GUIDELINE FOR THE PRESCRIBING AND MONITORING OF ANTICONVULSANTS USED AS MOOD STABILISERS IN ADULTS

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PLEASE NOTE THERE ARE SEPARATE GUIDELINES FOR THE PRESCRIBING AND MONITORING OF LITHIUM AND FOR THE PRESCRIBING OF ORAL ANTIPSYCHOTICS

1. GENERAL STATEMENTS

- Anticonvulsants used as mood stabilisers should be initiated in secondary care mental health services

- Service users prescribed mood stabilisers should receive supplies from secondary care mental health services until the letter confirming transfer of prescribing is signed by the GP and returned to the Consultant. This includes service users discharged from inpatient settings who have been newly initiated on mood stabilisers

- A service user's clinical condition must be stabilised before requesting transfer of prescribing, see responsibilities on page 6. Once the service user is stabilised on a mood stabiliser they should be considered for shared care between mental health services and the GP.

- Whoever initiates tests for monitoring mood stabilising therapy is responsible for acting on levels outside normal/target ranges

- Prescribers must have a system for checking, identifying and dealing with medicines that might adversely interact with mood stabilisers. The side effect profile must be checked prior to initiating any new medication. There must be effective communication between all healthcare practitioners involved with service users on mood stabilisers to ensure that the impact of interacting medicines is considered when making clinical decisions

- Service users with severe and enduring mental health illness and prescribed mood stabilisers are not generally discharged from secondary care mental health services. Discharge may be considered in response to a service user who expressly indicates that they do not want to remain within secondary care mental health services or who are deemed to be clinically stable and are adherent to treatment and compliant with monitoring requirements. Where a service user has severe and enduring mental health illness, discharge arrangements should involve a proper discussion with the GP and the rationale for discharge must be clearly documented. Service users who have been discharged from secondary care mental health services should only be referred back to secondary care if their mood stabilising therapy becomes unstable (see requests for review on page 7)

- Secondary care mental health services have a responsibility to provide advice to primary care on the management of service users treated with mood stabilisers

- If prescribing outside of the product's licence, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's "Good practice in prescribing and managing medicines and devices" for further information.

2. BACKGROUND

2.1 **Lamotrigine** is recommended by NICE in service users with bipolar depression who prefer it or in those who have failed to respond to treatment with fluoxetine combined with olanzapine or treatment with quetiapine. It is also recommended in addition to lithium therapy, if the response is not adequate despite maintaining the recommended lithium levels. Lamotrigine is not recommended to treat mania.

Lamotrigine is licensed for:

- Prevention of depressive episodes in patients with bipolar disorder who experience predominantly depressive episodes.

Lamotrigine is **not** indicated for the acute treatment of manic or depressive episodes.

2.2 **Valproate** is recommended by NICE for the treatment of mania and hypomania. It is also recommended for the longer term treatment if lithium is ineffective or poorly tolerated or not suitable.

Note: Valproate Refers to 3 formulations of valproate available in the UK: sodium valproate, valproic acid and semi-sodium valproate. Sodium valproate and valproic acid have UK marketing authorisation for the treatment of epilepsy. Semi-sodium valproate has a UK marketing authorisation for the treatment of acute mania and for continuation treatment in people who have had mania that has responded to treatment with semi-sodium valproate. Both semi-sodium and sodium valproate are metabolised to valproic acid (also known as valproate), which is the pharmacologically active component.

Semi-sodium valproate is licensed for:

- Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated

- The continuation of treatment after manic episode could be considered in patients who have responded to semi-sodium valproate for acute mania

Valproate should not be prescribed to girls and women of childbearing potential (see 3.2).

2.3 **Carbamazepine** is licensed for the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy, however it is not listed amongst medications recommended by NICE for the treatment of bipolar disorder.

3. INITIATING THE TREATMENT, SPECIAL CAUTIONS AND ADVICE FOR SERVICE USERS

Concurrent medication must be checked for interactions. For advice on dose and monitoring – please refer to Appendix 2.

