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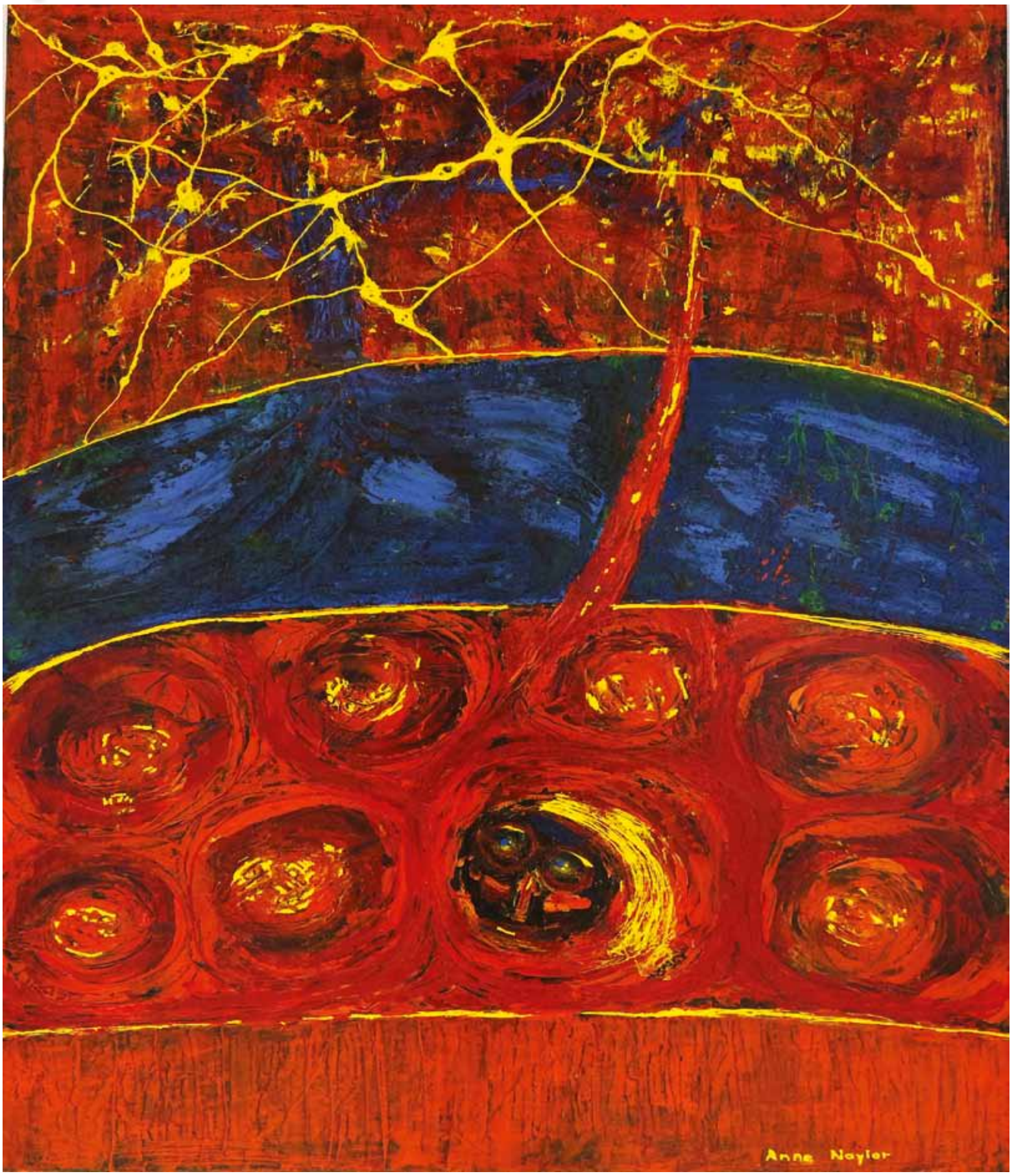

The Lithium Membrain. Artwork by Anne Naylor, author of *Art from Adversity: A Life with Bipolar*.

Why, When and How to Prescribe Lithium

The Good, the bad and the ugly

DESCRIPTIONS of mania and melancholia were documented as early as the first century, as detailed by the ancient Greek scholar, Aretaeus of Cappadocia, who recognised a cluster of seemingly disparate symptoms—intense joyfulness, irritability and unexplainable sorrow—all occurring in the same individual. His observations, along with others from the 19th century, laid the foundation for Kraepelin's description of manic-depressive illness in which the two poles of emotion are conjoined.

Modern day medicine recognises recurrent episodes of depression and mania as bipolar disorder, which is in essence a descendent of manic-depression. Bipolar disorder is a lifelong, chronic mood disorder with a progressive course. The condition incurs an enormous cost over time to both the patient and their family and society as a whole, with profound psychosocial and interpersonal consequences, long-term unemployment, medical comorbidity and a marked increased risk of suicide and suicide attempts (1). In the absence of a cure, patients with bipolar disorder require lifelong management, and thus the GP's role is central

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to the delivery of effective treatment and monitoring of mood stability, treatment adherence and medication tolerability over time.

Lithium

Lithium has been used in the management of mood disorders ever since its rediscovery in Australia by John Cade over 60 years ago, and has held ground throughout many developments in psychopharmacology. Its use in the treatment of bipolar disorder has continued in spite of a changing backdrop in the classification and treatment of bipolar disorder, and maintains its position as gold standard treatment for prophylaxis of recurrent mood episodes.

