Northamptonshire Healthcare
NHS Foundation Trust

MMG023 GUIDELINES FOR THE MONITORING OF ANTIMANIC AND PROPHYLACTIC MEDICATION IN BIPOLAR DISORDER

Table of Contents

Why we need this Policy

This document is based on NICE Clinical guidance 185[1] Bipolar Disorder with references to the BAP guidelines [2] and some locally agreed additions which are indicated in the text.

What the Policy is trying to do

To provide guidance for prescribers on the monitoring required for patients on this group of medicines.

Which stakeholders have been involved in the creation of this Policy

Medicines Management Committee

Any required definitions/explanations

FBC- Full Blood Count

eGFR – estimated Glomerular Filtration rate

NPSA - National Patient Safety Agency

ECG – Electrocardiogram

NHFT - Northamptonshire Healthcare NHS Foundation Trust

SIADH – Syndrome of Inappropriate Antidiuretic Hormone secretion

Key duties

Medicines Management Committee

Will approve and review these guidelines

Medical Director

Is responsible for the dissemination of this guideline to their Clinical Directors and Clinical Tutors

Clinical Directors

Are responsible for the dissemination and implementation of the guideline in their service areas

Heads of Service/hospitals

Are responsible for the dissemination and implementation of the guideline in their service areas

Doctors

Are responsible for reviewing the patient's side effects and monitoring in accordance with these guidelines and acting on the test results.

Policy detail

For all patients on these medicines agreed arrangements for prescribing, monitoring and treating any problems either by the GP or the CMHT should be considered. This is in addition to the annual health check in primary care for all patients with bipolar disorder which should include thyroid function, blood (plasma) glucose, lipid levels, including cholesterol, for all patients over 40, and blood pressure. Weight, smoking status and alcohol use should also be included in the GP's annual

health check. The results of the health check should be given to the patient and healthcare professionals in primary and secondary care (including whether the person refused any tests).

Lithium

When starting lithium as long-term treatment a patient specific shared-care arrangement should be established with the patient's GP for prescribing lithium and monitoring adverse effects[1]. This agreement should detail the arrangements for the regular monitoring of plasma lithium levels and how blood test results will be shared. The prescriber writing the prescription for lithium has responsibility for ensuring this monitoring occurs but local arrangements may differ as to who actually undertakes this monitoring**.**

At the start of lithium therapy and throughout their treatment patients should receive ongoing verbal and written information and a record book to track lithium levels and other tests. [3] NHFT uses the NPSA patient information pack (containing a record book, information booklet and alert card) also known as the purple booklet. These are available for patients initiated as inpatients from pharmacy or from the Planned Care and Recovery Teams (PCART – previously CMHT) bases for outpatients. Patients already established on therapy should receive a booklet from their GP**.**

When patients are admitted on lithium the team should ensure they have the most recent lithium level available to them and should consider rechecking the level at the earliest opportunity. For patients who remain inpatients for prolonged periods systems must be in place to ensure routine monitoring of lithium plasma levels, renal function, etc. occur at the appropriate intervals.

Baseline Measurements

General medical history and physical examination [2]

- Urea and electrolytes
- FBC[1]
- Serum Creatinine, eGFR [4]
- Thyroid Function (T_3, T_4, TSH)
- ECG if risk factors for, or existing, cardiovascular disease
- 24 hour creatinine clearance if history of renal infection or renal problems
- Calcium [5,1]
- Weight and height
- Pregnancy test (in women of childbearing age) [2]
- Baseline prolactin level is recommended for <18 years of age [1]

Initial Monitoring

Lithium Level

- When managing acute episodes of mania, aim for 0.6 – 0.8mmol/L normally, or 0.8 – 1.0mmol/L if patient has relapsed previously on lithium or has sub-syndromal symptoms. [1] (Elderly patients are more sensitive to undesirable effects. Aim for a lower range). Monitor carefully for symptoms of lithium toxicity.
- Plasma levels of 0.4-0.8mmol/L are generally considered safe and effective as prophylaxis.[6]
- Aim to maintain plasma lithium level between 0.6 and 0.8 mmol per litre in patients being prescribed Lithium for the first time.[1]

