Prescribing and monitoring lithium therapy: summary of a safety report from the National Patient Safety Agency

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Why read this summary?
Lithium is a commonly prescribed drug for treating bipolar disorder and unipolar (refractory) depression. Over 800,000 prescriptions for lithium salts were dispensed in England in 2008.1

Lithium has a narrow therapeutic range and may be affected by changes in renal function and fluid balance (for example, when a person is dehydrated or pregnant).2 It’s tolerability profile also provides challenges for prescribing, as adverse effects such as fine tremor may be confused with the coarse tremor seen in toxicity. Lithium treatment increases the risk of clinical hypothyroidism and renal insufficiency (both acute and chronic). Thus, tailoring doses for individual patients, with careful monitoring of lithium concentrations, estimated glomerular filtration rate, and thyroid stimulating hormone, is essential.

Treatment is usually started by a psychiatrist, with longer term care and monitoring by a general practitioner, who can be guided by the relevant quality outcome framework (QOF) target for lithium monitoring in the general practitioner contract. The 2006 guidelines from the National Institute for Health and Clinical Excellence (NICE) set out clear standards for lithium monitoring, including measurement of serum lithium concentrations every three months and assessment of thyroid and renal function every six months. These guidelines are more stringent than the current quality outcome framework targets for England.3

A quality improvement programme showed that mental health trusts often do not have electronic systems that reliably communicate test results between laboratories and health trusts often do not have electronic systems that reliably communicate test results between the laboratory and the clinical team or between primary and secondary care.4

It also showed the shortcomings in the monitoring standards of QOF and NICE and a lack of understanding among patients of side effects and signs of toxicity.5

The National Patient Safety Agency (NPSA) received 567 incident reports between October 2003 and December 2008 relating to poor lithium management, including two cases of severe harm where failures in monitoring led to lithium toxicity and admission to hospital in a critical condition. In addition, litigation data over the past 10 years show two deaths and 12 cases of severe harm, again where system failures in monitoring led to patient harms.

A typical incident report to the NPSA reads: "Emergency admission of patient for lithium toxicity in a critical condition. Unfortunately his lithium levels were out of date. The last level was within the therapeutic range, hence his lithium was re-authorised. Unfortunately, it appeared his outpatient appointments had been subject to cancellations hence his lithium levels were not being regularly monitored. Patient at time of report was being ventilated."

This summary is based on a patient safety alert issued in December 2009 by the NPSA in collaboration with the Prescribing Observatory for Mental Health and the National Pharmacy Association to improve the safety of lithium therapy, with key actions for staff (www.nrls.npsa.nhs.uk/resources/type/alerts?entryid45=65426&p=1).

Problems identified by the National Patient Safety Agency
• Poor monitoring of lithium blood concentrations and complementary blood tests, with associated inadequate systems for supporting recommended biochemical monitoring of patients prescribed lithium and the prompt communication of test results across care settings.
• A failure to inform patients of recognised side effects and prepare them to be vigilant for signs of incipient lithium toxicity.

What can we do?
• The NPSA asked healthcare organisations to review their local systems for ensuring that blood test results are communicated between laboratories and prescribers. The NPSA has also provided practitioners with a standard patient information pack, which includes a patient held record book to track lithium serum concentrations and relevant clinical tests.
• Individual practitioners who are monitoring patients taking lithium should:
  - Issue repeat prescriptions only when they are satisfied that it is safe to do so, as informed by the serum lithium concentration and the results of biochemical monitoring.
  - Monitor serum lithium concentrations every three months, aiming for therapeutic concentrations (guidance range 0.6-1.0 mmol/l)6 at which side effects can be tolerated with no toxic effects (the box lists side effects of treatment and signs of toxicity). Higher concentrations may be required for younger patients with predominantly manic symptoms7
  - Monitor older patients carefully for clinical features of toxicity (box), as they can experience toxicity even at the upper end of the guidance range8
Main expected side effects of lithium treatment and key clinical features of toxicity