At present, lithium is regarded as first-line treatment within international guidelines for the treatment of bipolar disorder (2). It is effective in relieving the acute symptoms of mania, and in achieving complete remission and prophylaxis of recurrent episodes. By virtue of this, long-term lithium therapy is very cost effective. It has demonstrated superiority over and placebo and valproate (3, 4), as well as antipsychotics (5-7), and in addition, has important neuroprotective and anti-suicidal properties (2, 8).

However, achieving the full therapeutic potential of lithium is dependent upon why, when and how lithium is prescribed and managed for patients with bipolar disorder. This article aims to outline the key considerations regarding the use of lithium in the treatment of bipolar disorder. In many cases, lithium therapy will be indicated by specialist assessment; but increasingly the responsibility of long-term management falls to the GP.

Being aware of associated risks of toxicity, the narrow therapeutic index of the drug, and knowledge of the bipolar disorder presentations for which lithium is best suited, will equip the clinician in providing effective and tailored treatment to individuals with this illness. This article emphasises the role of the GP in monitoring both efficacy and toxicity, and working with specialists and shared care teams.

"There are so many 'good news' stories about bipolar disorder, including mine. Many of us are living with bipolar disorder and other forms of mental illness and coping very well. You just don't know who we are." - Anne

Anne Naylor, artist and author of Art from Adversity: A Life with Bipolar (9) co-authors this article and provides perspective and insight from her experience in receiving lithium treatment.

Why prescribe lithium?

Treats and prevents mood episodes

DESPITE a lack of 'Big Pharma' backing, lithium has remained the benchmark treatment for bipolar disorder and has widespread support across international clinical practice guidelines. Lithium can be used in both acute and chronic stages of mood stabilisation and is currently recommended as first-line treatment for the prophylaxis of bipolar disorder. Therefore, lithium treatment satisfies the three essential criteria of a mood stabiliser, effectively relieving the acute symptoms of 1) mania and 2) depression, while most importantly 3) preventing relapse of future episodes. Because of the long-term nature of this illness, management of bipolar disorder requires prophylaxis—not just acute or symptomatic-based care.

The BALANCE study (10) attested to the gold-standard status of lithium therapy in the long-term prophylactic treatment of bipolar disorder, by confirming the effectiveness of lithium monotherapy over valproate monotherapy in significantly preventing relapse over a two year randomised open-label trial. Indeed, in the absence of a cure for bipolar disorder, the focus shifts to prophylaxis as the main goal of treating bipolar disorder. In doing so, lithium therapy prevents hospitalisation and reduces the risk of suicide.

"What goes up must come down. For every high there is an equal or greater low. The worst thing is that there is no escape. After the cycles happen once, twice and ten more times, you know it will happen again, and again." - Anne

Anti-suicidal and neuroprotective benefits

Lithium has a recognised anti-suicidal effect with long-term administration. It is known that individuals with bipolar disorder face a risk of suicide and attempt suicide10 times more often than the general population (1), a risk that is reduced by up to 70% with lithium treatment (11, 12). This anti-suicidal effect of lithium treatment has been attributed to the 'anti-impulsive' and 'anti-aggressive' properties of the medication. When taken alongside the strong empirical support for lithium in preventing relapse in bipolar disorder, the anti-suicidal action emphasises that this medication deserves great consideration in treating this psychiatric group.

In addition to this, lithium has important neuroprotective properties that limit damage to the brain (13). It is known that every episode of mania and depression incurs a cost to neural functioning, resulting in cell loss via excitatory neurotoxicity. Over time, this can represent substantial neuroprogression in this condition. Importantly, lithium prevents such deterioration, and in possessing this property, the treatment is being considered for its application in degenerative diseases such as Parkinson's disease, Alzheimer's disease and Huntington's disease.

When to prescribe

"The good news is that bipolar disorder is eminently treatable" - Anne

WHEN should lithium therapy be initiated? What considerations do psychiatrists take into account when prescribing lithium to patients? This section describes the cases in which lithium treatment might be preferred for the treatment of bipolar disorder.

The vast majority of new lithium prescriptions come through psychiatrists in Australia. However, the ongoing management of these cases is typically managed in shared care between the GP and the psychiatrist. When the psychiatrist assesses a patient, they base their decision to initiate lithium therapy on a number of considerations. First and foremost, lithium therapy is suited specifically to patients with a 'classic' manic-depressive presentation, who present with clear periods of remission and who do not have significant psychiatric comorbidity (Figure 1). Additionally, lithium demonstrates efficacy in patients with a family history of episodic bipolar disorder. When commenced early in the illness course, the treatment provides the best opportunity for favourable long-term outcomes.

The diagnosis

Lithium therapy is best suited to diagnoses of bipolar disorder or recurrent depression, where there are marked periods of remission and recognisable episodes of mood disturbance. The criteria for depressive episodes include persistent anhedonia (inability to experience pleasure) and/or depressed mood for at least two weeks; whereas manic episodes consist of persistently elevated mood for at least one week (see Box 1 for full DSM-5 criteria). Some patients may also present with a hypomanic episode, which is a less extreme form of mania characterised by fewer symptoms and shorter duration (at least four days, but less than seven). In bipolar disorder subtypes, lithium has specificity within the 'classic' manic-depressive presentation of bipolar I disorder. Unlike other bipolar subtypes that are similarly marked by the polarity of mood symptoms, classic bipolar I disorder has a recognisable trajectory, typically commencing with a depressive episode in early adulthood, followed by periods of symptom-free remission with recurrent (predominantly depressive, but also manic) episodes over its course. The onset of illness may initially point to a diagnosis of major depression. However, in the case of recurrent depressive episodes, the clinician must not rule out the possibility of future manic episodes that may be successfully treated with lithium.

