the 1960s. This led to an interest to try carbamazepine in mania and to the discovery that carbamazepine could produce useful inter-episode effects. The effects of valproate on mood were similarly discovered in France in the 1960s where lithium use never became widespread.[5–7]

p0145 In 1980, the example of valproate and carbamazepine led to the idea that anticonvulsants might help mood disorders in much the same way as they helped convulsive disorders – by reducing kindling. The notion was that each episode of a mood disorder kindled a further episode, in the same way that each epileptic fit increases the vulnerability to the next fit. This hypothesis led on to the systematic testing of every new anticonvulsant that has emerged on the market to see whether it might do something useful.

p0150 The awkward fact that electroconvulsive therapy (ECT) can help mania and depression it was argued resulted from its increasing seizure thresholds making further fits less likely. But little mention was made of the fact that lithium is pro-convulsant rather than anticonvulsant. Nor is any mention made of the fact that clozapine, which is widely thought to be in some way mood enhancing, is also pro-convulsant.[8]

p0155 The kindling idea led to the concept of a mood-stabiliser. The term had first applied to oestrogen and progesterone and later clozapine and cannabis before it was picked up by the marketing department at Abbott to promote valproate. In 1995, even though only shown to be effective for mania, valproate was launched in the US as Depakote, a mood-stabiliser. There was no evidence that it stabilised moods. If Abbott had claimed Depakote was prophylactic, the FDA would likely have sued them, but the company could claim it was a mood-stabiliser because the term has no definition. It suggests prophylaxis – an ability to ward off future episodes. It suggested that Depakote, and all of the other drugs now called mood stabilizers, were new forms of lithium.

p0160 There are two ways in which a drug might act as a mood-stabiliser. One would be to reduce kindling; in which case all anticonvulsants should help but they don't. Lithium furthermore is not anticonvulsant. If mood-stabilisers worked by reducing kindling, the takers of these drugs should not notice anything useful about them other than that they reduced the frequency of episodes of mood disorder, in much the same way that patients on anticonvulsants for epilepsy do not talk about anything useful the drug does for them – they keep a record of whether they are having more or fewer fits.

p0165 The other way a mood-stabiliser might work would be if each does something useful. For instance, valproate is sedative, gabapentin is anxiolytic, carbamazepine has anti-irritability or anti-impulsive effects, and lamotrigine may produce a sense of well-being. If they all act in different ways, conceivably they each could suit different patients, and if the drug was helping, patients should be able to say this helps me because it does X or Y or Z. At present, however, there is no interest to pursue research like this that suits patients but not companies. Companies prefer the idea that if one mood-stabiliser doesn't work, you should be on several of them. But the more drugs a person takes, the harder it is to read the signals of what each might be doing.

p0170 Linked to the emergence of mood-stabilisation, there has been a trend to reinterpret personality disorders as mood disorders. Borderline, emotionally unstable and explosive personality disorders, some claim, involve an affective dysregulation at their core, and sustained treatment with a 'mood-stabiliser' helps. Many also argue that any patient with a recurrent mood disorder should be taken off antidepressants and treated with mood-stabilisers instead.

p0175 These drugs are all called mood-stabilisers but it is by no means clear that drugs such as gabapentin are mood-stabilisers in the same sense as lithium is. Gabapentin is more anxiolytic than other compounds considered here. It is therefore not a surprise that some patients with affective dysregulation may be helped by it. But the argument becomes circular if the response of patients to gabapentin is taken to show that they have a mood disorder because gabapentin is classified as a mood-stabiliser. In this way the concept of bipolar disorder can expand to include almost everyone who has 'nerves' of any sort.

p0180 There is little evidence that anything except lithium is a mood-stabiliser. Indeed there is some evidence that despite the availability of so many more 'mood-stabilising' drugs now patients with bipolar disorder are doing worse than they were 100 years ago.[9] If the various different drugs do not correct an abnormality, then in fact they provide another physiological stressor (a pharmacological life event) to an already vulnerable system and are likely in the long run to destabilise and make things worse rather than better. There is therefore a need to make sure that people are on a drug that suits them and not just on a mood-stabiliser because that's what you do for people who have bipolar disorder. Calling something a stabiliser doesn't make it one.

LITHIUM AS A MOOD-STABILISER

s0015

p0185 Lithium affects such a large number of processes that 50 years after its introduction there is still no consensus on what its key physiological effects are. The surprise is that it acts so widely but yet has relatively specific clinical effects.

p0190 Since the early 1960s, there has been a clear body of evidence pointing to a role for lithium in the prevention of episodes of mania and depression in bipolar affective disorders. Many individuals who have been treated in hospital for mania are maintained on lithium for years or decades to prevent recurrences in what is known to be a recurrent disorder. The evidence that lithium prevents recurrences is better than the evidence for anything else.

p0195 Lithium has been linked to a lower rate of suicide than have other mood-stabilisers. This may stem from the fact that compliance with lithium may indicate

someone who is generally more responsible and concerned about their condition and thus at lower risk of suicide. The same argument should apply to valproate and carbamazepine, but suicides in patients maintained on lithium seem lower than in these other two patient groups. Lithium may not prevent suicide, but it seems less likely to provoke suicidality. All other mood stabilisers increase suicidality.

p0200 There is some evidence indicating a role for lithium in recurrent depression. The current wisdom is that lithium is indicated if there are as many as two episodes per year or three episodes of depression over the course of 2 years. The efficacy of lithium, however, seems to fall off once there are more than four episodes of a depressive disorder a year.