**Expected side effects of lithium**
- Fine tremor
- Dry mouth
- Altered taste sensation
- Increased thirst
- Increased frequency of urination
- Mild nausea
- Increased thirst
- Altered taste sensation
- Dry mouth
- Fine tremor

**Key features of lithium toxicity**
- Vomiting or diarrhoea
- Coarse tremor (larger movements, especially of hands)
- Muscle weakness
- General lack of coordination, including ataxia
- Slurred speech
- General lack of coordination, including ataxia
- Muscle weakness

-Monitor thyroid and renal function every six months and more often if renal function is impaired. If serum urea and creatinine concentrations become raised seek advice from a renal physician and/or psychiatrist as there are trade-offs between risks of renal impairment and unmanaged bipolar disorder.
-Monitor patients carefully for clinical and biochemical evidence of hypothyroidism. Be especially vigilant for women starting lithium at age 40–59 years, whose risk is much greater than the average risk for men (>20% vs 4.5%).
-The clinical symptoms overlap with those of depression so can easily be missed.
-Ask patients to use the lithium record book and explain its importance. The record book will be the key record for all the health professionals they encounter in different settings, with up to date information on the type and dose of lithium they are taking, side effects they can expect, how these differ from more serious signs of toxicity that they must look out for, and what may cause toxicity (box; record available at www.nrls.npsa.nhs.uk/resources/type/alerts/?entryid45=65426).
-Consider the potential for concomitant medication (such as angiotensin converting enzyme inhibitors; thiazides and related diuretics; and non-steroidal anti-inflammatory drugs) to reduce the renal excretion of lithium and precipitate toxicity. Use of concomitant medication that may affect lithium therapy should be accompanied by more frequent monitoring of the serum lithium concentration.

Further details are given in the NICE guidelines and see figure.

**What else do we need to know?**

In developing the patient safety alert, the NPSA was aware of variation in the prescribing and monitoring of lithium treatment across primary and secondary care, with different approaches to shared care. Health services research to identify cost effective models of care and sharing of good practice would be welcome.

**How will we know when practice has become safer?**

Healthcare organisations were given until December 2010 to implement the actions in this patient safety alert and are required to report compliance at that point. By 6 October 2010, only a fifth (70) of the 356 organisations required to take action had reported compliance to the Central Alerting Service. The NPSA will continue to monitor incidents reported by staff. The current quality improvement programme of lithium monitoring will continue, with further clinical audits to measure performance against the standards noted above.

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Primary HIV infection encompasses the biological and clinical manifestations of the period between initial contact with the virus and the appearance of specific antibodies.  

Why is primary HIV infection missed?  
Primary HIV infection is symptomatic in most individuals but is easy to miss. In a cohort study of 46 patients with primary HIV infection, only a quarter of those with acute presentations caused by primary HIV infection were correctly diagnosed in various acute and primary care settings in the United States. The diagnosis of primary HIV infection was also missed at initial presentation in 19 of 40 patients (48%) in the United Kingdom. The infection may be missed because the symptoms are transient, often lasting less than two weeks, and tend to overlap with those of infections that are much more common in clinical practice. Failure to elicit a history of exposure to the virus, reluctance to test, and lack of awareness of the limitations of testing in the acute phase may also contribute to diagnostic delay.  

Why does this matter?  
The diagnosis of primary HIV infection has individual and public health benefits. If the infection is not recognised, a clinically silent phase follows, during which CD4 T lymphocyte counts gradually decline. Early diagnosis allows monitoring for the onset of immunodeficiency and timely institution of high active antiretroviral treatment. Late diagnosis is associated with HIV-related morbidity and mortality and adds to the cost of antiretroviral treatment. Patients with primary HIV infection have high levels of viraemia and are more likely to transmit the infection by sexual contact. Counselling may thus reduce sexual risk behaviours and transmission of infection.  

