The role of lithium clinics in the treatment of bipolar disorder

**REFERENCES**


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**ABSTRACT** Shaw, M. (2004) The role of lithium clinics in the treatment of bipolar disorder. *Nursing Times;* 100: 27, 42–46. Bipolar affective disorder is a serious and enduring mental health problem, which is associated with high mortality rates worldwide. Lithium is a first-rank treatment for this disorder but with its narrow therapeutic range and associated risks of toxicity, careful monitoring of its use is mandatory. Lithium clinics ensure that patients using this therapy have access to appropriate monitoring on a regular basis, providing immediate results for lithium level testing. Clinics also provide support and education, encouraging patients to take responsibility for monitoring the side-effects of their treatment.

Lithium therapy remains a key component in the treatment of psychiatric conditions where the main symptoms are mood changes. As with many psychotropic drugs, lithium requires strict monitoring as it works within a relatively narrow therapeutic range – too little and it will be ineffective, too much and it could be toxic. Patients who are prescribed lithium must have access to robust monitoring protocols to reduce the risk of physical harm caused by toxicity.

In the UK lithium is licensed for the treatment and prophylaxis of mania, bipolar disorder, and recurrent depression (British Medical Association and Royal Pharmaceutical Society of Great Britain, 2003). As a general rule, lower dosages are used in patients who have recurrent depressive disorders, usually in combination with antidepressant therapy, and higher dosages are used in patients with bipolar affective disorder. Higher dosage regimens are also associated with patients who experience severe disabling manic episodes. Older people tend to receive lower doses of lithium.

Bipolar affective disorder

Mood disorders occur across a spectrum, with mania at one extreme, severe depression at the other, and intermediate stages between these two extremes (Table 1). We all occupy a position within the affective spectrum and our position on this continuum can fluctuate.

Manic depression or bipolar affective disorder is classified as bipolar I illness (BPI) and is characterised by distinct episodes of mania contrasting with episodes of severe depression. Bipolar II illness (BPII) is a less severe form of the condition with depression alternating with periods of hypomania. Hypomania differs from ‘true’ mania in that this state does not include psychotic symptoms (such as hallucinations) or lead to severe social and occupational dysfunction.

Cyclothymia is a condition in which the person experiences numerous brief episodes of hypomania and minor depression. These classifications are based on the International Classification of Diseases, in the UK the ICD-10 (World Health Organization, 1992).

**Manic episodes**

Manic episodes are characterised by at least one week of profound mood disturbance with elation, irritability, or expansiveness and include three or more of the following symptoms:

- Grandiosity;
- Diminished need for sleep;
- Excessive talking/pressure of speech;
- Excessive engagement in pleasurable activities, often with painful consequences;
- Distractability;
- Increased activity (including sexual activity);
- Racing thoughts/flights of ideas.

Such mood disturbances will cause impairment at work, or danger to the patient or others.

**Hypomanic episodes**

Hypomanic episodes are characterised by at least four days of elevated, expansive or irritable mood, with three or more of the following symptoms:

- Grandiosity or inflated self-esteem;
- Diminished need for sleep;
- Pressured speech;
- Racing thoughts/flights of ideas;
- Mood disturbances that are observable to others;
- Distractability;
- Psychomotor agitation;
- Engagement in activities that have a potential to result in painful consequences.

**TABLE 1. THE AFFECTIVE SPECTRUM**

<table>
<thead>
<tr>
<th>Mania</th>
<th>Hypomania</th>
<th>Well</th>
<th>Mild depression</th>
<th>Moderate depression</th>
<th>Severe depression</th>
</tr>
</thead>
</table>

**Engagement in activities that have a potential to result in painful consequences.**

- Grandiosity or inflated self-esteem;
- Diminished need for sleep;
- Pressured speech;
- Racing thoughts/flights of ideas;
- Mood disturbances that are observable to others;
- Distractability;
- Psychomotor agitation;
- Engagement in activities that have a potential to result in painful consequences.
Major depressive episodes

Major depressive episodes are characterised by five or more of the following symptoms, with at least one being a depressed mood lasting two weeks or more:
- Depressed mood;
- Weight loss or gain;
- Hypersomnia or insomnia;
- Preoccupation with death or suicide;
- Psychomotor retardation or agitation;
- Diminished pleasure or interest;
- Decreased concentration or marked indecisiveness;
- Loss of energy.