p0205 The traditional wisdom had been that it was necessary to start prophylactic lithium after one manic episode, but now any patient with a manic episode is likely to be advised they need a mood-stabiliser. At the opposite end of the spectrum, lithium does not seem to help in what are called rapidly cycling mood disorders, where there are four or more episodes of a mood disorder per year. Overall, because of its withdrawal effects, there are estimates that patients have to stay on treatment for at least 2.5 years before they are likely to have had fewer episodes than they would have had had they not started lithium.

p0210 Table 7.1 gives the main lithium preparations.

s0020 DOSAGE

p0215 Unlike other psychotropic drugs, there is a clear window for lithium levels in the blood, below which level the drug appears not to work and above which its toxic effects outweigh its benefits.

p0220 In the acute treatment of mania or depression, a plasma level between 0.9 and 1.4 mmol/L is needed. Anything from 150 to 4200 mg of lithium per day AU:4 may be needed to achieve these levels. For the prophylaxis (prevention) of affective episodes, blood levels between 0.4 and 0.8 mmol/L are adequate.[10] Because of the dynamics of lithium, blood needs to be taken 12 hours after the last dose and 7 days after a change of dose to give plasma levels time to stabilise.

p0225 Because of its effects on the kidney, there was a tradition of giving lithium in divided doses. Concern about kidney toxicity also led to the production of slow-release preparations of lithium to give more even plasma levels. It became customary to give these slow-release preparations in a divided dose in the morning and the evening.

p0230 However, it now appears that a single pulse of lithium, giving a high plasma level at one point in the day and falling off to a lower steady-state level, may be less toxic than a moderate level the whole time. The implication is that lithium should perhaps be given as a single dose at one point in

t0010 **Table 7.1** ***Lithium***

Generic drug name	UK trade name	US trade name
Lithium carbonate	Camcolit/Priadel	Eskalith/Lithobid
Lithium citrate	Priadel liquid/Litarex/Li-liquid	–

p0235 the day and that slow-release formulations are no better than conventional preparations.

There have been close to 50 different preparations of lithium on the market. In many countries companies have been eliminating many of these versions recently and pushing up the price of the remaining preparations. In addition to conventional and slow-release forms, the main differences are between lithium citrate and lithium carbonate. Lithium carbonate is more common, but some prefer citrate to carbonate.

p0240 The list of lithium's hazards is fearsome, but this is because no company has been trying to hide the hazards. Lithium has the profile all drugs should have. Any symposia about lithium have typically been about its side effects and how to manage these, whilst symposia for all other drugs are aimed at increasing sales rather than safety.

b0010

User issues

s0025 p0245

Lithium withdrawal and dependence

At present one of the most contentious issues in lithium treatment is whether there may, for some people, be a withdrawal syndrome on stopping treatment. In clinical practice, people who have just stopped their treatment seem to relapse with striking frequency but is this because they had begun to go high and therefore stopped treatment after the new illness episode had started? This has led to a series of vigorous disputes.

p0250 Whilst it is difficult to control for all the factors that may be involved, the consensus of opinion on this issue at present would appear to be that some people, perhaps up to one-third or one-half, may have a withdrawal problem. This can be minimised by tapering the dose slowly.[11] Because of this lithium probably best suits those who will take it regularly and commit to it indefinitely. Early discontinuation may bring a next illness episode forward so that it is necessary to commit to lithium for over 2 years to reduce the frequency of episodes.

b0015

User issues

s0030 p0255

Side effects of lithium

There is a considerable rate of non-compliance with lithium. The usual reasons given are that takers dislike the weight gain, poor memory, tremor, thirst and tiredness. Other reasons cited are that takers miss the highs that they normally get when not on lithium or that they feel well and therefore see no need to continue with treatment. Some discontinue because they are bothered by the idea of drug treatment itself.

s0035 p0260

Tremor

Individuals on lithium may develop a fine rapid tremor. This is not ominous, although it may interfere with daily living by causing tea to spill from cups, for example. It will usually clear when the lithium is discontinued. If problematic it can sometimes be helped by the addition of a beta-blocker such as propranolol.

User issues—cont'd

s0040 Thirst and urinary frequency

p0265 Lithium causes an inability to concentrate urine, which leads to the passing of greater volumes of urine than normal. This loss of water leads to thirst. Lithium antagonises the action of vasopressin, antidiuretic hormone (ADH), and this leads to an inability to concentrate urine, with a consequent loss of body water and thirst.

p0270 This inability to concentrate urine produces one of lithium's most troublesome complaints, which is having to pass water during the night. Up to 50% of people have this side effect. Some may even wet the bed. This is normally reversible once lithium is stopped. A small proportion of people may have a residual problem in concentrating urine when lithium is discontinued.

p0275 As lithium leads to fluid loss, it leads to thirst and a perception of a dry mouth. Paradoxically, however, it increases the production of saliva, so mouths are not actually drier than normal. It may also lead to an enlargement of the salivary glands.

s0045 Kidney problems

p0280 In a small proportion of people, lithium can produce chronic kidney problems involving the destruction of kidney cells and a permanent impairment of the ability to concentrate urine. This is more common in individuals who have been exposed to toxic doses of lithium at some point.

p0285 Kidney function should be tested before commencing lithium and 6-monthly afterwards, especially in people who develop urinary frequency, particularly at night. In such subjects a lower plasma level of lithium (0.4–0.6 mmol/L) is advisable.