- Lower plasma levels of lithium may be better at preventing relapse of bipolar depression and higher levels better to prevent mania. [6]
- A single night-time dose of Priadel m/r tablets is recommended. If lithium needs to be given as a liquid this should be taken BD as it is not a modified release preparation. When a liquid preparation is used the level should be taken prior to the morning dose with a target of 0.5-0.8mmol/L. Similarly if tablets are taken BD for any reason. [7]
- Testing should be done 5-7 days after initiation and after every change of dose or formulation or interacting drug.
- Levels need to be taken 12 hours post dose and should always be taken at the same time to give consistent results
- Weekly monitoring is required until patient is stabilised at the target level (usually 4 to 5 weeks) and after every dose change[1]
- The Path Lab should be requested to also send results of any lithium level tests to the GP.

Routine Monitoring

- **Weight.** When needed if patient gains weight rapidly.
- **FBC.** Only if clinically indicated.

Three monthly:

- Monitor Lithium levels every three months for the first year[1]. More frequently if any changes in medication with potential interactions.

Six Monthly:

- Plasma lithium level to be measured every six months after the first year[1] or every three months for patients >65, patients taking medication that interacts with Lithium, patients at risk of impaired renal and/or thyroid function, have raised calcium levels or other complications, patients who have compliance issues and patients whose last plasma lithium level was 0.8 mmol/L or higher
- Serum creatinine (care if levels rising, monitor more frequently; over 100 micromol/L (female) or 120 micromol/L (male) – warning sign; over 140 micromol/L – refer to renal physician) [8, 9]. Clinicians may wish to consider monitoring serum creatinine more frequently in patients over 65
- Measure more frequently if patient starts taking medicines such as ACE inhibitors, diuretics or NSAIDs.
- T_3, T_4 and TSH (every 4-6 weeks if TSH raised)
- Electrolytes including sodium level. Clinicians may wish to consider monitoring electrolytes more frequently in patients over 65
- Calcium (monitor for increased levels due to the risk of lithium induced hyperparathyroidism) [5, 10] *(Not included in NICE)*

Annually (or more frequently if clinical concerns)**:**

- ECG if history of cardiac dysfunction or suspected cardiac dysfunction. (ECG changes which have been seen in patients on lithium include reversible flattening or inversion of T-waves and QT prolongation). (*Not included in NICE)*

Drug Interactions

This list is not exhaustive, for a complete list refer to the BNF, Stockley's and also the product information within the Summary of Product Characteristics.

Lithium levels increased by:

- Diuretics- Loop diuretics are safer compared to thiazide diuretics. Any effect will be apparent in the first month. [4]
- ACE inhibitors and angiotension ll antagonists- It may take over several weeks to develop. ACE inhibitors may increase the risk of hospitalisation from lithium toxicity in the elderly by seven folds. [4]
- NSAIDs except aspirin and sulindac. (NSAIDs should not be used PRN. If regular NSAID is essential, lithium dose should be decreased and levels monitored carefully. **N.B.** Ibuprofen is available OTC – patients need to be informed of this interaction).
- Sodium or fluid depletion (e.g. from vomiting, diarrhoea or dehydration)

Lithium levels deceased by:

- Xanthines e.g. theophylline
- increase in dietary salt including sodium containing antacids[12]

Neurotoxicity or other adverse effects (possibly without increased lithium level) may occur with: clozapine, diltiazem, verapamil, fluoxetine, fluvoxamine, **antipsychotics**, metronidazole, methyldopa, metoclopramide, domperidone, carbamazepine, steroids, ACE inhibitors, thiazide diuretics and NSAIDs[4]

Because of the narrow therapeutic index of lithium, the possibility of an interaction should be checked before adding or removing any concurrent medication.