These depressive symptoms will cause significant impairment and distress.

Epidemiology

Bipolar disorder is a major illness, with a lifetime prevalence in the UK of one per cent of the population (Silverstone and Romans, 1996). This compares with a lifetime prevalence of six per cent for unipolar depression (Hales et al, 1999).

There is no difference in prevalence between men and women (Keller and Baker, 1991). The incidence of bipolar disorder is higher in those who are first-degree relatives of people with the disorder.

Pathophysiology

The aetiology and pathophysiology of bipolar disorder have not been determined, despite the amount of research that has been undertaken. Theories of causation abound and range from biological, genetic, and biochemical factors at one end of the spectrum to social and anthropological causes at the other end. The reality seems to suggest that bipolar disorder arises from a combination of these factors.

The biochemistry of the brain also seems to be important in the development of the condition. It has been suggested that the disorder results from a dysfunction of the G-protein/second messenger system operating in neurones using noradrenalin and serotonin to regulate mood. Between 25 and 30 per cent of patients with bipolar disorder attempt suicide at least once and the actual suicide rate for this group of people ranges from major suicide attempts at least once and the actual suicide rate for this group of people ranges from 12 to 19 per cent (Goodwin and Jamison, 1990).

Treatment options

Patients with a diagnosis of bipolar disorder can usually be expected to be treated with some form of mood-stabilising medication. Until fairly recently the three major mood stabilisers in use have been lithium, carbamazepine, and valproate.

The latter two drugs are also first-rank treatments for epilepsy. Olanzapine (an atypical antipsychotic drug) has recently been licensed for use in the treatment of bipolar disorder (McElroy et al, 1998). All these drugs have their place in treatment options and the drug of choice for one patient with bipolar disorder may not necessarily suit another. Contraindications, potential side-effect profiles, and the patient’s life situation will provide the parameters for a prescribing decision.

For many people, treatment of their condition may involve a combination of different medications. One or more mood stabilisers, the addition of antidepressants, antipsychotics, and drugs used to control the side-effects of these drugs, can create a very complicated level of polypharmacy.

The patient’s symptomatology and personal response to treatment will determine the drug and dosage regimen. However, the use of lithium in the treatment of bipolar disorder remains popular with prescribers despite more recent additions to the choice of drug treatment options (Schou, 2001).

The history of lithium therapy

Lithium is a metal but occurs naturally as salts contained in inorganic ores. It has been used in medicine for at least 150 years (Amidisen, 1987). In the mid-19th century it was used in the treatment of gout. In 1865 mania and melancholia were incorporated into the group of gouty diseases and were therefore treated with salts that contained lithium.

In 1880 Carl Lange treated patients experiencing periodic depression with alkaline salts, which resulted in the ingestion of 5–25mmol of lithium a day (although he did not recognise lithium as the active ingredient). By the early 1950s lithium salts became widely used in the US as a salt substitute in cardiac patients. This caused many

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patients to become lithium toxic and subsequently lithium-induced renal toxicity was identified.

Also in the 1950s John Cade started to use lithium in the treatment of psychotic illnesses and he observed a very good response in patients with mania. However, many of these patients treated with lithium in the early days experienced lithium toxicity.

In the early 1970s Hartigan Baasstrup published a double-blind discontinuation study that showed beyond question the efficacy of lithium therapy (Baasstrup et al., 1970). By this time the pharmacokinetics of lithium were understood and the monitoring of serum lithium concentrations was introduced.