HOW COMMON IS PRIMARY HIV INFECTION?  
Symptoms are present in 50-90% of individuals with primary HIV infection. During 2008 there were 7298 new diagnoses of HIV in the United Kingdom. In the same year, 27% of the estimated 83,000 people with HIV were thought to be unaware of their infection (because many people only realise they have HIV infection when they develop full blown AIDS). The two groups with the highest HIV prevalence in the UK are men who have sex with men, and black African heterosexuals. The number of new infections acquired heterosexually increased by 53% (from 740 to 1130 cases) from 2004 to 2008. The estimated numbers of new infections acquired through injecting drug use and mother to child transmission (170 and 110 cases respectively in 2008) have remained stable since the start of the epidemic.  

CASE SCENARIO  
A previously healthy 19 year old man was admitted to our medical ward with a history of fever, sore throat, and a maculopapular rash on his trunk. An upper respiratory tract infection had been diagnosed in the community a few days before. A monospot test (for infectious mononucleosis caused by Epstein-Barr virus) was negative, and he initially denied risky sexual behaviour and declined an offer of HIV testing. His symptoms improved, but before discharge he mentioned to the ward sister that he had had a casual sexual encounter with a man a few weeks earlier. He then consented to an HIV test, which was positive for the p24 antigen.  

How is it diagnosed?  
Clinical features  
Fever is the most common symptom, present in 80-90% of patients. It typically appears two to four weeks after the infection and is commonly associated with sore throat and cervical lymphadenopathy. This may lead to the erroneous diagnosis of mononucleosis or tonsillitis. A non-specific maculopapular rash is seen in over 40% of patients but may be difficult to detect in patients with darkly pigmented skin. Headache may be present in over 50% of patients and may suggest HIV invasion of the central nervous system, an early event in the natural course of the infection. Primary HIV infection must be included in the differential diagnosis of patients presenting with aseptic meningitis.  

Diagnosis is easier if the patient volunteers the information of possible exposure to HIV or is known to belong to a high risk group for the disease. Disclosing this information may, however, be difficult both for the patient and the doctor (case scenario) owing to the need to probe into the sensitive issues, such as high risk sexual behaviour and substance misuse. These difficulties can be magnified when clinical contact is occasional and there is little time to forge a close doctor-patient relationship. If a patient refuses a test, explore the reasons for this and correct any inaccurate beliefs about infection or the consequences of testing; document the patient’s reasons for declining the test.  

In developed countries, men having sex with men represent the category most at risk of primary HIV infection. Unprotected anal (less commonly oral) intercourse remains the primary route for transmission. Most heterosexual patients with HIV in the United Kingdom have contracted the disease abroad, mostly in sub-Saharan Africa. However, the number of people infected heterosexually in the UK is increasing. Transmission through injecting drug use and mother to child transmission have remained low since the start of the epidemic.
PRACTICE

Investigations

By definition, primary HIV infection precedes seroconversion, and therefore testing limited to viral antibodies may initially convey negative or borderline results. The infection is characterised by a high plasma virus load, and direct testing for viral antigen (p24 antigen) or nucleic acid (HIV RNA) usually confirms the diagnosis (figure). Although p24 antigen testing is less sensitive than HIV RNA (88.7% vs 100%), it is usually preferred in non-specialist settings because it is less expensive (£2 vs £7.5 in our institution) and associated with fewer false positive results (100% vs 97.4% specificity). Nowadays testing for antibodies and p24 antigen can be carried out simultaneously, and clinicians should liaise with local laboratories about available tests. As highlighted in a recent statement by the British Association of Sexual Health and HIV (BASHH), patients presenting very early after onset of symptoms may still be missed by currently available tests. When such tests first give negative results, follow-up testing is recommended three months later. Antibodies are detectable three to 12 weeks after infection but may occasionally take as long as six to 12 months to appear. Pretest counselling does not usually need to be lengthy but should cover the benefits of testing and how the results will be conveyed. Written consent is also not routinely necessary as this may discourage the test by according it special status.

How is it managed?

After diagnosis, refer the patient immediately to a specialist for further investigation and management. Results should be clearly communicated in person and in a confidential environment. Avoid detailed counselling after HIV testing but reassure the patient that their symptoms are temporary and do not reflect permanent immunosuppression and that the condition is treatable. Also explore available support to the patient for coping with the diagnosis. Finally, discuss appropriate measures to prevent onward transmission of infection.