p0290 Ordinarily, testing for urea and creatinine is a sufficient screening procedure for renal function. To avoid kidney toxicity, it is important to avoid inadvertent overdosing (see Lithium overdose and Drug interactions below).

s0050 Weight gain

p0295 Up to 50% of people put on lithium gain 5 kg in weight or more. The reasons for this weight gain are not clear. The thirst induced by lithium may lead people to drink more calories than they would otherwise do. If thirsty, people on lithium should stick to water only.

p0300 Lithium may also increase appetite by reducing the effectiveness of insulin in the body, which stimulates appetite centres in the brain. Or it may lower basal metabolic rates so that less food is burnt off as energy during the day.

s0055 Diarrhoea

p0305 Diarrhoea is common early in a course of treatment. Some people may continue to have loose stools for as long as they remain on the drug. In a minority of individuals, there may be constipation.

p0310 Diarrhoea is also a symptom of lithium toxicity. If an individual develops diarrhoea, toxicity should be considered. In the case of toxicity, the diarrhoea is likely to be accompanied by nausea, vomiting and tremor.

s0060 Nausea/abdominal discomfort

p0315 Up to one-third of people taking lithium have a certain amount of nausea or more vague abdominal discomfort for the first weeks of treatment. This may occasionally be severe and lead to discontinuation of the drug. There may also be a sensation of bloating or painfulness in the lower abdominal area, one cause of which may be having a fuller than usual bladder owing to the effects of lithium on water concentration. Lithium can sometimes cause a loss of taste for food with a consequent loss of appetite.

Continued

User issues—cont'd

s0065
p0320

Discoordination

A rarely mentioned but important side effect of lithium is that it may cause episodic discoordination or muscle weakness. This side effect may not be uncommon. As one individual writing on psychiatric drugs has put it, the first thing she knew about lithium discoordination was when she fell down the stairs. What appears to happen is that there is a brief momentary loss of coordination and/or muscle strength. This leads to a feeling that a fall is imminent, a feeling that is often described as feeling dizzy or faint but in actual fact is neither dizziness nor faintness.[12]

s0070
p0325

Skin and hair changes

Lithium may cause a variety of skin rashes, eruptions or irritations. The commonest problems are a simple skin rash, pustules or acne. Occasionally there are more exfoliative irritations that, in the extreme, may amount to psoriasis. Changes in the texture of the nails, with pitting, may point to a predisposition to psoriasis and perhaps should lead to a discontinuation of treatment. These problems usually clear up once the drug is stopped but recur once it is restarted. Lithium accumulates in skin and sensitivity to that accumulation leads to problems. Normally a tetracycline antibiotic would be given to treat acne, but tetracyclines are contraindicated with lithium because of kidney problems. Increased omega-3 fatty acids may be of some benefit.[13]

p0330 In about 5% of people there may be marked hair loss on lithium (alopecia). This usually clears even whilst remaining on treatment, but occasionally it will resolve only once the drug has been discontinued.

s0075
p0335

White cells

Lithium increases the number of white cells in the blood. This will not be noticed by anyone on treatment, but it may cause a doctor to wonder about an infection, as infections also lead to an increased white cell count. This effect of lithium is sometimes used in the management of leukaemias and other blood disorders.

s0080
p0340

Hypothyroidism

Lithium can lead to underactivity of the thyroid gland. The signs of this are dry skin, dry hair, hoarseness, weight gain, hair loss, sluggishness, constipation and sensitivity to the cold. On blood tests, there are low thyroid hormone (T_4 and T_3) levels and increased thyroid-stimulating hormone (TSH) levels, and the thyroid gland may enlarge to produce a goitre. The likelihood of either hypothyroidism or goitre is increased in women over the age of 45 years and in individuals who have thyroid antibodies (these are naturally present in up to 9% of the population). Before starting lithium, it is therefore routine practice to monitor both thyroid and kidney function, and both should be repeated at anything from 3-monthly to yearly intervals.

s0085
p0345

Hyperparathyroidism (overactivity of the parathyroid gland)

Lithium commonly leads to an increase in serum parathyroid hormone levels. This will in rare cases lead to excessive calcium levels in the blood, the symptoms of which are similar to the side effects of lithium itself: thirst, increased urine, loss of appetite and nausea.

s0090
p0350

Tiredness

A relatively common complaint of patients on lithium is tiredness. In some instances, this may be quite marked. Trying to tease apart what is caused by depression and what is caused by lithium may be difficult.

User issues—cont'd

s0095 Tension and restlessness

p0355 In a small proportion of cases, lithium may give rise to tense, restless feelings. It may be difficult to decide whether lithium is causing the problem or not if a taker is also on antidepressants or antipsychotics. A further reason, of course, is that tense restlessness may be part and parcel of a depressive disorder or may occur naturally.

s0100 Concentration and memory problems

p0360 There are a number of reports that lithium can interfere with memory and concentration. Again this is difficult to judge as disturbances of memory and concentration occur in depression. On the other hand, volunteers taking lithium also report difficulties with memory and concentration.

s0105 Confusion and distractibility

p0365 In toxic doses, lithium causes confusion and distractibility. Normally, toxic effects occur when lithium concentration goes over 1.5 mmol/L, but it is possible to have central nervous system toxicity in the presence of essentially normal plasma levels of lithium. In cases of toxicity, confusion and distractibility are likely to be accompanied by nausea and vomiting as well as a variety of involuntary movements such as tremor.

p0370 Toxicity is more likely if the subject has recently been put on other drugs, particularly antipsychotics. It may also occur if they have developed an increased temperature or decreased their fluid intake because of an infection and have become dehydrated. It can even happen if dehydration occurs because of an altered salt intake.

s0110 Headache

p0375 Recurrent headaches are a rare side effect of lithium. If they occur, they should be treated seriously. They may indicate raised intracranial pressure. This clears up once the lithium is discontinued but must be detected as early as possible.