3.1 Lamotrigine

Please note lamotrigine can cause serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis; most rashes occur in the first 8 weeks. Rash is sometimes associated with hypersensitivity syndrome and is more common in patients with history of allergy or rash from other antiepileptic drugs. Consider withdrawal if rash or signs of hypersensitivity syndrome develop. Factors associated with increased risk of serious skin reactions include concomitant use of valproate, initial lamotrigine dosing higher than recommended and more rapid dose escalation than recommended.

Service users must be advised to contact their doctor immediately if they develop a rash while the dose is being increased.

Medication leaflet:
http://www.choiceandmedication.org/generate.php?sid=117&fname=pilllamotrigine.pdf

3.2 Valproate

Valproate is associated with the highest risk of major and minor congenital malformations (in particular neural tube defects), and long-term neurodevelopmental effects. Valporate is now contraindicated in girls and women of childbearing potential unless the conditions of the valproate pregnancy prevention programme, called PREVENT are met. A toolkit has been developed by MHRA to provide information for service users and prescribers on risks of taking valproate and pregnancy. Please refer to https://www.gov.uk/government/publications/toolkit-on-the-risks-of-valproate-medicines-in-female-patients for the most current information. **This information must be provided to all female service users taking valproate and the checklist should be completed by the prescriber on initiation of therapy.**

Healthcare professionals who seek to prescribe valproate to their female patients must make sure they are enrolled in the pregnancy prevention programme (PPP). This includes the completion of a signed risk acknowledgement form when their treatment is reviewed by a specialist, at least annually. Prescribers must therefore make arrangements to ensure that patients are reviewed by a specialist at least annually.

Liver dysfunction (including fatal hepatic failure) has occurred in association with valproate (especially in children under 3 years and in those with metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation) usually in the first 6 months and usually involving multiple antiepileptic therapy. Raised liver enzymes during valproate treatment are usually transient but service users should be reassessed clinically and liver function (including prothrombin time) monitored until return to normal. Discontinue if abnormally prolonged prothrombin time (particularly in association with other relevant abnormalities).

Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase). Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, valproate should be discontinued.

Blood dyscrasias have been associated with valproate. Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in the case of spontaneous bruising or bleeding.

Advise people taking valproate, and their carers, how to recognise the signs and symptoms of blood and liver disorders and to seek immediate medical help if any of these develop. Stop valproate immediately if abnormal liver function or blood dyscrasia is detected.

Medication leaflet:
http://www.choiceandmedication.org/generate.php?sid=117&fname=pillvalproate.pdf

▼Please note all valproate containing medicines are subject to additional monitoring by MHRA

3.3 Carbamazepine

Agranulocytosis and aplastic anaemia have been associated with carbamazepine; however, due to the very low incidence of these conditions, meaningful risk estimates for carbamazepine are difficult to obtain. This risk should always be carefully considered on initiation of treatment (service user education) and when initiating any new medications.

Serious dermatological reactions, including toxic epidermal necrolysis and Stevens Johnson syndrome have been reported very rarely with carbamazepine. Service users with serious dermatological reactions may require hospitalisation, as these conditions may be life-threatening and may be fatal. If signs and symptoms suggestive of severe skin reactions appear, carbamazepine should be withdrawn at once and alternative therapy should be considered.

Medication leaflet:
http://www.choiceandmedication.org/generate.php?sid=117&fname=pillcarbamazepine.pdf

Note: Confirmation that the service user has received written information or verbal advice must be noted in the Patient Electronic Record / the service user's healthcare record.

4. ROUTINE MONITORING

Please refer to Appendix 1

5. SIDE EFFECTS

Please refer to the Products Summaries of Characteristics and the current BNF for the detailed advice.

6. INTERACTIONS

Please refer to the Products Summaries of Characteristics and the current BNF for the detailed advice.