Importantly, lithium is effective in treating conditions where there is a classic episodic pattern of illness. However, there is a lack of diagnostic clarity between bipolar I disorder and bipolar II disorder. This has resulted from a lack of clarity in DSM-5, which has collapsed a myriad of presentations into the bipolar II diagnosis. In practice, this category lacks diagnostic distinction from the bipolar I diagnosis. Within this arbitrary category there is considerable heterogeneity of presentations, where the relief of symptoms is more variable.

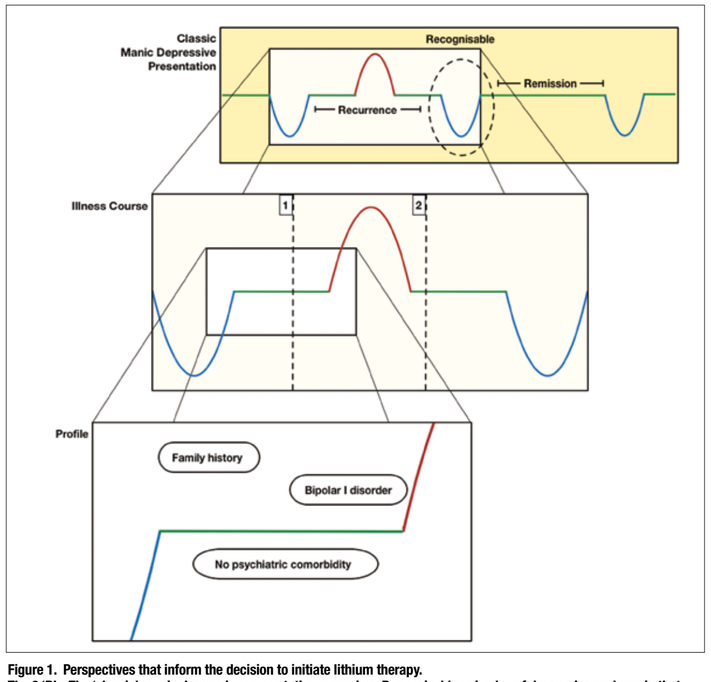

Figure 1. Perspectives that inform the decision to initiate lithium therapy.
The 3 'R's. The 'classic' manic depressive presentation comprises Recognizable episodes of depression and mania that are Recurrent and separated by periods of Remission. The illness course considers the onset of the first episode: at point 1, the patient has experienced one depressive episode, therefore lithium therapy remains a therapeutic option. At point 2, lithium therapy is indicated following the onset of a manic episode. Patient profile features indicating a patient's suitability to lithium treatment include a family history of episodic bipolar disorder, a 'classic' bipolar I disorder presentation, defined by mania, and no psychiatric comorbidity.

Lithium is better suited to the more discrete presentation of bipolar I disorder, but can be effective as an augmentation strategy for recurrent treatment-resistant depression.

Illness course

In most cases, the rationale for commencing lithium therapy early in the course of the illness is to set the therapeutic actions in motion as the acute symptoms diminish. In the long term, it is in relapse prevention where lithium excels. However, there are numerous benefits for commencing lithium early in the illness course. At the outset of treatment, there can be a delay in symptom reduction of 2-3 weeks (2). However, commencing this prophylactic agent early in the course of the illness, in addition to any short-term agents used to assist the resolution of and reduce the severity of the acute episode (such as benzodiazepines, anticonvulsants, or antipsychotics administered during hospitalisation), provides the best opportunity for good long-term outcomes (14, 15).

"Lithium really helps stabilise my mood. I still swing a lot (I have rapid cycling bipolar), but not nearly as much as I did without the lithium." - Anne

Manic Episode

A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

- Inflated self-esteem or grandiosity.
- Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
- More talkative than usual or pressure to keep talking.
- Flight of ideas or subjective experience that thoughts are racing.
- Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
- Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
- Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

Major Depressive Episode

Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

- Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, or hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
- Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)
- Insomnia or hypersomnia nearly every day.
- Psychomotor agitation or retardation nearly every day (observable by others; not merely subjective feelings of restlessness or being slowed down).
- Fatigue or loss of energy nearly every day.
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

How to manage lithium treatment

When commencing lithium therapy it is important to establish an infrastructure of shared care between the specialist and GP. This sets the foundation for the management of the patient's long-term treatment. Once the acute symptoms have been relieved, the long-term goal in lithium treatment is to prevent future episodes, while minimising side effects and ensuring treatment adherence. This is achieved through regular monitoring practices that assess lithium plasma levels and potential adverse effects.

Initiating lithium therapy

Before starting a patient is started on lithium, conduct baseline medical screening to assess contraindications and set the reference point for future monitoring practices. In particular, baseline assessment should address renal, thyroid, cardiac and metabolic functioning, all of which might affect, or be affected by, lithium treatment (16, 17). Baseline measures must establish cardiovascular functioning using ECG, as well as FBC, thyroid and renal function, pregnancy testing, physical examination and tests for urea and electrolytes (16, 18; see Table 1 for monitoring schedule). Be aware of potential interactions with other drugs (e.g., diuretics, common non-steroidal anti-inflammatory drugs) and contraindications (e.g., significant renal dysfunction, hypothyroidism, or hyponatraemia). In most instances, it is recommended lithium is discontinued before a planned pregnancy, with alternative management in place guided by a specialist (Category D). Paediatric use of lithium is generally not recommended. In the elderly, lithium doses may need to be lowered for reduced excretion. If lithium is prescribed, it is also most important at this early stage to inform the patient about how lithium therapy is conducted and monitored, its side effects as well as lifestyle factors that may interact with lithium treatment. Early psycho-education should cover the importance of treatment adherence, recognising signs of acute toxicity and relapse prevention, while also educating on lifestyle factors, for example maintaining a normal diet with adequate salt and fluid intake and limiting the impact of excessive sweating that may result from heavy exercise (18).

