Chapter 4: Central Nervous System

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Minor amendment to valproate and topiramate guidance – approved at Sheffield APG, January 2025

Chapter 4: Central Nervous System

General information on support and services (also see under individual sections):

- NHS Sheffield Talking Therapies (including self-help guides and courses)
- Sheffield Flourish and their Sheffield Mental Health Guide (providing information on local support, groups, activities and development of skills) and suicide support and prevention advice.
- Sheffield Health and Social Care Choice and Medication for patient information to support shared decisions around medication for mental health conditions. Choice and Medication patient information leaflets are available on specific drugs; often including pregnancy advice and leaflets adapted for easier reading.
- Sheffield City Council link to Drugs and alcohol support.
- Mental health, user friendly and evidence-based information: RCPSYCH

Dependence Forming Medicines (DFM)

Benzodiazepines, z-drugs, opioid pain medicines and gabapentinoids are associated with a risk of dependence and withdrawal. Antidepressants are associated with withdrawal. As such during regular medication reviews and when considering prescribing a DFM, healthcare professionals should openly discuss with the patient (with consideration for their health literacy):

- intended outcome from prescribing.
- potential benefits, risks, and harm of the treatment
- decisions about whether to continue, stop or taper treatment.

To support prescribers with this, resources within the formulary are highlighted as **DFM resource.**

References for further details:

- NICE NG215: Medicines associated with dependence or withdrawal symptoms: safe prescribing and withdrawal management for adults (visual summary Before starting medicines associated with dependence or withdrawal symptoms and visual summary Reviewing medicines associated with dependence or withdrawal symptom.
- Prescribed medicines review: report NHSE: Optimising personalised care for adults prescribed medicines associated with dependence or withdrawal symptoms: Framework for action for integrated care boards (ICBs) and primary care.

4.1.1 Hypnotics

Non-pharmacological treatments should be considered first line.

Zopiclone or zolpidem. Use in short courses only (intermittently for no more than 14 days), use with particular caution if drug or alcohol misuse is suspected.

NICE TA 77 (Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia)

Before prescribing a hypnotic the cause of the insomnia should be established and, where possible, underlying factors should be treated.

Patient information to promote better sleep: DFM resource

- NHS – Better sleep and Insomnia (including link to self-assessment)

- NHS Sheffield Talking Therapies self-help guides – 'Sleeping problems'

Hypnotics, including benzodiazepines should be used to treat insomnia only when it is severe, disabling, or causing the patient extreme distress. A detailed assessment should take place before prescribing a hypnotic. They should be used with caution in the elderly because of the risk of falls and injury.

Use beyond 2-4 weeks or to treat mild anxiety is not appropriate. Not licensed for long term use (maximum 4 weeks). Tolerance to hypnotic effect can develop within 3 to 14 days of continuous use.

For further information, including withdrawal advice, see:

- BNF Hypnotic treatment summary.
- NICE CKS topic insomnia for managing short-term (< 3 months) and long term (> 3 months) insomnia; and offers benzodiazepine and z-drug withdrawal advice[DFM resource]

Melatonin shared care in children.

4.1.2 Anxiolytics

Non-pharmacological treatments should be considered first line.

Diazepam – short-term use (intermittently for no more than 14 days), use with particular caution if drug or alcohol misuse is suspected.

Benzodiazepines should only be used for short term relief (two to four weeks only) of severe disabling anxiety. Avoid long-term use. The use of benzodiazepines to treat short-term 'mild' anxiety is inappropriate.

Consider and be aware of tolerance and dependence. Limit to the lowest dose and duration and extra caution should be taken when prescribing to patients with alcohol and drug misuse and marked personality disorder patients.

Benzodiazepines should not be used as sole treatment for chronic anxiety and are not appropriate for treating depression, panic disorder or chronic psychosis. A stepped approach should be used to manage generalised anxiety disorder (GAD):

- NICE CG113
- NHS Sheffield Talking Therapies for self-help guides and courses
- Local pathway: Generalised Anxiety Disorder (GAD) - Adults[DFM resource] for advice on GAD and drug treatment selection.

If drug treatment is appropriate, sertraline should be considered first choice SSRI for
GAD if a person chooses pharmacological therapy, despite not having UK marketing authorisation for this. Informed consent should be obtained and documented.

Regular and close monitoring of patients who are withdrawing from benzodiazepines is recommended. For further advice: Benzodiazepine and z-drug withdrawal[DFM resource], BNF and NICE NG215 (Medicines associated with

dependence or withdrawal symptoms: safe prescribing and withdrawal management for adults.

MHRA Drug Safety Update:
Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression MHRA Drug Safety Update Mar 2020.

4.2.1 Antipsychotic drugs - See appendix 1 for further information on antipsychotics

Specialist initiation recommended – early referral to secondary care or specialist required.

4.2.2 Antipsychotic depot injections - See appendix 1 for further information on antipsychotics

All drugs in this section are specialist initiation.