Carbamazepine is a potent inducer of hepatic cytochrome enzymes and is metabolised by CYP3A4. Plasma levels of most antidepressants, most antipsychotics, benzodiazepines, some cholinesterase inhibitors, methadone, thyroxine, theophylline, oestrogens and other steroids may be reduced by carbamazepine, resulting in treatment failure. Drugs that inhibit CYP3A4 will increase carbamazepine plasma levels and may precipitate toxicity. Examples include cimetidine, diltiazem, verapamil, erythromycin and some SSRIs. Also the risk of agranulocytosis caused by carbamazepine is greatly increased if co-prescribed with clozapine, therefore these medications must not be prescribed together. Please note there are numerous medications that can cause agranulocytosis.

When prescribing valproate, be aware of its interactions with other anticonvulsants (particularly carbamazepine and lamotrigine).

7. RESPONSIBILITIES

7.1 Secondary Care Mental Health Services

- Initial comprehensive assessment and liaison with health professionals
- Pre-treatment screening – as per guidelines
- Service user information – as per guidelines
- Initiation and supply of medication during dose titration until the service user is stabilised on a mood stabiliser and has had a 3 month monitoring check and until transfer of prescribing is formally accepted by the service user's GP and primary care team
- Inform GP that a mood stabiliser has been initiated
- Request the GP to prescribe via a formal request to the GP and primary care team on an individual service user basis via a letter (see Appendix 2)
- NAViGO should continue to prescribe medication for the service user until written confirmation has been received from the GP (as per the letter in appendix 2)
- The initial letter from the secondary care team should include drug name, dose form, strength, dose instructions, prescribed indication, optimum target range of plasma level where applicable, and a review schedule for the service user
- If service users are open to the service, an annual CPA review will be undertaken to which the GP will be invited. Information relating to the review to be forwarded to the GP and primary care team within 2 weeks of the appointment.
- Notify the GP and primary care team if the service user does not present for review in the specialist clinic, in line with NAViGO DNA policy
- Provide a point of contact during working hours for any queries related to prescribing or monitoring
- Agree to take back prescribing and monitoring responsibility if the therapy unstable

7.2 General Practitioner and Primary Care Team

- Acknowledge and accept secondary care team request for transfer of prescribing within 4 weeks of receipt of request
- Undertake monitoring and review as per guidelines
- Responsibilities for and provision of regular prescriptions for medication at the dosage recommended by the secondary care team but not exceeding BNF dosage limit
- To be aware of potential side effects and to inform the secondary care team of suspected side effects
- To be aware of potential drug interactions with mood stabilisers and prescribe accordingly
- Stop issuing prescriptions if notified by the secondary care team
- Seek urgent advice from the secondary care team if the service user develops any severe side effects - see appendix 3
- Seek advice from the secondary team if the female service user becomes pregnant or is planning to start a family – see appendix 3
- Document in the service user's record whether transfer of prescribing has been accepted / declined

8. REQUESTS FOR REVIEW BY SECONDARY CARE MENTAL HEALTH SERVICES

Referral of all service users to Mental Health Services will be via the single point of access. GPs are requested to clearly state reason for review (see below) and urgency – see form in Appendix 3.

- Service user functioning declines significantly
- Non-compliance or suspected non-compliance with treatment or monitoring
- Pregnancy or planning pregnancy
- Breast feeding

- Initiation of interacting medication
- Lack of or concern over efficacy
- Intermittent or poor adherence with treatment
- Tolerability or side effect problems
- Service user request to discontinue treatment or review treatment
- Comorbid alcohol or drug misuse suspected

9. CONTACT FOR SUPPORT AND ADVICE

Consultant Psychiatrist	Base	Contact number
Dr Wojciech Gierynski	Harrison House, Grimsby	01472 252366
Dr Ana Tamas	Harrison House, Grimsby	01472 252366
Dr Aamer Sajjad	Harrison House, Grimsby	01472 252366
Dr Beata Tarczon-Nowicka	Rharian Fields, Stanage Lodge, Grimsby	01472 808450
Dr Kris Kielan	Weelsby View Health Centre, Grimsby	01472 255293
Dr Ragaei Zitoun	The Gardens DPoW	0303330142
Dr Joji		
Dr Aresh Lokesh	Community Older People's	01472 625832
Single Point of Access		01472 256256 Option 3 or email NAV.MHSinglePointofAccess@nhs.net