Dosage and administration

Lithium is usually administered as carbonate (citrate is less common). Initially, total daily doses range from 500-1000 mg and increase within the first three days to up to 2000 mg. Patients should take divided tablet doses (usually 250 mg) with food. Do not us diuretics during lithium therapy without dosage adjustment. It is not uncommon at the commencement of treatment that higher lithium plasma levels are accepted in order to treat acute symptoms.

Upon commencement, measure baseline plasma concentration levels within three days, and thereafter weekly. Once remission occurs, plasma levels should be stabilised within 0.6 – 0.8 mmol/L at lower doses (500-1000 mg/day). Different pathology laboratories provide widely varying reference intervals for serum lithium concentrations during the maintenance phase of treatment and GPs should therefor exercise caution. We recommend 0.6 – 0.8 mmol/L in accordance with local guidelines (2). In order to best estimate the stability of levels within the therapeutic band, draw blood 12 hours after the last dose, immediately prior to the next dose. Small, divided daily doses are generally best tolerated in the early course of treatment, as they reduce the risk of acute side effects. Dosage can then be increased, gradually titrating serum levels to achieve the highest dose tolerated without side effects, ranging between 0.5 – 1.2 mmol/L (16). However, if tolerated, a single daily dose may be preferred. Compared with a multiple dose regimen, a daily single-dose regimen induces less polyuria and thus reduces long-term risk of renal damage (2).

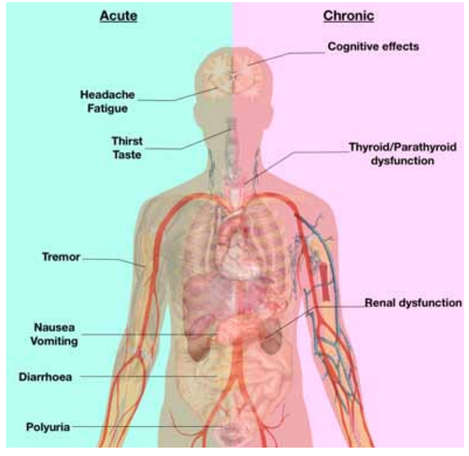

Figure 2. Acute and chronic side effects of lithium therapy.

If tolerated, a single dose taken at night (16, 19) can also be reduced by up to 25% in dose. Alternatively, a higher dose extended release tablet may be used. This can help avoid side effects, such as fatigue, and increase compliance in some patients (2, 18, 20).

Long-term monitoring

A stable, long-term therapeutic relationship that offers continuity of care is a key determinant of outcomes in patients taking lithium, and over the course of the illness, regular contact with the GP facilitates this. The setting of primary care not only allows the consideration of the overall history of the patient, but provides the scope for gauging the broader impact of the illness on the individual, their family and their work and incorporating this in long-term treatment.

Lithium has a narrow therapeutic index and a small risk of adverse effects from chronic toxicity. A regular monitoring practice must take into account the presenting symptomology, lithium plasma levels, as well the presence of adverse effects. Aside from monitoring and mitigating the chronic side effects of lithium treatment (Figure 2), the goal is to optimise treatment for each patient, achieving an acceptable balance between mood stability and reducing adverse effects and toxicity.

Monitoring for side effects

Lithium treatment is associated with both acute and long terms side effects (Figure 2) that should be

Table 1: Lithium therapy monitoring regimen

Investigations/examinations[a] (months)		0	6	12	24
Renal	Urea	◆	◆	◆	◆
	Creatinine	◆	◆	◆	◆
	Electrolytes	◆		◆	◆
Endocrine	TSH	◆	◆	◆	◆
	Serum Ca^{2+}	◆		◆	◆
Physical	Waist circumference	◆		◆	◆
	BMI	◆		◆	◆

Note. a Abnormal findings should prompt investigation and more frequent monitoring. Any significant change in mood state should prompt a repeat of investigations. Women of childbearing age should be advised that there is a risk of congenital malformation while taking lithium therapy and that it is difficult to quantify. A baseline ECG should be considered in patients over 40 years of age. (BMI: body mass index; TSH: thyroid stimulating hormone.)

identified and managed via routine monitoring. When lithium treatment is first commenced, acute side effects are common due to the rapid increases of plasma lithium concentration. These include at tremor, general fatigue, diarrhoea, thirst, polyuria, nausea, headache and vomiting (21, 22), however, in most cases, these acute side effects subside after a day or so. Generally, the occurrence and severity of adverse effects are directly related to serum levels (rather than dose), and acute adverse effects generally subside after stabilisation. Therefore, with scheduled titration taking into account elimination factors, it is suggested that patients and GPs persist with lithium at least 7 days (until stabilisation has occurred).

Chronic side effects over long term lithium treatment can affect renal and endocrine function, as well as cognitive function. In addition, there is an elevated risk of obesity and metabolic syndrome as well as cardiovascular disease in this condition (23), but this is exacerbated much less so with lithium therapy than with the chronic use of other drugs such as the atypical antipsychotics. Table 1 suggests a timetable for side effect assessment during lithium prophylaxis, at 6 month intervals in the first year of treatment, and yearly thereafter. Follow this schedule as long as the patient is in remission. However, a prompt repeat of investigations should take place in the event of a significant change in mood state, or treatment emergent signs and symptoms, or patient complaints of adverse effects. Always consider abnormal health findings in light of the patient's lithium therapy and past pathology results.