Signs of Toxicity

Toxic effects reliably occur at levels > 1.5mmol/L and usually consist of GI effects (increasing anorexia, nausea and diarrhoea) and CNS effects (muscle weakness, drowsiness, ataxia, coarse tremor and muscle twitching). Above 2mmol/L, increased disorientation and seizures occur, which can progress to coma and death. [4]

Prescribing information

Lithium is available as two salts; carbonate and citrate. Lithium carbonate is available as standard and modified–release tablets and Lithium citrate is available as liquid. Please be aware that these are **not** bioequivalent and prescribers (with support from the NHFT Pharmacy Team) must ensure that the correct dose is prescribed when switching between tablet and liquid formulations and weekly monitoring is required until levels are stable for at least four levels. When switching between the two salts, the following procedures must be followed:

- Lithium must be prescribed by brand e.g. Priadel tablets, Priadel Liquid, Li-liquid, etc.
- The dose written on the chart must be the dose of the salt prescribed. For example when prescribing the liquid the dose must be for lithium citrate
- When switching from carbonate to citrate ensure that the dose is written in both milligram and millilitres. For example Priadel Liquid: 520mg = 5mL and Li-Liquid 509mg = 5mL

Calculating dose when switching from lithium carbonate to lithium citrate:

Lithium carbonate 200mg tablets are approximately equivalent to 5mL of lithium citrate liquid. So the 5mL dose is equivalent to 520mg of lithium citrate if using Priadel Liquid, and 509mg of lithium citrate if using Li-liquid.

NOTES:

Any patient started on lithium must be informed of the need for regular monitoring and the reasons for this. They must also be educated about signs of toxicity, interactions etc. Pharmacy can help with patient counselling when required.

Usual staring dose of lithium is 400mg at night (200mg in the elderly). [4]

See also clinical competency 21 Lithium toxicity

Carbamazepine

Carbamazepine is used for mania (not first line).

Carbamazepine is licensed for the prophylaxis of bipolar disorder but is not licensed for the treatment of acute mania

Initial Monitoring

General medical history with special attention to blood dyscrasias or liver disease [2]

FBC

- Low incidence of agranulocytosis and aplastic anaemia
- Early leucopenias usually transient and benign. Discontinue if it is severe, progressive or accompanied by clinical manifestations e.g. fever or sore throat.

LFTs

- If any clinical symptoms occur monitor more frequently and consider discontinuation.
- Discontinue if aggravated liver dysfunction or acute liver disease.

U&Es [4]

- Electolytes in the elderly, who may be at higher risk of hyponatraemia [2]

Weight and height

Carbamazepine level

Induces its own metabolism so steady state is not reached for 1-2 weeks. Check levels 2 weeks after initiation and two weeks after dose change. [4]

Six months after starting

- FBCs
- LFTs
- U&Es
- Carbamazepine level
- Weight and height if patient gains weight rapidly

Routine Monitoring

Six monthly

- U&Es
- Carbamazepine level. NB therapeutic and toxic levels are close.

Additional Monitoring

Carbamazepine level

- Consider if toxicity suspected (>12mg/L) or possible noncompliance.
- May be helpful if adequate response not obtained. Trough levels >7mg/L are associated with therapeutic response in bipolar disorder but evidence is limited.
- Levels are taken pre-dose unless toxicity is suspected. Details of time sample is taken, dose etc., must be given. Monitoring is less important than clinical vigilance for potentially adverse effects [2]

FBC

- If fever, sore throat, etc.

U+E's

- If symptoms of SIADH

Monitor for **rashes and skin reactions** which may indicate hypersensitivity. If toxic epidermal necrolysis or Stevens-Johnson syndrome is suspected, discontinue immediately.

Drug Interactions

- There are many potential serious interactions including:-
- Levels of carbamazepine raised by:
    - erythromycin/clarithromycin
    - diltiazem/verapamil
    - Cimetidine
    - fluoxetine/fluvoxamine
- Complex interactions with other antiepileptic drugs
- Reduction in contraceptive effect of oral contraceptives
- Reduction of anticoagulant effect of warfarin
- As carbamazepine is an enzyme inducer it reduces levels of many other medicines
- Contraindicated with clozapine
- Neurotoxicity with lithium without increased plasma levels

The list above is not exhaustive for a complete list refer to the BNF and also the product information within the Summary of Product Characteristics

Use of carbamazepine in acute mania

Carbamazepine should not be used routinely in the treatment of acute mania

Although licensed for the prophylaxis of bipolar disorder carbamazepine is not licensed for the treatment of acute mania.