By 1977 practitioners were aware of the fact that long-term lithium use could induce chronic, irreversible renal damage. It became evident that patients treated with lithium exhibited varying degrees of hypothyroidism. Worryingly, in some parts of the world lithium salts are still freely available as remedies for rheumatoid and gouty diseases.

The action of lithium

The action of lithium is not well understood (Stahl, 1997). One theory is that lithium accelerates the presynaptic destruction of catecholamines (serotonin, dopamine, and norepinephrine), inhibits the transmitter release of the synapse, and clears postsynaptic receptor sensitivity with the result that the presumed overactive catecholamine systems in mania are corrected.

However, currently the most accepted theory is lithium blockade of the inositol-triphosphate and diphosphate system in the central nervous system, with its effects on the second messengers necessary for alpha-adrenergic and muscarinic transmission (Katzung, 1992).

Lithium is prescribed most frequently as a carbonate, although lithium citrate is also available. It is an oral-only preparation and ideally patients should only need to take a single daily dose, generally at night to reduce the impact of side-effects.

Lithium is rapidly absorbed from the gastrointestinal tract. Absorption from the gut is complete within eight hours and peak plasma concentrations are seen two to four hours after a dose. The distribution volume of lithium approximates to the body water volume, although its concentration in white matter, thyroid, and bones is several times higher than its concentration in plasma. There is no binding to plasma proteins and lithium excretion occurs almost entirely via the kidneys.

The elimination half-life varies with the patient’s age and ranges from 8–20 hours in younger patients who have normal renal function, to 30–40 hours in older patients or those with renal impairment (Aronson and Reynolds, 1992).

Lithium toxicity

The risk of lithium toxicity is an important drawback of the treatment. Toxicity can lead to death or to permanent damage of the cerebellum (Schou, 2001). Deaths due to lithium toxicity occur at a rate of 14 per million prescriptions of lithium (Henry, 1996). When the concentration of lithium in the blood rises to a critical level (for example, as a result of increased intake or reduced removal by the kidneys) the patient starts to experience symptoms of toxicity.

Therapeutic lithium concentrations are within the range of 0.4–1.0mmol/L. Concentrations in excess of 2.0mmol/L are associated with serious toxicity (British Medical Association and Royal Pharmaceutical Society of Great Britain, 2003). Factors that can lead to toxicity are listed in Table 2. Other risk factors include change in diet, change in activity/habits, change in water supply, change in electrolyte balance, prolonged unconsciousness, surgery with narcosis, low intake of table salt, and travel to a hot climate (Schou, 1993).

Signs of lithium toxicity include a coarse tremor, ataxia (stumbling, unsteady gait), dysarthria (slurred speech as if intoxicated with alcohol), gastrointestinal disturbances (vomiting and diarrhoea), blurred vision, drowsiness, confusion, and palpitations (Price and Heninger, 1994) (Table 3).

In addition to the potential toxic effects of lithium, there are other related side-effects, including:

- Tremor;
- Nausea, vomiting and diarrhoea;
- Polyuria;
- Polydipsia.

Side-effects are generally more severe at higher doses. However, they may persist at even very small doses.

Contraindications include renal impairment, cardiac disease, and conditions that involve sodium imbalance.

<table>
<thead>
<tr>
<th>Toxic effect</th>
<th>Plasma lithium level (mmol/L)</th>
<th>Symptoms and signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>1.0–1.5</td>
<td>Impaired concentration, lethargy, irritability, muscle weakness, tremor, slurred speech, and nausea.</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.6–2.5</td>
<td>Disorientation, confusion, drowsiness, restlessness, unsteady gait, coarse tremor, dysarthria, muscle fasciculation, and vomiting.</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt;2.5</td>
<td>Impaired consciousness with progression to coma, delirium, ataxia, generalised fasciculations, extra pyramidal symptoms, convulsions, and impaired renal function.</td>
</tr>
</tbody>
</table>
Lithium should be used with caution by pregnant women or those who are breastfeeding, older people, people receiving treatment for diabetes, people with myasthenia gravis, those who have had surgery, and those who are driving or operating machinery.