User issues

b0020

s0115 **Lithium overdose**

p0380 Lithium becomes toxic at levels over 1.5 mmol/L with a risk of enduring damage when the levels are more than 2 mmol/L. The side effects most commonly found in toxic doses are nausea, vomiting, diarrhoea, tremor and confusion.

p0385 Toxicity may occur without the individual overdosing as such. Dehydration from excessive perspiration, a high temperature or restricted fluid intake may raise plasma levels. In addition, other drugs may increase plasma levels (see Drug interactions below). Inadvertent overdosage may come about simply by altering salt intake. In occasional cases, toxicity seems to occur even in the presence of an apparently normal lithium level.

p0390 The first treatment for toxicity is to give large volumes of isotonic saline (water with salt added to the level normally found in blood) intravenously. If lithium levels exceed 4 mmol/L, dialysis is usually indicated.

User issues

Contraindications to lithium therapy

Lithium is contraindicated or should be taken with caution in:

- Pregnancy. At present, studies in animals and surveys of babies who have been delivered by mothers who have been on lithium both at the time of conception and throughout gestation suggest that there is a small increased risk of heart defects in the child.

Later in the pregnancy, the risk to the foetus is less, but lithium has been linked to neonatal hypothyroidism. It also becomes difficult in pregnancy to know what plasma lithium levels mean, given that pregnancy brings about a large increase in body water.

There is a risk of lithium intoxication to both mother and baby after delivery, as the extra body water shrinks rapidly and may increase plasma lithium levels. For these reasons, it may be prudent to discontinue lithium during pregnancy.

u0110

- Breastfeeding. Lithium gets into breast milk. Whilst it is not clear if lithium poses a risk to children reared on breast milk, this is clearly of concern. If breastfeeding whilst on lithium, it may make sense to take lithium once a day only and to ensure that feeds have taken place before the lithium dose to ensure the lowest possible level of lithium in the breast milk.

u0115

- Cardiac conditions. One-fifth or more of patients on lithium have increased QT intervals on electrocardiograph (ECG) recordings. This can be a significant problem if the person is also on another psychotropic drug as most are likely to increase QT intervals.

u0120

- Neurological disorders, such as Parkinson's disease, Huntington's disease or any other organic neurological condition.

u0125

- Kidney disease.

u0130

- Thyroid disease.

u0135

- Ulcerative colitis or irritable bowel syndrome.

u0140

- Psoriasis, acne or hair loss.

u0145

- Systemic lupus erythematosus.

u0150

- Cataracts.

User issues

Drug interactions

b0030

Diuretics

s0125

Diuretics lead to water loss, which may lead to an increase in lithium plasma levels and accidental lithium toxicity. If it is necessary to use diuretics, the lithium dose may have to be reduced. Theoretically the best diuretic to use with lithium is amiloride.

s0130
p0460

Painkillers

Lithium should be combined cautiously with most common analgesics. Most of them increase lithium levels and risk lithium toxicity. For mild and occasional aches, pains and fever, the best painkiller or anti-inflammatory agent to use is probably paracetamol. For more severe painful or rheumatoid conditions, it appears that the best treatment is sulindac, which lowers lithium levels. All other drugs are usable with extra monitoring of plasma lithium levels.

s0135
p0465

User issues —cont'd

s0140 Others

p0470 Lithium antagonises the effects of most social drugs. The effects of alcohol, cocaine, amphetamines and other stimulants are all reduced. Tea and coffee, however, and related drugs such as theophylline, which is used for asthma, may lead to a lowering of lithium levels.

p0475 Lithium may also interact with calcium channel blockers, used to treat angina, hypertension or cardiac arrhythmias, and with angiotensin-converting enzyme (ACE) inhibitors, used in the treatment of hypertension.

s0145

THE ANTICONVULSANT MOOD-STABILISERS

p0480 The role of anticonvulsants in mood-stabilisation begins with carbamazepine and valproate.

p0485 Carbamazepine was discovered by Teruo Okuma in Japan.[7] Both lithium and carbamazepine seem to have some anti-irritability action – carbamazepine is used in the management of aggression, in what are sometimes called episodic dyscontrol syndromes, and lithium has also been shown to be useful in aggression. Carbamazepine is also commonly used for, and can be remarkably beneficial for, chronic neuropathic pain syndromes, especially trigeminal neuralgia. Other anticonvulsants such as gabapentin seem to share this action.

p0490 It seems unlikely that common anti-irritability actions are what underpin the benefits of both carbamazepine and lithium in recurrent mood disorders, as the two drugs seem to be useful for different patients, with claims that lithium is more useful for the classical and purer forms of bipolar mood disorder and carbamazepine for more irritable, dysphoric forms of mania.[14] Carbamazepine, like lithium, seems to be more useful for manic than depressive states.