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Approximate time course of viral and antibody changes during primary HIV infection

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Patient consent obtained.


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A memorable patient

Being prepared

When I asked a patient attending the emergency department for his drug history he retrieved a paper from his pocket. It was the size of the relevant box on my clerking form and contained a typed list of his 23 medications, complete with his name, date of birth, and hospital number. On its back was double sided tape so that I could attach it to the notes.

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Patient consent not required (patient anonymised, dead, or hypothetical).

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RATIONAL TESTING

Investigation of peripheral neuropathy

Richard Hughes

The investigation of the cause of symmetrical polyneuropathy should be guided by careful history taking and examination

A 65 year old woman presented with gradual onset of burning pain and loss of feeling in her toes spreading up to her ankles over three months. She had no family history of similar illness and no known other disease. She drank only the occasional glass of wine, and had not been exposed to any drugs or known toxins. Examination was normal except that she had a body mass index of 32, absent ankle reflexes; absent flexor plantar responses; and reduced pinprick, light touch, and vibration sensation in her toes.

What is the next investigation?
The clinical picture points to a diagnosis of a distal symmetrical polyneuropathy of large myelinated nerve fibres (causing numbness, impaired light touch and vibration sensation, and loss of ankle reflexes) and small myelinated and unmyelinated nerve fibres (causing pain and impaired pain sensation). Similar symptoms could be caused by a myelopathy, but the absent ankle reflexes and flexor plantar responses rule this out. Cauda equina lesions would probably cause back pain and sphincter problems, which were not present.

The investigations should be guided by the clinical picture. Questioning had already made hereditary neuropathy and neuropathy related to alcohol, drugs, and toxins unlikely. Toxins, apart from alcohol, are now rare causes, but arsenic and organic solvents need to be considered. Many drugs can cause peripheral neuropathy (box), so check the side effects of any drug that the patient is taking.

Polyneuropathy may arise in the course of many illnesses, particularly diabetes. Table 1 lists other common causes. Thus, in a general practice setting, initial testing would reasonably include the blood tests listed in table 2.

Table 1 | Most common causes of symmetrical neuropathy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>11-41% (depending on duration, type, and control of diabetes)</td>
</tr>
<tr>
<td>Paraproteinaemia</td>
<td>9-10%</td>
</tr>
<tr>
<td>Alcohol misuse</td>
<td>7%</td>
</tr>
<tr>
<td>Renal failure</td>
<td>4%</td>
</tr>
<tr>
<td>Vitamin B-12 deficiency</td>
<td>3.6%</td>
</tr>
<tr>
<td>HIV infection</td>
<td>16%, but depends on the population studied and is usually much lower</td>
</tr>
<tr>
<td>Chronic idiopathic axonal neuropathy</td>
<td>10-40% of different hospital series</td>
</tr>
</tbody>
</table>

Unless the cause can be identified and treated, the patient will need immediate specialist referral. Two of the most common and easily treated causes, diabetes and alcohol misuse, can often be identified and managed in primary care. Always refer patients with severe symptoms, rapidly progressive disease, or additional motor symptoms. Further testing should include nerve conduction studies to identify whether the neuropathy is purely sensory or also affects motor nerve fibres, and whether the primary pathology is axonal (causing dying back of axons) or demyelinating (affecting Schwann cells and myelin sheaths). Most neuropathies, especially distal symmetrical sensory neuropathies, are axonal. The causes of demyelinating neuropathy are more limited and more likely to be inflammatory and treatable. Paraneoplastic neuropathy is uncommon but a concern with recent onset neuropathy, and the possibility of an underlying neoplasm—especially a small cell lung carcinoma—should not be forgotten. Many other systemic diseases—such as sarcoidosis, Sjögren’s syndrome, and the vasculitides—can cause a painful symmetrical distal sensory neuropathy, but in these diseases an asymmetrical picture of multiple mononeuropathy is more typical.