There are no guidelines on its use for this indication in the BNF, the Tegretol SPC or in Martindale. They all, however, state that (in the treatment of epilepsy) it is essential to build up the dose slowly with increments of 100-200mg every two weeks.

Because of the lack of published evidence as to the rate at which the dose of carbamazepine can be safely increased in the treatment of acute mania, and NICE guidance, it is recommended that:-

a) It is not used routinely

b) It is started at 200mg BD and the BNF titration (100-200mg every 2 weeks) recommended for use in epilepsy is followed

c) Prescribing outside these guidelines should only be done by a Consultant and should be documented in the single patient record

d) Clinicians refer to NICE Guidance

If a patient with acute mania is already taking carbamazepine, do not routinely increase the dose. Consider adding an antipsychotic.

Signs of Toxicity

Double vision, ataxia, headache, nausea, dizziness

NOTES: Warn patient to report immediately any fever, sore throat, rash, mouth ulcers, easy bruising or bleeding.

See also Trust guidance for the use of carbamazepine in acute mania MM-G-016.

Valproate

Initial Monitoring

General medical history with special attention to hepatic, haematological and bleeding abnormalities and physical examination [2]

LFTs

- Risk of severe liver damage is highest in first 6 months and if multiple therapy is involved.
- Raised liver enzymes may be seen and are usually transient or respond to a reduction in dose.
- Prothrombin rate most relevant. An abnormally prolonged prothrombin time, especially if associated with other abnormalities, requires cessation of treatment.

FBC

Weight and height

Pregnancy test in women of childbearing age [2]

Six months after starting

- FBC
- LFTs
- Weight if patient gains weight rapidly

Routine Monitoring

None required

Additional Monitoring

Valproate level

Not required routinely unless inadequate response obtained or evidence of poor adherence or toxicity. [4] Trough levels should be taken and the target range is 50-100mg/L are associated with therapeutic response in bipolar disorder. It takes 2-3 days for the level to reach steady state. [4]

Spontaneous bruising or bleeding

Indicates the need for a FBC with bleeding time and coagulation tests [11]

Drug interactions

This list below is not exhaustive for a complete list refer to the BNF and also the product information within the Summary of Product Characteristics

- Complex interactions with other antiepileptic's. Toxic effect of carbamazepine may be potentiated and concurrent use might increase the incidence of sodium valproate-induced hepatotoxicity.
- The serum concentrations of lamotrigine can be increased by valproate. Concurrent use of valproate and lamotrigine has been associated with skin rashes, tremor and other toxic reactions [12]
- Anticoagulant effect of warfarin possibly increased.[4]
- The effects of antipsychotics, MAOIs, antidepressants and benzodiazepines may be potentiated.
- Cimetidine and erythromycin may increase levels.

NOTE: Patients should be told to seek immediate medical attention if they develop symptoms of pancreatitis e.g. abdominal pain, nausea and vomiting. They should also be told to immediately report sudden onset of anorexia, lethargy, drowsiness or asthenia as these conditions may precede jaundice and may warrant immediate withdrawal of valproate. Monitor sedation, tremor and gait disturbance in older people.

Prescribing Precautions for Valproate:

The MHRA have recently updated guidelines for prescribing valproate to woman of childbearing potential (April 2018) to state that valproate must no longer be used in any woman or girls able to have children unless the patient has a **pregnancy prevention programme** in place. This is designed to make sure patients are fully aware of the risks and the need to avoid becoming pregnant.