p0495 Valproate, which comes from valproic acid, is an oil that was used as a butter substitute in Germany during the Second World War. Afterwards, it was used as a solvent for a variety of medicines. In this form its anticonvulsant properties were discovered in the early 1960s. Pierre Lambert discovered its mood-stabilising properties later in the 1960s.[6]

p0500 The use of valproate increased dramatically during the 1990s because of a vigorous promotion of semi-sodium valproate (Depakote – see Table 7.2) in

t0015 **Table 7.2** *The anticonvulsant mood-stabilisers*

Generic drug name	UK trade name	US trade name	Mode of action
Carbamazepine	Tegretol/Teril CR	Tegretol	Sodium channels
Oxcarbazepine	Trileptal	Trileptal	Sodium channels
Lamotrigine	Lamictal	Lamictal	Sodium channels
Sodium valproate	Epilim	Depakene	GABA-ergic
Semi-sodium valproate	Depakote	Depakote	GABA-ergic
Gabapentin	Neurontin	Neurontin	GABA-ergic
Pregabalin	Lyrica	Lyrica	GABA-ergic
Topiramate	Topamax	Topamax	Sodium channels, GABA-ergic, carbonic anhydrase inhibitor
Zonisamide	Zonegran	Zonegran	Sodium channels, GABA-ergic, carbonic anhydrase inhibitor
Levetiracetam	Keppra	Keppra	Unknown

the US. Sodium valproate (Epilim) and valproic acid (Convulex) were used elsewhere, and sodium valpromide is also available in France. All versions of this drug break down to valproic acid in the body. It is ethically difficult to run trials of either valproate or other anticonvulsants in patients with bipolar syndromes or other recurrent mood disorders because of the need to randomise patients at high risk of suicide to placebo for possibly several years to demonstrate a reduction in the rate of recurrences. Instead, agents such as valproate have been through trials in mania or depression, and their use as prophylactic agents has spread from there. Valproate has a clear antimanic action, possibly in large part because of its initial sedative effects.

p0505

Its popularity has meant that there are now large patient databases in which its use can be compared to that of lithium. Whilst these are not randomised trials, so patient selection factors may influence the results, at present lithium use is linked to a lower rate of suicides and suicidal acts than valproate. At the moment, as with other anticonvulsants, valproate is being used widely in borderline personality disorders, post-traumatic stress disorders, panic disorder, pain syndromes and dysphoric mood disorders with accompanying alcohol and drug misuse.[13]

s0150

MODE OF ACTION

p0510

The anticonvulsants can be divided by their mechanism of action into three groups – sodium channel blockers, gamma-aminobutyric acid (GABA)-acting drugs, carbonic anhydrase inhibitors and levetiracetam (see Table 7.2).

p0515

Even though they have different modes of action, the anticonvulsants have many effects in common. They induce suicidality, cause birth defects, lengthen QT intervals, cause cognitive problems and have effects on skin. Teasing out the profile of effects of anticonvulsants is trickier than teasing out the profile of antipsychotics and antidepressants because these drugs are usually co-prescribed.

p0520

But the common problems are clear partly because these drugs are used for epilepsy and migraine as well as for mood disorders and these problems show up where there are no other confounding treatments and no psychiatric illnesses to confound the picture.

p0525

The common effects will be dealt with here and individual effects below.

s0155

SUICIDALITY

p0530

Just as antidepressants and antipsychotics do, anticonvulsants induce suicidal behaviour and ideation. In the case of the antidepressants, there is a better understanding of akathisia and disinhibition that leads on to suicide. The anticonvulsants can cause a dysphoria but less obviously cause the kind of akathisia seen with selective serotonin reuptake inhibitors (SSRIs) and antipsychotics. Where the antipsychotics typically induce dysphoria and suicidality within hours or days, and antidepressants typically do so in days or weeks, the anticonvulsants are more likely to do so in weeks or months. Over weeks or months, there can also be personality changes in the person taking the medication.

p0535

These drugs are also likely to lead to aggressive behaviour and hostile or even homicidal behaviour with levetiracetam (Keppra) and topiramate appearing to be the worst. Keppra rage is well-known in internet chat groups.

s0160

BIRTH DEFECTS

p0540 The risk of birth defects with sodium valproate is well known, and its use is contraindicated in pregnancy. But in fact most if not all anticonvulsants appear to have a capability to cause a full range of birth defects, including severe neurological problems like spina bifida, but also mental impairment or developmental delay or what is increasingly termed autistic spectrum disorder. As with all drugs that cause birth defects, anticonvulsants are linked to a high rate of miscarriages (spontaneous abortions).

p0545 The term foetal valproate syndrome (FVS) is now well known, but in fact foetal anticonvulsant syndrome (FACS) was described earlier than FVS.

s0165

SKIN PROBLEMS

p0550 The risk of Stevens-Johnson syndrome came to the fore with the use of lamotrigine for mood disorders. This lethal disorder in which the upper level of the skin peels away was new for mental health and grabbed the imagination. But all anticonvulsants can cause this problem or a closely related toxic epidermal necrosis. To complicate matters, all cause a range of skin rashes and eruptions and exanthema so both those on treatment and those looking after them, who typically know little about skin conditions, can become very alarmed and wonder if what they are seeing might be lethal. It usually won't be lethal but has to be checked out.