Despite all this lithium is still recommended by most authorities as the first-choice drug for the long-term management of bipolar disorder (Cookson, 1997).

There is evidence to show that treatment with lithium reduces the suicide mortality rate of people with bipolar disorder by 80 per cent (Coppen, 1994). This evidence is particularly important when taking into account that people with bipolar disorder have a mortality rate of up to three times that of the general population (Goodwin and Jamison, 1990). Due to the risks and side-effects associated with lithium treatment, effective monitoring during use of the drug is essential.

The concept of the lithium clinic was pioneered by psychiatrists in the 1960s as part of the movement to establish specialist clinics for conditions such as epilepsy and diabetes. The primary function of the lithium clinic is to provide an expert assessment and treatment setting in which treatment is supervised, lithium levels are regularly monitored, and other tests such as thyroid and renal function are provided (Abou-Saleh, 1990).

One of the crucial components of the service has to be risk reduction, by regular monitoring and support. This is especially relevant considering that 10 per cent of claims for negligence within psychiatric care are associated with lithium therapy (Medical Protection Society, 1989).

A portable ion-selective electrolyte analyser for analysing lithium levels (King et al, 1991) is invaluable once the nursing team has been trained in venepuncture and use of the equipment. The lithium analyser enables staff to provide lithium concentrations that are both accurate and immediate for patients attending the clinic.

### TABLE 5. ACTIVITIES OF THE LITHIUM CLINIC

<table>
<thead>
<tr>
<th>Activity</th>
<th>Documentation</th>
<th>Communication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Educating the patient about the condition, treatment, side-effects, and risks</td>
<td>Counselling chart in individual notes, letters</td>
<td>Educational sessions documented in letters to GP/psychiatrist</td>
</tr>
<tr>
<td>Obtaining blood samples. Every three months: lithium level, thyroid function, electrolytes. Every six months: liver function and full blood count, glucometer test. Yearly: calcium level. Other samples requested by medical officer or in response to symptoms</td>
<td>Record of date and time, any samples obtained, letters</td>
<td>GP informed of what samples taken</td>
</tr>
<tr>
<td>Lithium level analysis using portable analyser</td>
<td>Lithium level recorded in individual clinic notes, letters</td>
<td>GP, pathology department, and psychiatrist informed</td>
</tr>
<tr>
<td>Blood pressure, pulse, and weight</td>
<td>Individual clinic notes, letters</td>
<td>GP and psychiatrist informed</td>
</tr>
<tr>
<td>Patient counselled regarding lithium result during clinic appointment, including appropriate action for high or low levels</td>
<td>Individual clinic notes, letters</td>
<td>Any outcome communicated by letter (or phone if urgent) to GP and psychiatrist</td>
</tr>
<tr>
<td>Assessment of current side-effect profile, advice and support in terms of managing side-effects (for example increasing the patient’s fluid intake)</td>
<td>Individual clinic notes, letters</td>
<td>Letter to GP and psychiatrist</td>
</tr>
<tr>
<td>General support as required</td>
<td>Individual clinic notes, letters</td>
<td>Any outcomes communicated to GP and psychiatrist</td>
</tr>
<tr>
<td>Referrals as appropriate, for example psychology and counselling department for cognitive behavioural therapy</td>
<td>Referral letters</td>
<td>Referral letter, case review as appropriate</td>
</tr>
</tbody>
</table>

### REFERENCES


Gary Brown, a 36-year-old man, had been taking lithium for at least eight years. His dosage (lithium carbonate 800mg at night) had been stable for most of this eight-year period. His diagnosis was bipolar II affective disorder, currently in remission (F31.7 on the ICD-10 International Classification of Mental Illness). Mr Brown had no other current prescriptions and worked as a long-distance lorry driver and was away from home for long periods. He was very careful not to miss any of his lithium doses as he was very concerned that if he missed a dose his mood would become very high and he would no longer be safe on the roads.