Monitoring efficacy: using the Lithiumeter to mitigate toxicity

Toxicity can be managed using the 'Lithiumeter' (Figure 3), which we have developed to guide lithium therapy according to blood plasma levels. Optimal levels for treatment initiation and maintenance are typically between 0.6 and 0.8 mmol/L, and should be individually tailored on the basis of recurrences and the nature of the episode (manic or depressive) (24). In acute phases, serum levels can be elevated to 0.6 – 1.0 mmol/L for mania and decreased to 0.4 – 0.8 for bipolar depression (2, 25; see Figure 3).

When treatment is commenced, or when dosage is adjusted, plasma levels must be checked on a weekly basis until they are stabilised to within the appropriate range. It is important that plasma levels are interpreted in the context of previous readings, and alongside current the presentation of symptoms and side effects. The clinician must always consider this, even if a plasma reading is within the therapeutic range, as an inconsistent plasma level may be an early sign of toxicity or an inconsistency in dosing. The management of side effects and toxicity should involve the consultation of an appropriate specialist: psychiatrist, renal physician or endocrinologist.

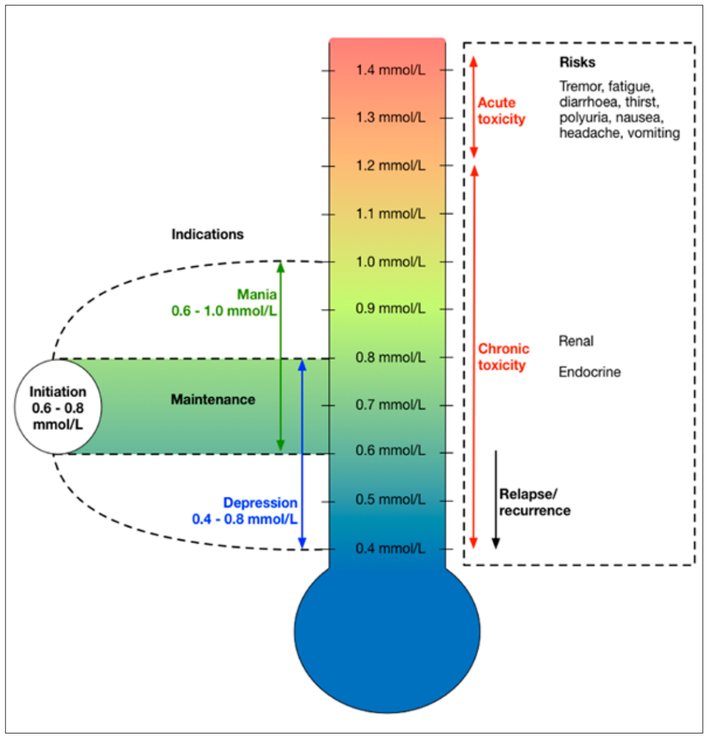

Figure 3. The Lithiumeter (adapted from Malhi et al., 2011). The Lithiumeter depicts indications and risks associated with lithium according to its blood plasma levels. Optimal levels for treatment initiation is between 0.6 and 0.8 mmol/L, and should be individually tailored on the basis of recurrences and polarity of symptoms. Risks: The risks associated with lithium therapy are illustrated on the right in red. Acute toxicity is likely at levels above 1.2 mmol/L, but, over time, even much lower therapeutic levels of lithium can lead to chronic toxicity, especially in elderly individuals. However, relapse/ recurrence is more likely at lower plasma lithium levels.

Collaborating with specialists

In the ongoing shared-care of patients receiving lithium therapy, collaboration with psychiatrists, endocrinologists and renal physicians is essential, as illustrated in Figure 4. Prior to the commencing lithium treatment, a psychiatrist consultation should oversee the decision to initiate lithium therapy. Specialists should also be consulted throughout the ongoing management of lithium treatment: the managing psychiatrist should also be consulted in the event of a "flare up" of mood symptoms, an abnormal monitoring finding or problems with treatment adherence. In the management of toxicity, the psychiatrist, as well as endocrinologist or renal physician must be involved to appropriately manage toxicity.

It is important here that the GP provides a comprehensive history of the patient's lithium therapy, including present and past pathology results and lithium levels, as well as a monitoring chart of presenting symptoms and side effects (see Table 2).

Boq???

Additional tertiary services: Lithium Clinics

While the managing physician typically conducts monitoring practices, additional tertiary services are available from lithium clinics providing outpatient specialised psychiatric care (26-32). This clinical model is being re-introduced in Australia, servicing the psycho-educational, monitoring and management needs of lithium users within a single tertiary setting.

The CADE Lithium Clinic is an outpatient psychiatry service based at Royal North Shore Hospital in Sydney, headed by Professor Gin Malhi. The main focus of the CADE Lithium Clinic is to centralise the provision of patient services, in order to improve treatment response to lithium, and to enhance patient satisfaction and overall outcomes of patients receiving lithium therapy.

Case studies

Case study one: difficulties when starting

Commencing lithium will involve initial dosage adjustments.

Xavier, a single 25-year-old, has been under the care of his GP for three years for treatment of major depression. He has become increasingly withdrawn over the past year. Xavier has been taking an SSRI for the past three years to treat his depressive episodes. However, over the past year he continues to report feelings of hopelessness and guilt but denies any suicidal ideation. Following a depressive episode 6 months ago, he deferred his university studies because of absence, and has since failed to attend regular check-ups with his GP.