s0170

CARDIAC EFFECTS

p0555 As with the antidepressants and antipsychotics, the anticonvulsants close to
AU:5 universally lengthen QT intervals. This effect is potentially more worrying in the case of mood-stabilisers as they are more likely to be combined with other drugs that also lengthen QT intervals. It may therefore be unclear which of several drugs is causing palpitations, tachycardia, an irregular pulse, heart failure or ECG abnormalities, but if any of these do happen, all elements of the treatment package will need review.

s0175

BURNING FEET

p0560 These drugs all cause peripheral sensory neuropathies. One of the classic signs of this is burning feet (causalgia). Hands, mouths and other parts of the body can burn also. Other features include a variety of bizarre sensations around the body or sensations of pain on temperature change. The paradox is that these drugs can also relieve pain. The worry is that they can end up causing
AU:6 conditions like the ones they were given for in the first instance.

p0565 Linked disturbances include tinnitus, visual disturbances like visual snow, altered taste perception and temperature dysregulation.

s0180

CARBAMAZEPINE AND OXCARBAZEPINE

p0570 There is a premium on finding who suits carbamazepine as the drug is not pleasant to take if it does not suit. On the other hand, carbamazepine is now

off-patent, and there are no company efforts to defend its reputation. A derivative of carbamazepine, oxcarbazepine, is now more commonly used for prophylactic purposes than carbamazepine but with little reason to believe it offers significant advantages.

b0035

User issues

s0185

Side effects of carbamazepine and oxcarbazepine

p0575

The side effects of these two drugs include dizziness, unsteadiness, balance disturbances, drowsiness, nausea, abdominal discomfort and visual disturbances including double vision, nystagmus and eye pain. One strange effect is facial oedema so that a person's face can change shape.

p0580

They cause disorientation, confusion and cognitive decline up to pseudodementia levels. They can sedate heavily up to a semi-comatose level. Skin rashes occur in up to 15% of takers. For some, these can be very unpleasant to take.

p0585

Carbamazepine can cause almost any metabolic or blood parameter to change: low white cell counts, anaemia, hypothyroidism and low sodium levels, increased liver enzymes, increased bilirubin and frank jaundice.

p0590

At present, the evidence suggests that lithium is better in the more classical forms of manic-depressive illness. Carbamazepine has also taken something of a backseat to other more recent anticonvulsants. Its efficacy in some forms of aggression and especially for pain syndromes is, however, undoubted.

p0595

In general, a plasma level of between 4 and 12 mg/L is aimed for. The dose needed to produce such a level may vary considerably. It is customary to start on a dose of 200 mg per day and increase slowly – usually 200 mg per week – aiming at a dose of 800–1200 mg per day.

p0600

If there are signs of fever, sore throat or infection of any sort, a white cell count should be performed; if this is low, it may be necessary to discontinue treatment. In general blood counts and liver function tests should be carried out at something between monthly and 3-monthly intervals as carbamazepine is linked to agranulocytosis and aplastic anaemia.

b0040

User issues

s0190

Drug interactions

p0605

Carbamazepine induces liver enzymes. As a consequence, many other medications are metabolised more rapidly, notably the contraceptive pill. This may mean that a number of treatments do not work as well as before. Essentially almost all other agents will have their levels reduced by carbamazepine. Carbamazepine also blocks calcium channels and therefore it should be used cautiously with calcium channel blockers.

s0195

Contraindications to carbamazepine

p0610

In pregnancy, as with valproate, carbamazepine is linked to spina bifida and neural tube defects and to a higher than expected rate of congenital abnormalities. It gets into breast milk and can potentially lead to problems for the child ranging from sedation through to withdrawal.

s0200

SODIUM AND SEMI-SODIUM VALPROATE

b0045

User issues

s0205

Side effects of valproate

p0620

The common side effects are nausea, stomach cramps and diarrhoea, tremor, lethargy and weight gain. Up to one in six takers find that their hair thins or changes in texture, often becoming curly. This may be related to zinc deficiency, and it is common to co-prescribe zinc with valproate. Valproate also commonly leads to irregular menses in up to one-half of the women taking it, as well as gynaecomastia, polycystic ovaries (in a third of women) and an increase in testosterone levels in nearly a fifth of women.[15]

p0625

As with other anticonvulsants, there may be lethargy, tremor, discoordination and slurred speech. These side effects and others are more likely in combination with antidepressants or antipsychotics. In addition, facial flushing, skin rashes and a variety of blood abnormalities including anaemia are possible. Bruising of any sort should be investigated and possibly lead to discontinuation. Valproate has been reported to trigger systemic lupus erythematosus reactions and is contraindicated in anyone with liver disease – so it should be used with caution in individuals with alcohol or other substance dependency. It should be used with caution in both children and the elderly.

AU:7

p0630

Dosages used in patients with mood disorders exceed those used for anticonvulsant therapy and range from 1200 to 2400 mg per day.

s0210

Drug interactions of valproate

p0635

Valproate inhibits liver enzymes, and this can lead to increases in co-administered drugs. For the most part, the co-administered drugs that have been looked at have been other anticonvulsants, but there also appear to be interactions with anticoagulants, salicylates, antibiotics, fluoxetine, sertraline, haloperidol, benzodiazepines and oral contraceptives.

s0215

Contraindications to valproate

p0640

Valproate is contraindicated in pregnancy because of FVS, which involves learning disabilities, dysmorphic facies, cardiac defects and limb malformations. Valproate also passes into breast milk, although at this point whether this is likely to be linked to problems for the child other than sedation is unclear.

s0220

LAMOTRIGINE

p0645

As with carbamazepine and valproate, lamotrigine began as an anticonvulsant. Like carbamazepine, it acts by blocking sodium channels on nerve cells and does so to an ever-greater extent the more the cell is in use. Reports from clinical practice that lamotrigine seemed to induce a sense of well-being led to trials in depression, with some evidence that it can be beneficial, although only a proportion of trials undertaken were ever published.[13] Lamotrigine seems to be antidepressant rather than antimanic. It is now used widely, especially in North America, in the management of mood disorders but with little good evidence for a prophylactic effect.

p0650

The usual dose is 100–200 mg daily, with the dose built up by 25 mg increments every 2 weeks. Doses up to 500 mg per day are used in some centres.