Primary care clinicians may undertake prescribing once a patient has been stabilised
on a depot by the specialist, as agreed on a case-by-case basis. Depot antipsychotics are amber on the drug traffic light list with the exception of olanzapine
and paliperidone, which are listed as red.

4.2.3 Drugs used for mania and hypomania

All drugs in this section are specialist initiation. Primary care clinicians may undertake prescribing in accordance with shared care arrangements.

NICE CG185 (bipolar disorder)

Warning – Lithium has a narrow therapeutic index and severe toxicity reactions can occur.

- Regular monitoring is required; see Bipolar Prescribing Guideline for monitoring details. All results should be recorded in the patient's handheld purple lithium record book. Replacement booklets can be ordered here.
- Preparations vary widely in bioavailability. Changing the preparation requires the same precautions as initiation of treatment. Lithium should always be prescribed by brand (Priadel ®, Camcolit® or Liskonum®).

From January 2024, **all new requests** to prescribe valproate in patients younger than 55 years should be accompanied by a completed Risk Acknowledgement Form (female or male), signed by two specialists.
Valproate is contraindicated in women and girls of childbearing potential unless there is a Pregnancy Prevention Programme (PPP) in place. In pregnancy, valproate is contraindicated for bipolar disorder and must only be used for epilepsy if there is no suitable alternative treatment.

There is a possible increased risk of neurodevelopmental disorders in children born to men treated with valproate in the 3 months prior to conception.
Further details can be found in SY Valproate Guidance in Primary Care, including links to all relevant national guidance, and MHRA Valproate safety measures.

Do NOT offer gabapentin or topiramate to treat bipolar disorder or lamotrigine to treat mania.

4.3 Antidepressant drugs

NICE NG222 (Depression in adults: treatment and management), which has categorised first line depression treatment into less severe and more severe depression.

Resources:

- Sheffield Guidelines for Primary Care Management of Depression DFM resource
- Older adult mental health protocol
- NHS Sheffield Talking Therapies
- Choice and Medication® patient information leaflets are available for individual drugs and include specific leaflets for pregnancy advice.

In less severe depression psychological support should be offered prior to prescribing antidepressants, but not withheld if the patient prefers the option or psychological interventions cause a prolonged delay to the treatment. When drug therapy is indicated psychological therapies should also be offered.

All antidepressants are equally effective but there is evidence that selective serotonin re-uptake inhibitors (SSRIs) are better tolerated and discontinued less frequently than Tricyclic Antidepressants (TCAs) due to side effects. Where an antidepressant is to be prescribed it should normally be an SSRI available in a generic form.

There is little difference between antidepressant effectiveness and decision should be made depending on patients' history, concomitant illness, suicide risk, interactions, and potential side-effects. Some medication such as TCAs are more dangerous in overdose and others can interact with commonly consumed food - monoamine oxidase inhibitors (MAOIs). SSRIs are most commonly used due to their tolerability, but some side-effects such as hyponatraemia, bleeds, sexual dysfunction can occur. Patient history should be considered, and shared decision should be made when prescribing the treatment.

Antidepressants should be continued for 6 months after remission. After 6 months review continued need, if there is a significant risk of relapse or history of recurrent depression continue for 2 years. Antidepressants should be withdrawn gradually over a period of 4 weeks or longer. See NICE CKS Switching antidepressants, SPS SSRIs to other antidepressants: switching in adults and RCPSYCH Stopping antidepressants DFM resource

When prescribing to patients 18 - 25 years or at risk of suicide assess for suicidality prior to starting prescription, 1 week after starting antidepressant or

increasing dose, review again after this as needed, but no later than 4 weeks. Take into account toxicity in overdose.

St John's wort should not be advised for people with depression because of uncertainty about appropriate doses, persistence of effect, variation in preparations, and potential serious interactions with other drugs.

Prescribing in children should be initiated by a specialist:
GPs may be asked to continue ongoing prescribing under shared care arrangements agreed on a case-by-case basis. Be mindful of prescription duration. NICE NG134 – Treatment of depression in children & young people

Further relevant NICE guidance:
- NICE CG91 - Depression in adults with a chronic physical health problem: recognition and management
- NICE NG215: Medicines associated with dependence or withdrawal symptoms: safe prescribing and withdrawal management for adults
- NICE CG192 - Antenatal and postnatal mental health
- NICE NG23 - Menopause: diagnosis and management
- NICE NG54 - Mental health problems in people with learning disabilities: prevention, assessment and management
- NICE CG142 - autism spectrum disorder in adults: diagnosis and management
- NG225 - Self-harm: assessment, management and preventing recurrence

4.3.1 Tricyclic & related antidepressant drugs

Lofepramine – less sedating
Clomipramine –sedating

Where an antidepressant is to be prescribed it should normally be an SSRI available in a generic form.
If prescribing a TCA consider, previous response, safety in overdose, interactions, and side effect profile. TCAs can be split into two groups of sedating or less sedating. Sedating can benefit patients with anxiety and less sedating for beneficial for withdrawn and apathetic patients. For more information see here. TCAs exhibit varying degrees of antimuscarinic effects and are dangerous in overdose due to cardiotoxicity. Lofepramine has a lower incidence of side-effects and is less dangerous in overdose but can be associated with hepatic toxicity.