The Northamptonshire Healthcare Foundation Trust (NHFT) has decided that valproate will not be prescribed to any women or girls of childbearing potential unless, under **exceptional** circumstances, the prescriber feels that all other alternative treatments have been exhausted. In these cases All prescribers must complete an application (see Appendix 1) and ask another consultant to review and confirm they agree with the proposed treatment plan .This is in addition to completing the pregnancy prevention program risk assessment form . The completed forms must then be scanned into the clinical record It is important that woman be informed not to stop taking valproate without first discussing this with their doctor. All woman and girls of childbearing age who are currently prescribed valproate should have their treatment reviewed. Prescribers must review and update the risk assessment on an annual basis

The valproate toolkits, published by the MHRA, have been reviewed and updated and are available via the link below. https://www.gov.uk/guidance/valproate-use-by-women-and-girls

Toolkit

View the Patient card

View the Patient booklet (contains pregnancy prevention programme guidelines)

View the Booklet for healthcare professionals (contains pregnancy prevention form)

View the Valproate annual risk acknowledgement form

View the MHRA press release.

View the Drug Safety Update.

1. Also see the following links for further information: Teratogenicity of valproate medicines
2. New regulatory measures for valproate medicines
3. Contraception and pregnancy prevention
4. Warnings added to the packaging of valproate medicines
5. New contraindication in pregnancy
6. Further information

Lamotrigine

No special monitoring tests required in addition to annual health check.

Antipsychotics

Initial Monitoring

- Blood (plasma) glucose at start, after 6 weeks and after 3 months. Olanzapine only – additional test one month after starting. More often if there is evidence of elevated levels [1]
- FBC, U&Es and LFTs at start of therapy with antipsychotics (except for amisulpride and sulpiride) then annually. More frequent monitoring of these parameters are required for patients on Clozapine or Olanzapine[13]
- Blood pressure monitoring is advised before starting antipsychotic therapy and during dose changes[13]
- Lipid profile at start, after 6 weeks and after 3 months (more often if evidence of elevated levels)
- Weight and height. Weight every 3 months for first year (more often if patient gains weight rapidly)
- Prolactin concentration (for risperidone and typical anti-psychotics) should be monitored at the start of therapy, at 6 months and yearly thereafter. Patients on antipsychotics not associated with hyperprolactinaemia should be considered for prolactin monitoring if they show symptoms of hyperprolactinaemia[13], ECG if risk factors for, or existing, cardiovascular disease
- Patients with schizophrenia should have physical health checks (including CV risk assessment) at least once per year[13]

For full prescribing information see the relevant Summary of Product Characteristics (SPC) available at http://emc.medicines.org.uk

Training requirements associated with this Policy

Mandatory Training

There is no mandatory training associated with this policy.

Specific Training not covered by Mandatory Training

Ad hoc training sessions based on an individual's training needs as defined within their annual appraisal or job description.

How this Policy will be monitored for compliance and effectiveness

There is no monitoring associated with this Guideline.

Equality considerations

See MMP001 Control of Medicines Policy.

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1	16.05.17	16.05.17	31.05.19	Review
2	11.09.18	11.09.18	30.09.20	Reviewed in line with guidance on valproate in women of childbearing potential
3	19.03.19	19.03.19	30.09.20	Amended to clarify prescribing information for different Lithium salts (solid and liquid presentations)

APPENDIX 1 - APPLICATION FOR USE OF VALPROATE IN WOMAN OF CHILDBEARING POTENTIAL

APPLICATION FOR USE OF VALPROATE IN WOMAN OF CHILDBEARING POTENTIAL

Patient's Name:
Date of Birth: …… **NHS No:** ……
Ward (if in-patient):
PCRT:
Diagnosis:
Current Therapy:
Previous Medication History:
Brief Clinical Summary:

Reasons why patient may benefit from use of Valproate /Why can alternatives not be used:

Does the patient have a pregnancy prevention programme in place?

Yes		No		

Have all other treatment options been exhausted?

Yes		No		

Consultant's name
Signature
Date
Please ask a consultant peer to review the detail in this form and acknowledge their support of the treatment plan below

Treatment plan agreement							
Yes		No		Referred for Clinical Director/ Deputy medical director action			
Comment							
Signature		Date					

APPROVED BY Deputy Medical Director /clinical director	Yes		No	
Comments				
Signature	Date			