10. SUPPORTING REFERENCES

1. Good Practice in Prescribing and managing medicines and devices. http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp
2. Bazire S Psychotropic Drug Directory 2012
3. The Maudsley Prescribing Guidelines. 13th edition 2018
4. BNF https://www.medicinescomplete.com/mc/bnf/current/
5. Summary of product information http://www.medicines.org.uk/emc/ accessed January 2020
6. National Institute for Health and Clinical Excellence, Bipolar Disorder : assessment and management CG185 September 2014
7. MHRA Toolkit on the risks of valproate medicines in female patients https://www.gov.uk/government/publications/toolkit-on-the-risks-of-valproate-medicines-in-female-patients

Appendix 1

Mood stabiliser	Indications for use	Baseline monitoring	Starting Dose	BNF Dose Range	Additional Monitoring	Comments*
Lamotrigine	Bipolar depression	FBC LFT U&E (ref. NICE)	25mg daily. NB use alternative day dosing if service user in receipt of valproate; avoid rapid dose escalation	50 – 200mg (ref. Maudsley 13th Edition) please refer to the BNF/SPC for further information	No additional monitoring	Third line therapy if no response to olanzapine + fluoxetine or quetiapine; Combination with lithium if no adequate response
Valproate	Acute mania, continuation of treatment for those who responded well	FBC LFT BMI / weight	Initially 750mg daily in 2-3 divided doses; Titrate dose upwards against response and side-effects. Controlled release sodium valproate (Epilim Chrono) can be given once daily. All other formulations must be administered at least twice daily	1-2g Semi-sodium valproate Sodium valproate is believed to produce plasma levels around 30% lower than corresponding doses of semi-sodium valproate Doses greater than 45 mg/kg daily require careful monitoring	NICE recommend that a FBC and LFTs should be repeated after 6 months, and that BMI should be monitored. Valproate SPCs recommend more frequent LFTs during the first 6 months, with albumin and clotting measured if enzyme levels are abnormal	NICE recommends valproate as a first-line option for the long term treatment where lithium is not appropriate or ineffective, and also in combination with lithium if treatment ineffective NOT to be used in women of child-bearing potential May reduce aggression in a range of psychiatric disorders (data weak, ref

						Maudsley 13th Edition)
Carbamazepine	Licensed for prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy	FBC LFT U&E BMI	Typically 100-200mg BD Gradual increases over 1-2 weeks to therapeutic levels (generally considered 4-12mg/L, and lower: 4-8mg/L if on other antiepileptics). Plasma levels should be checked 2–4 weeks after an increase in dose (trough sample)	Typically 400-600mg daily (max 1600mg daily)	NICE recommend that U&Es, FBC and LFTs should be repeated after 6 months, and that weight (or BMI) should also be monitored. Carbamazepine levels – 6 monthly	Not listed in NICE CG 185 **Maudsley - Also used for Mania (not first line), bipolar depression (evidence weak), unipolar depression (evidence weak), and prophylaxis of bipolar disorder (third line after antipsychotics and valproate) (ref. Maudsley 13th Edition)* Risk of teratogenicity, interacts with CC

* NB NICE indicates the choice of therapy should include the service user's preference

Appendix 2

Page 1 of 3: REQUEST BY THE SPECIALIST CLINICIAN FOR THE SERVICE USER'S GP TO ENTER INTO THE TRANSFER OF PRESCRIBING AGREEMENT

INSERT CLINIC ADDRESS

REF: Silverlink ID
NHS NO:

Tel No:
Fax no:

Date of Clinic:
Date Typed:

The contents of this letter are confidential and may not be disclosed without the consent of the writer

GP ADDRESS

Dear Dr

RE **JOE BLOGG, DOB ADDRESS**

Your service user has been attending **INSERT NAME OF CLINIC** and has been prescribed *medication / dose / frequency.* He/she has been stabilised on treatment. It is felt that he/she will benefit from continuing this medication under the terms of the attached guideline. The treatment and risks of harm to unborn child* (*delete if not applicable) have been explained to the service user and the Valproate Patient Guide* issued.