User issues

Side effects of lamotrigine

The side effects of lamotrigine overlap heavily with those of carbamazepine – almost all those reported for carbamazepine occur with it also. The commonest initial problems are rashes and fevers. A real hazard is a skin condition called Stevens–Johnson syndrome. This occurs more often in children and adolescents than in adults and is more likely when the dosage is increased quickly. In order to avoid triggering this reaction, lamotrigine is usually increased slowly over a few weeks of treatment. This skin problem shows as a tingling or itch before it develops into a rash. If caught early, there is little problem. Left too late, the condition has been fatal. The occurrence of any rash early in treatment should lead to an evaluation and possibly discontinuation of treatment.

These skin reactions are hypersensitivity reactions. However, hypersensitivity can occur without an obvious skin reaction. The signs in this case are fever, swollen lymph glands, puffiness of the face and abnormalities of liver function. Other side effects include headaches, dizziness, lack of coordination, nausea, blurred vision and either drowsiness or insomnia.

Combinations with valproate are likely to lead to an increase in lamotrigine levels and consequent toxicity. Carbamazepine, in contrast, lowers lamotrigine levels. When added to another anticonvulsant, in addition to changes in the dosage levels, there may also be a multiplication of neuropsychiatric side effects, with blurred vision, discoordination and other similar side effects becoming more common.

Lamotrigine is a risky drug to take even if there is a benefit. It should not be taken just because it is supposed to be a mood-stabiliser.

GABAPENTIN AND PREGABALIN

Gabapentin and pregabalin are essentially the same drug. Gabapentin breaks down to pregabalin in the body. Unlike lamotrigine or valproate, neither gabapentin nor pregabalin have been shown to be effective in clinical trials for mania or depression. Despite this, their use for mood disorders has increased dramatically. This may stem from an anxiolytic profile, which is appreciated by many patients. These drugs are quite benzodiazepine-like. Both can produce significant dependence.

Many people with substance-abuse and chronic personality-based problems now receive one of these drugs, with claims of benefits – leading to a circular argument that these patients must lie on a bipolar spectrum. The marketing of pregabalin has targeted women with fibromyalgia – low-grade chronic pain conditions are one of the biggest markets in medicine.

User issues

Side effects of gabapentin and pregabalin

The common side effects are drowsiness, dizziness, discoordination, visual disturbances, headaches, tremor, nausea and vomiting, slurred speech and throat pains of various sorts. Pancreatitis, liver problems and Stevens–Johnson

User issues —cont'd

syndrome have also been reported. Many people taking them, however, find them almost free of side effects and quite agreeable – which may be risky in terms of dependence.

p0690 The usual dose of gabapentin and pregabalin for convulsive disorders is up to 900 mg per day, but up to 3600 mg has been used in mood disorders. Withdrawal reactions have been reported and therefore tapering should be gradual. 'Poop-out' – an apparent loss of effect – has also been reported.

s0240

TOPIRAMATE AND LEVETIRACETAM

p0695 Even more than other anticonvulsants, these two drugs lead to a wide range of behavioural changes that are in fact neurological or semi-neurological problems. The taker can become discoordinated, clumsy and disoriented or develop slurred speech. Almost anything can happen as the Alice in Wonderland syndrome linked to topiramate indicates – where the person sees objects changing size or shape in front of their eyes. Whilst all anticonvulsants can lead to agitation and aggression, levetiracetam is linked to a well-known Keppra rage.

AU:8

p0700 The clinical picture may look like hysteria in part because the events reported can seem bizarre or like catatonia because it actually does contain catatonic features like echolalia or echopraxia. There is a risk that what happens may be viewed as part of an underlying illness and lead to inappropriate treatment rather than a removal of the triggering treatment. With these two drugs, families or carers are more likely to report the person has had a change of personality.

b0060 **User issues**

s0245 **Side effects of topiramate and levetiracetam**

p0705 In addition to the above, topiramate is linked to visual problems from glaucoma to retinal changes including macular degeneration. It is particularly likely to be linked to facial pain and eye pain and, on the other hand, a range of odd sensations around the body including numbness.

p0710 Where other anticonvulsants all cause skin problems, levetiracetam in addition is linked to acne and other facial problems such as burning mouth and painfully cracked lips.

s0250

ANTIPSYCHOTICS AS MOOD-STABILISERS

p0715 Almost all the second-generation antipsychotics have sought to position themselves as mood-stabilisers – especially olanzapine, risperidone, quetiapine and aripiprazole. The only drug with a licence for this purpose is olanzapine, gained on the basis of trials that may be better interpreted as showing olanzapine causes dependence and continuing treatment minimises withdrawal.[16]

p0720 In practice, for the past 50 years antipsychotics have been used in bipolar disorders during both remission and acute phases but in lower doses during

remission. A judicious use of an antipsychotic with lithium on a pragmatic basis seemed useful in some cases, but nobody called these antipsychotics mood-stabilisers. The recent marketing of second-generation antipsychotics misleadingly suggests that the use of recent antipsychotics in bipolar disorder is curative in a way that older antipsychotics were not.