Xavier was recently admitted to hospital in the context of a manic episode, and the consulting psychiatrist diagnoses bipolar I. His acute mania is initially treated with a combination of antipsychotics and benzodiazepines and his psychiatrist then gradated him to ongoing treatment with lithium, to be managed by his GP. The psychiatrist obtains baseline monitoring (full blood count, urea, creatinine, electrolytes, TSH, serum Ca 2+) and commences lithium therapy at a daily dose of 2000 mg. With resolution of the manic episode and discharge from hospital, Xavier returns to the care of his GP after one week of lithium therapy. As indicated by the psychiatrist, bloods are re-ordered by the GP. In this consultation, Xavier complains of polyuria, tremor, diarrhoea, thirst and metallic taste and questions the rationale for continuing with lithium treatment. While he reports receiving initial instructions on lithium treatment at the time of his hospitalisation, he admits that his hospitalisation was quite a stressful time. Now the episode has passed, he is unsure whether lithium is necessary, particularly given the significant side effects. Blood results at one week indicate a plasma concentration of 1.20 mmol/L, which raises concerns about potential toxicity. The GP shares this result with the consulting psychiatrist, who urges that lithium continue to be trialled, but the dose should be reduced to 1250mg to minimise acute side effects. At the next visit to the GP, the GP discusses this new dosage schedule with Xavier. The GP stresses that lithium can be extremely effective once the right balance and correct dosage are achieved. Xavier agrees to continue with lithium treatment and return after one week. At three weeks, the plasma concentration is 0.5 mmol/L, and Xavier complains of irritability and psychomotor agitation. Following consultation with the psychiatrist, the GP gradually adjusts the daily dose at weekly intervals. Plasma concentrations readings are checked and stabilised weekly at 0.5 mmol/L, 0.60 mmol/L. 0.65 mmol/L and 0.60 mmol/L. After four weeks, side effects are absent. At his most recent visit, Xavier reports a positive attitude toward lithium treatment, euthymic mood and the feeling of stability from the treatment. He has moved back home and hopes to return to his university studies in the coming semester. His GP encourages returning to studies and discusses strategies for adherence over the next year, emphasising the importance of maintaining a balanced lifestyle, with regular exercise, a healthy diet and social support. The GP sets out a treatment plan for ongoing monitoring at 1 month, 3 months, 6 months and 12 months and reminds Xavier of the signs of relapse, and responding to illness triggers.

Case study two: problems down the line

Monitoring over time is crucial, and sharing this information with specialists is essential.

Susannah, aged 45, has been receiving lithium and lamotrigine treatment for 5 years following a diagnosis of bipolar I disorder. After some initial adjustments to dosage, she has responded well to the treatment and has not experienced an emergent mood episode since commencing treatment. Her GP conducts 6-monthly monitoring of plasma concentration, renal and endocrine levels, as well as physical assessment. Over time, her concentration levels have remained stable, as have her renal and endocrine readings. However, her waist circumference has increased over the past 24 months as a result of inactivity. Susannah presents complaining of headache and intermittent double vision persisting over the past 14 days. This has left her feeling distressed and irritable as it has stopped her from driving and has impeded her ability to work. She requests an MRI investigation, and her GP organised this; no abnormal finding was reported. The GP considers potential drug toxicity, so seeks a psychiatrist opinion. The GP compiles the patient's comprehensive monitoring chart (Table 2) and shares this information with the managing psychiatrist, flagging the patient's steady increase in weight, presenting symptoms and slightly higher creatinine level. The psychiatrist advises the GP to decrease the lithium dosage to 1500 mg, based on the elevated plasma concentration reading of 0.79 mmol/L and the higher creatinine clearance level. Although the plasma concentration level is considered within a therapeutic range, within the context of Susannah's symptoms and creatinine level, the psychiatrist deems this as a potential risk to kidney function. Susannah returns after one week with no complaints of double vision and greater mood stability. She continues on the lower daily dose of 1500 mg.

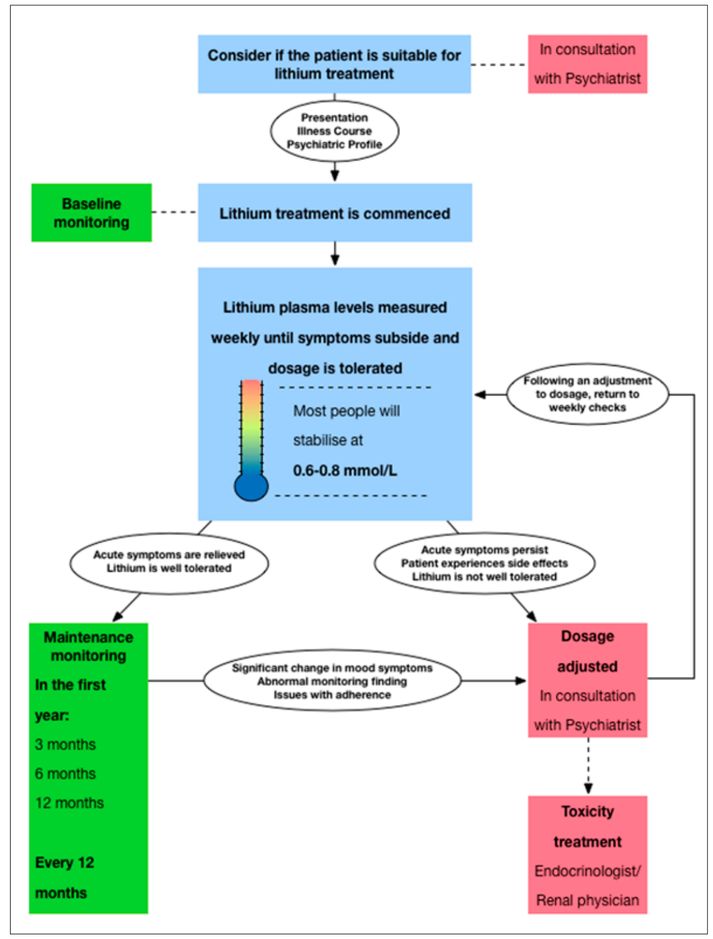

Figure 4. Collaborative care in lithium treatment.