Please use page 3 of this pro forma to indicate if you would like to participate in the transfer of prescribing. Additionally, can you inform me of any changes made to other medication prescribed by yourselves? (Especially when changes involve medicines that interact with *medication)*.

I have enclosed the service user's most recent monitoring results and the service user's next tests are due in…….

Yours sincerely

Name

Consultant Psychiatrist

CC – Service user

PRIVATE & CONFIDENTIAL

Service user details NHS No.	Date of request _____ GP Name _____ Practice_____

Indication of treatment:	Secondary care prescriber:
Care co-ordinator:	Contact No:
Service user is stabilised on:	Dose and frequency:

Please contact the Care co-ordinator, or the out of hours crisis team on INSERT TEL. NUMBER HERE…… if you require advice or:

- Non-compliance or suspected non-compliance with treatment or monitoring
- Pregnancy or planning pregnancy
- Breast feeding
- Initiation of interacting medication
- Lack of or concern over efficacy
- Intermittent or poor adherence with treatment
- Service user functioning declines significantly
- Tolerability or side effect problems
- Service user request to discontinue treatment or review treatment
- Comorbid alcohol or drug misuse suspected

Monitoring results	**Date**	**Result**	**Date next due**
FBC			
Weight and BMI			
U & E			
LFT			

Service user given 28 day prescription on: ***INSERT DATE***
Next prescription due on: ***INSERT DATE***

Service user details NHS No.

Date of request _____

GP Name _____

Practice _____

- ☐ Yes. I agree to accept prescribing for this medication with this service user as set out in the 'Guideline for the prescribing and monitoring of anticonvulsants used as mood stabilisers in in adults'.
- ☐ I have concerns relating to the treatment or monitoring arrangements and would like to discuss these before accepting prescribing for this medication with this service user.
- ☐ No. I would not like to accept prescribing for this medication with service user as:

Even if you do not agree to accept prescribing please record that the service user has been initiated on the medication identified above within your clinical system.

Please sign and return within 14 days to:

Email back notification of acceptance to :
NAV.MHSinglePointofAccess@nhs.net

Name:
Date:
GP / On behalf of GP

Please also attach a copy to the service user's notes

Appendix 3

REQUEST FOR REVIEW BY NAViGO

This service user has previously been seen but requires a review.

Service User Name:	Consultant Psychiatrist:
DOB:	Care Co-ordinator:
NHS Number:	GP Practice:
Tel No:	Referrer:
	Date:

Please put an 'X' in the boxes that apply

Urgency level	
Within 24 hours	
Within 48 hours	
Within 14 days	
Within 28 days	

PLEASE INDICATE WHY REVIEW IS NEEDED:

Please put an 'X' in the boxes that apply (not mandatory)

Diagnosis/Clinical Signs/Symptoms	
Mood Disorder (Depression)	
Anxiety Disorder	
Psychotic Disorder	
Bipolar Disorder	
Personality Disorder	
Somatoform Disorder	
Sleep Disorder	
History of Abuse/Trauma/PTSD	
Other	

Reason for review	
Service user functioning declines significantly	
Non-compliance or suspected non-compliance with treatment or monitoring	
Pregnancy or planning pregnancy	
Breast feeding	
Initiation of interacting medication	
Lack of or concern over Efficacy	
Intermittent or poor adherence with treatment	
Tolerability or side effect problems	
Service user request to discontinue treatment or review treatment	
Comorbid alcohol or drug misuse suspected	
Poor treatment response	
Risk to the person or others	

Please email to NAV.MHSinglePointofAccess@nhs.net