Mr Brown was a regular attender at the lithium clinic and his lithium levels varied very little – usually ranging between 0.7mmol/L and 0.8mmol/L – well within the expected range for concentrations at 12 hours after an 800mg dose of lithium carbonate. Samples taken during visits to the lithium clinic had been within normal parameters. However, at his next lithium clinic appointment Mr Brown’s lithium level was found to be 1.06mmol/L, which is slightly above the therapeutic range of 0.4–1.0mmol/L. He also reported polydipsia, polyuria, and a fine hand tremor.

The possible reasons for this were explored at the time of his appointment. He had not increased the lithium dose, or taken too many tablets, the sample was 12 hours post dose, he had not altered his diet (including salt intake) or fluid intake, and he had not been prescribed any other medication. However, when asked Mr Brown said he had taken doses of ibuprofen in response to a prolonged period of toothache. Ibuprofen is known to reduce lithium clearance thus raising lithium levels.

He was advised to immediately stop taking ibuprofen (using aspirin or paracetamol instead for pain relief) and to seek dental advice, omit his next dose of lithium, increase his fluid intake, and to attend the clinic in seven days time to be reassessed. He was also given advice on the signs of toxicity.

He followed all these suggestions and on his return to the clinic he presented with a lithium level of 0.79mmol/L. The side-effects he had reported were now reduced. This case study demonstrates the importance of routine monitoring. If Mr Brown had continued ingesting ibuprofen he could have become toxic, which at the very best would have disrupted his lithium treatment. It also shows that patients need to be given appropriate information and that this is repeated at intervals. With more frequent reminders about ibuprofen, Mr Brown may have used aspirin or paracetamol instead, and in general take more responsibility for his own treatment.

In the author’s locality patients are seen before starting lithium therapy for education about their proposed treatment (this sometimes involves a visit to the psychiatric wards) and pre-lithium screening, including the following tests (Taylor et al, 2003):

- Blood pressure;
- Body weight;
- Electrocardiogram (by referral to cardiology);
- Electrolyte analysis;
- Thyroid function;

Further examinations may be indicated by the patient’s medical history (Birch et al, 1993). Education (discussion and video presentation and patient information leaflets), information about possible side-effects, symptoms of toxicity and what to do if this happens, and possible risk situations, such as dehydration, are discussed with the patient before they start to take lithium.

As lack of concordance with treatment represents the most frequent cause of treatment failure (Gitlin et al, 1984), and abrupt discontinuation of lithium is associated with significantly higher relapse rates (Baldessarini et al, 1996), it is beneficial to offer sensitive and supportive information about lithium treatment. If the patient is provided with accurate information and has a good idea of what to expect, she or he is far more likely to remain concordant, even during the first few weeks when the side-effects are more frequent and prolonged (Gitlin and Jamison, 1984).

Once patients have been assessed as medically fit to start lithium therapy (including thyroid function and renal function levels within range) they will attend the lithium clinic weekly until the dose has been stable for four weeks and the interval time is then expanded. Healthy patients under 65 attend every three months, and others every two months or more frequently depending on their mental presentation.

Table 4 summarises activity of the lithium clinic. The emphasis of activities may vary, for example newly diagnosed and newly treated patients will require much more time within the counselling framework than patients who have been taking lithium for many years. The average duration of each clinic appointment should be about 30 minutes.

As stated, some people will require much longer appointment times, especially if they are experiencing an increased level of unwanted effects or if mental health problems recur. When patients present with abnormal lithium levels, the clinic nurse needs to be able to work with the patient to determine factors that may have influenced lithium level fluctuation. The case study (Box 1) highlights such a situation.

**Conclusion**

Lithium clinics provide a crucial service for patients prescribed this very effective but potentially toxic mood stabiliser. Such clinics enable the clinician and patient to have a certain amount of reassurance that treatment is effectively monitored and support networks in place. I feel that our lithium clinics have been hugely successful and this is supported by feedback from our patients.