p0725 There is clearly a place for antipsychotics for real manic-depressive illness. It may well be that some of the most dramatic responses to clozapine happen in patients who are bipolar. This being said, the risks of using drugs like olanzapine which cause dramatic weight gain, induce diabetes, cause akathisia and precipitate suicide, must be questioned in anything but the most severely ill patients.

p0730 The marketing of these antipsychotics has aimed at trying to persuade prescribers that almost any nervous problem in primary care might be bipolar disorder, especially in those who fail to respond to antidepressants or have substance misuse and personality problems. Once a person becomes bipolar the implication is that they need to stay on a mood-stabiliser for life. There is no evidence that this is a good idea.

p0735 The data behind aripiprazole offers a cautionary tale.[17] This was licensed for mood-stabilisation on the back of a multicentre study involving US and Mexican hospitals. It turns out that there were no differences between it and placebo in the over 20 US hospitals recruiting patients, but in the two Mexican hospitals it was wonderfully effective and placebo was without effect. It was only when the Mexican 'data' was added to the American data that the slightest benefit could be shown.

b0065 **USER ISSUES**

s0255 **Side effects of antipsychotics**

p0740 AU:9 AU:10 When used as mood-stabilisers, the antipsychotics have all the side effects outlined in Chapter 3, including dyskinesias, dystonias, Parkinsonism, demotivation, akathisia, tardive dyskinesia, weight gain, metabolic syndrome and diabetes. The hazards outlined here focus on certain key areas where the antipsychotics compare with other mood-stabilisers.

p0745 One of the major issues with mood-stabilisers outlined above is the risks posed by treatment in pregnancy and breastfeeding. In contrast to valproate, carbamazepine and lithium, the risks to the foetus at one point seemed less with older antipsychotics. But this lack of evidence may hinge on the fact that until recently anyone given these drugs had schizophrenia and were much less likely to get pregnant. Wider use of these drugs may bring the risks more clearly to light. It typically takes a decade or two for the risks of a treatment in pregnancy to emerge.

p0750 All antipsychotics except clozapine increase lactation, but in general they are incompatible with breastfeeding because of the risks of dependence and withdrawal posed to the baby.

p0755 This is a particular issue in women with bipolar disorders, who are at a much higher risk of postpartum psychosis than other groups. The very first manifestation of bipolar disorder may in fact be in the form of a postpartum psychosis. The best possible management of such episodes may be of considerable importance therefore to the future well-being of both mother and child.

s0260

COCKTAIL TREATMENT

p0760 In the 1980s, the big issue in schizophrenia treatment was mega doses of antipsychotics. The issue in bipolar disorder is cocktail treatment. Patients who are 'resistant' to one mood-stabiliser often end up on cocktails of six or seven 'mood-stabilisers'. This practice rests on a misinterpretation of what clinical trials show. Trials are portrayed as showing that anticonvulsants or antipsychotics 'work' for bipolar disorders, when in fact the trials have only shown usefulness in mania and even in mania the correct interpretation is that these trials have shown that it is not correct to say this drug does nothing more than placebo. Exactly what the benefit is, is less certain, and may be little more than a sedative effect.

p0765 Putting people on five or six drugs that have all been shown to work sounds reasonable to many people and might overcome their scruples about drugs or concerns as to whether they were really ill enough to be on this many drugs. Putting people on five or six drugs, regarding the effects of each of which we are deeply uncertain, is a very different matter. But none of these drugs, except perhaps lithium, has been clearly shown to reduce the frequency of episodes. Because they are called mood-stabilisers, however, the assumption is that this must be what they do. If the drugs can't be shown to reduce episodes, the sensible basis for taking them would lie in the taker being able to identify something useful a particular drug does for them. Few people, however, are likely to be able to pick out a useful something like this from any drug if they are taking five or six different drugs.

p0770 In the case of rapidly cycling mood disorders or other resistant mood disorders, treatment may often be part of the problem. Many of the mood-stabilisers interfere with a variety of vitamins such as folate, or essential minerals such as zinc, making a clinical response much less likely. Rather than add to cocktails, an earlier consideration of adding diet and hygienic manoeuvres to a drug would seem a better bet.

p0775 All of these 'stabilisers' cause significant withdrawal problems in at least a proportion of cases. Dose reduction therefore must be gradual. Convulsions and a range of other problems have been produced by over-rapid cessation.

s0265

CODA

p0780 There are two further issues to consider here. There is reason to doubt that many 'mood-stabilisers' do much good, but there is no reason to doubt they have a psychotropic effect. The problems may stem from efforts to shoe-horn these effects into a categorical model of disease that assumes mental disorders are like bacterial infections and that the role of drugs is to eliminate them. This is the way companies are forced to bring their drugs on the market at present. The alternative is that the drugs interact with dimensions of our personalities, so that some agents will suit one person and others will suit another, in which case the task becomes one of identifying what the drugs do for the patient and maximising effects that are useful.

p0785 A second issue is that although there has been an explosion of interest in bipolar disorders in recent years, and apparently a lot more drugs and a lot

more information, in fact the quality of that information is extraordinarily poor with few studies being done for purposes other than marketing and few of the data publicly available.

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