Table 2: Maintenance monitoring chart for Susannah

	24 months ago	18 months ago	12 months ago	6 months ago	Present reading
Lithium dose	2000 mg	2000 mg	2000 mg	2000 mg	2000 mg
Plasma concentration	0.59 mmol/L	0.60 mmol/L	0.59 mmol/L	0.65 mmol/L	0.79 mmol/L
Urea	✔	✔	✔	✔	High
Creatinine	✔	✔	✔	✔	High
Electrolytes	✔	✔	✔	✔	✔
TSH	✔	✔	✔	✔	✔
Serum Ca^{2+}	✔	✔	✔	✔	✔
Waist circumference	78cm	80cm	80cm	83cm	85cm
BMI	25	26	27	29	29
Mood symptoms	Nil	Nil	Nil	Nil	Nil
Other medication	Lamotrigine (dose)	Lamotrigine (dose)	Lamotrigine (dose)	Lamotrigine (dose)	Lamotrigine (dose)
Patient complaints	Nil	Nil	Nil	Weight gain	Weight gain Blurred vision Irritability, distress
Other				MRI at local radiology – no ab	MRI at local radiology – no abnormal findings

Note.✔= Normal range

Online resources

The CADE Lithium Clinic, Royal North Shore Hospital, NSW
www.cadeclinic.com/content/cadeclinic/contacts/index.php?

Further reading

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Available on request from howtotreat@cirrusmedia.com.au

Anne's story

"When I was first diagnosed with bipolar disorder I was prescribed lithium. It was a reasonable dose and I had sudden and severe side effects, mainly gastrointestinal. I stopped taking the lithium and assumed that it was yet another medication that didn't agree with me and I would not be able to take. I was then prescribed lamotrigine with an antipsychotic. Three years later, my new (third) psychiatrist suggested I undertake another trial of lithium as my mood was still unstable. This time there were no side effects and I continue to take lamotrigine and lithium today.

For me personally, in terms of treatment, I continue to seek out the medications I tolerate the best, and I put up with the side effects. I persist with the ongoing challenge of getting the mix just right, the continual trade-offs between the benefits and the side effects. I do everything I can to prevent relapse. I anticipate my triggers and intervene early. I force myself to go to bed at a reasonable time, as I know that sleep is crucial. I exercise and eat a diet of vegetables, fruit, meat, fish and whole grains. I don't eat all the nice things in life such as chocolate, biscuits, junk food, meat pies, processed meats, pizza, chips, hamburgers, white bread, sugar or soft drink. I take fish oil and vitamin supplements. I don't smoke or drink and manage stress to the best of my ability. I do all of these things religiously, except, of course, when I don't.

It is very important to have confidence in your doctor and to see them regularly. This is why. If you trust your doctor, and have a good relationship with them, you will be more likely to follow their advice at times when your judgment is impaired.

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There can be serious side effects with lithium if it is not monitored well. I have experienced one of the more unusual side effects – hyperparathyroidism. I was lucky that my GP picked up on a pattern of mildly elevated calcium levels in blood tests that had been ordered by my psychiatrist. My GP got onto it quickly. She didn't just recommend she watch it and wait, as has happened to other people with the same condition. I needed surgery, which was carried out quickly. I was very grateful to my GP for her knowledge, quick action and sharing of blood test results with my psychiatrist.

I believe that it is thanks to my medication that I function so well, can work productively and am able to contribute to my family and to society. My life, and the lives of my husband and children would not be the same without it. I am inordinately grateful for the current medications that ameliorate the worst effects of what is a severely debilitating illness."

Anne's experience with lithium treatment in rapid cycling bipolar has seen her episodes reduce in severity and duration (Figure 5). With the ongoing support of her family, her psychiatrist and her GP, she is a successful mother of four, professional, published author and artist. She shares her experiences with mental illness through poetry and art in her book, Art from Adversity: A Life with Bipolar.

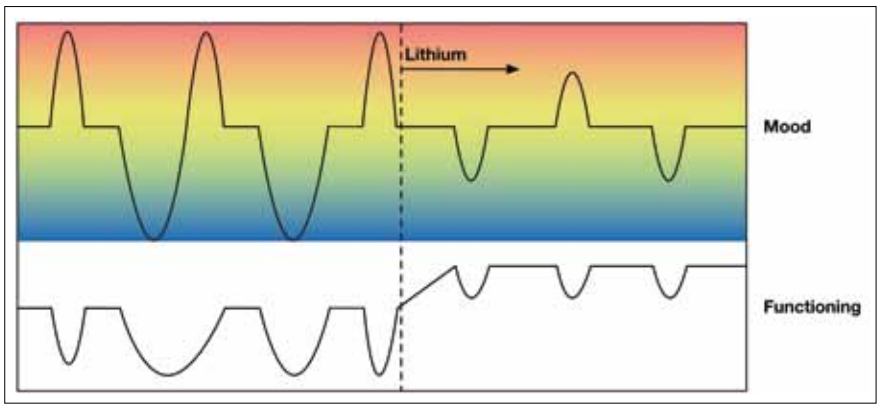

Figure 5. Anne's Mood chart illustrating her response to lithium treatment. Upon the commencement of lithium treatment, her manic and depressive episodes became shorter in duration and less severe. She reports greater stability and functionality from her lithium treatment.