Outcome
Fasting blood glucose, full blood count, erythrocyte sedimentation rate, liver and renal function, serum immunofixation electrophoresis, and concentrations of thyroid stimulating hormone were all normal and her serum vitamin B-12 concentration was low normal. She was referred to a neurologist, and nerve conduction tests showed reduced sensory action potentials, normal motor nerve conduction consistent with a sensory axonal neuropathy, and no evidence of demyelination. A glucose tolerance test showed impaired glucose tolerance but not diabetes, borderline serum cholesterol, and raised triglycerides. Further investigations including tests for antineuronal antibodies, which are present in about half of people with paraneoplastic neuropathy, and chest radiography were negative. Because she had no family history or other features of a hereditary neuropathy, genetic testing was not performed. Serum methylmalonic acid, a vitamin B-12
Impaired glucose tolerance has been found in 25-36% of patients—about twice as often as in controls. One study found a closer association with hypertriglyceridaemia, a feature of the metabolic syndrome, than with impaired glucose tolerance. The condition is slowly progressive, with increasing difficulty in walking and often persistent neuropathic pain. Systematic reviews have provided evidence for short term benefit from amitriptyline, pregabalin, duloxetine, and tramadol for pain, but in the long term patients often manage their symptoms without drugs because of adverse side effects.

<table>
<thead>
<tr>
<th>Drugs that cause peripheral neuropathy</th>
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<tbody>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>Bortezomib</td>
</tr>
<tr>
<td>Chloroquine</td>
</tr>
<tr>
<td>Dapsone</td>
</tr>
<tr>
<td>Disulfiram</td>
</tr>
<tr>
<td>Ethambutol</td>
</tr>
<tr>
<td>Gold</td>
</tr>
<tr>
<td>Isoniazid</td>
</tr>
<tr>
<td>Metronidazole</td>
</tr>
<tr>
<td>Misonidazole</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>Nitrous oxide (with a myelopathy)</td>
</tr>
<tr>
<td>Nucleoside analogue reverse transcriptase inhibitors:</td>
</tr>
<tr>
<td>zalcitabine, didanosine, and stavudine</td>
</tr>
<tr>
<td>Phenytoin</td>
</tr>
<tr>
<td>Platinum: cispłat and carboplatin</td>
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<tr>
<td>Podophyllin</td>
</tr>
<tr>
<td>Pyridoxine</td>
</tr>
<tr>
<td>Suramin</td>
</tr>
<tr>
<td>Taxanes: paclitaxel and docetaxel</td>
</tr>
<tr>
<td>Thalidomide</td>
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<tr>
<td>Vincristine</td>
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</table>

A diagnosis of chronic idiopathic axonal neuropathy is not understood and is probably heterogeneous. In some patients it may be related to the metabolic syndrome because

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Initial investigations of symmetrical neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>Detects</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Liver function</td>
<td>Occult alcohol misuse; systemic disease</td>
</tr>
<tr>
<td>Full blood count</td>
<td>Occult alcohol misuse; systemic disease</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>Systemic disease</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Thyroid stimulating hormone concentration</td>
<td>Myxoedema</td>
</tr>
<tr>
<td>Serum protein immunofixation electrophoresis</td>
<td>Serum paraprotein</td>
</tr>
<tr>
<td>Vitamin B-12</td>
<td>Vitamin B-12 deficiency</td>
</tr>
<tr>
<td>HIV serology (in at risk patients)</td>
<td>HIV infection</td>
</tr>
</tbody>
</table>

Food (and cranberry juice) for thought

A hospital patient being anticoagulated asked what medicines interacted with warfarin. I named a few medications and ended by saying, “oh, and cranberry juice of course.”

The patient confessed to having drunk cranberry juice the day before, although the patient didn’t normally drink it. On asking if a visitor had brought it in, I was surprised to learn that it had come with the hospital meal: “I just ticked the option for fruit juice, and yesterday’s juice was cranberry.”

Luckily this was of no consequence for the patient, who went on to be discharged uneventfully. Although the current literature is calling into question the interaction between coumarins and cranberry products, perhaps we should err on the side of caution and not supply cranberry juice to hospital inpatients until a definitive answer is known.

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