Landscape of the Mind. **Artwork by Anne Naylor, author of *Art from Adversity: A Life with Bipolar.***

Conclusion

The role of the GP is central to providing ongoing care, optimising lithium treatment, the mitigation of adverse side effects and the observation of mood symptoms over time. Primary care facilitates the ideal setting for treating the patient long-term and importantly maintaining rapport and treatment adherence over time.

Take-home messages

- Lithium is the go-to treatment for 'classic' bipolar disorder presentations (clear episodes of depression and mania, with periods of remission), and the best outcomes are achieved when treatment is initiated early in the illness course.
- Lithium acts an effective mood stabiliser, relieves acute mania and depression and excels in relapse prevention. Lithium is recommended by all international guidelines.
- At the commencement of treatment, dosage requires initial refinement to optimise serum concentration levels. The 'Lithiumeter' is used to determine this.
- Regular monitoring for efficacy and side effects is suggested in long-term management. , Investigate any patient complaints or adverse events.
- The GP is central to the continuity of care, ensures patient adherence, and collaborates when necessary with psychiatrists, endocrinologists and renal physicians.
- Specialised outpatient lithium clinics, such as the CADE Lithium Clinic, provide centralised services tailored to patients receiving lithium treatment.

How to Treat Quiz

Why, when and how to prescribe lithium — 4 March 2016

INSTRUCTIONS

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points.
We no longer accept quizzes by post or fax.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.

GO ONLINE TO COMPLETE THE QUIZ

www.australiandoctor.com.au/education/how-to-treat

1. Which TWO statements regarding bipolar disorder are correct?
a) Bipolar disorder is a new illness of the twenty-first century.
b) Bipolar disorder is a lifelong, chronic mood disorder with a biological basis and progressive course.
c) The consequences of bipolar disorder include psychosocial and interpersonal issues, long-term unemployment, medical comorbidity and an increased risk of suicide and suicide attempts.
d) Bipolar disorder is a curable condition.

2. Which THREE of the following statements give support to why lithium should be prescribed for bipolar disorder?
a) Lithium is regarded as first line for the treatment of bipolar disorder.
b) Lithium is effective in relieving the acute symptoms of mania, and in achieving complete remission and prophylaxis of recurrent episodes.
c) Lithium is an expensive drug, and as a result is not a cost effective long term solution.
d) Lithium has significant neuroprotective and anti-suicidal properties.

3. Which TWO statements form part of the classic 3 Rs that describe the presentation of bipolar disorder to which lithium is ideally suited?
a) Resilience
b) Recognisable
c) Refractory
d) Recurrent

4. Which THREE statements regarding when lithium should be commenced are correct?
a) In most cases, the rationale for commencing lithium therapy early in the course of the illness is to allow the therapeutic actions to be set in motion as the acute symptoms diminish.
b) There are numerous benefits for commencing lithium early in the illness course.
c) The therapeutic effects of lithium are evident within one half-life.
d) Commencing lithium early in the course of the illness provides the best opportunity for good long-term.

5. Which TWO are acute side effects of lithium?
a) Headache
b) Renal dysfunction
c) Cognitive decline
d) Tremor

6. Which THREE are chronic side effects of lithium?
a) Polyuria
b) Cognitive effects
c) Thyroid/parathyroid dysfunction
d) Renal dysfunction

7. Which TWO statements regarding initiating lithium therapy are correct?
a) Prior to initiating lithium conduct baseline assessment of renal, thyroid, cardiac and metabolic functioning.
b) Lithium is safe in pregnancy.
c) Contraindications to lithium include significant renal dysfunction, hypothyroidism, or hyponatraemia.
d) Additional precautions are not required in the elderly when prescribing lithium.

8. Which THREE statements regarding lithium dosage and administration are correct?
a) Initially, total daily doses range from 500-1000 mg and increase within the first three days to up to 2000 mg.
b) At the commencement of treatment higher lithium plasma levels are accepted in order to treat acute symptoms.
c) Local guidelines recommend a plasma level of 0.6 – 0.8 mmol/L once remission occurs.
d) All pathology labs adhere to the same reference interval of 0.6 – 0.8 mmol/L when reporting on lithium plasma concentration levels.

9. Which TWO statements regarding side effects of lithium treatment are correct?
a) Lithium has a board therapeutic index and a small risk of adverse effects from chronic toxicity.
b) A regular monitoring practice must take into account the presenting symptomology, lithium plasma levels, as well the presence of adverse effects.
c) Generally, the occurrence and severity of adverse effects are directly related to the lithium dose.
d) The elevated risk of obesity, metabolic syndrome and cardiovascular disease in bipolar disorder is exacerbated much less so with lithium therapy than with the atypical antipsychotics.

10. Which THREE statements regarding monitoring practices are correct?
a) Plasma concentration level and side effect assessments should only be conducted when the patient presents with a side effect complaint.
b) A prompt repeat of investigations should take place in the event of a significant change in mood state, or treatment emergent signs and symptoms, or patient complaints of adverse effects.
c) It is important that plasma levels are interpreted in the context of previous readings, and alongside current presentation of symptoms and side effects.
d) An inconsistent plasma level may be an early sign of toxicity or an inconsistency in dosing.

CPD QUIZ UPDATE

The RACGP requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2014-16 triennium. You can complete this online along with the quiz at **www.australiandoctor.com.au.** Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

Australian Doctor Education

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NEXT WEEK Next week's HTT ????