For information on anticholinergic cognitive burden score see - ACB Calculator and Medichec.

Both dosulepin and trimipramine are in the Sheffield STOP list. Dosulepin is black on the TLDL and should be only initiated by a specialist.

4.3.3 Selective serotonin reuptake inhibitors

Citalopram
Fluoxetine
Sertraline

SSRIs are better tolerated and safer in overdose than other classes, less sedating and fewer antimuscarinic effects than TCA, and less interactions with food than MAOIs. Citalopram, fluoxetine, and sertraline are recommended as first line choices taking into account patient's individual circumstances.

Citalopram - Citalopram is contraindicated in people with known QT prolongation, or in people taking other medicines known to prolong QT interval. For citalopram the maximum daily dose is 40 mg for adults and 20 mg for patients older than 65 years and those with hepatic impairment. MHRA Drug Safety Update Dec 2011.

Fluoxetine – simple dosing instructions, long half-life therefore less likely to experience withdrawal effects but a high propensity for drug interactions.

Sertraline – formulary choice in patients with a recent myocardial infarction or unstable angina. See SPS Choosing an antidepressant people with coronary heart disease for further information.

Paroxetine - is associated with a higher incidence of discontinuation symptoms. Drug to drug interactions are common.

4.3.4 Other antidepressant drugs

Mirtazapine: may be useful where weight gain is not a concern/ poor appetite is present and sedation is preferable.

Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs):

Duloxetine and venlafaxine may be considered after failure to respond to first and second line treatment (NICE NG222 and local guidance: Depression Pharmacological Treatment Guidelines). Both are contraindicated in uncontrolled hypertension and caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure.

Venlafaxine: More toxic in overdose than SSRIs; higher risk of discontinuation reaction. Dose-related increases in blood pressure have been commonly reported. Doses above 300mg daily are classed as amber on the drug traffic light list and should be initiated by a specialist.

Vortioxetine is a newer antidepressant recommended for treating major depressive episodes in adults whose condition has responded inadequately to 2 antidepressants within the current episode. See NICE TA367 for more information.

Reboxetine and agomelatine: RED on the TLDL.

Augmentation strategies with lithium or antipsychotics: Seek specialist advice.

MAOIs have dangerous interactions with food and medication and should be initiated by specialists. A washout period is required when switching to and from MAOIs.

4.4 CNS stimulants and drugs used for attention deficit hyperactivity disorder

All the drugs in this section are **specialist initiated**. Clinicians may undertake prescribing in accordance with shared care arrangements.

Shared Care / Prescribing Guideline for The management of prescribing for Attention Deficit/Hyperactivity Disorder (ADHD).

NICE NG87 (attention deficit hyperactivity disorder)
If slow-release methylphenidate 18, 27, 36 or 54mg tablets are prescribed, Delmosart® prolonged release is the preferred brand – Brand prescribing is recommended.

4.5 Drugs used in the treatment of obesity

Orlistat

NICE CG189 for the recommendations on the use of orlistat in adults and children.

Liraglutide (Saxenda®) and semaglutide (Wegovy®) for managing overweight and obesity are classified as red on the TLDL. The pathway for prescribing these, in line with NICE TA664 and TA875 , is via a specialist tier 3 weight management service, which for Sheffield is "Way to Wellness", a 12 month programme, provided by Oviva UK.

Before patients can access the Tier 3 service they will need to complete a Tier 2 programme, which is delivered by More Life, details of which can be found here: Sheffield - Morelife UK (more-life.co.uk). Both self-referral and referral via GPs are accepted into the Tier 2 service.

On completion of the Tier 2 service and if patients are eligible primary care will need to refer patients onto the Tier 3 service, details of how to refer will be provided by the Tier 2 provider upon discharge from the service.

Therefore, primary care prescribers are not currently able to prescribe Saxenda® or Wegovy® .

Naltrexone/bupropion (Mysimba®) is classified as grey on the TLDL in line with NICE TA494 which states this is not recommended for the management of overweight and obesity in adults.

4.6 Drugs used in nausea & vertigo

Nausea and vomiting advice during pregnancy – see SPS.
Nausea and vomiting in palliative care – see Sheffield Palliative Care Formulary

Cinnarizine
Cyclizine
Domperidone - Restricted to use in the relief of nausea and vomiting only in 12 years of age or older and weighing 35 kg or more. Use at the lowest

effective dose for the shortest possible time. Usually, the maximum treatment duration should not exceed one week.
Metoclopramide – Maximum treatment duration is 5 days.
Prochlorperazine – acute use, caution dystonic reactions. Caution in children and the elderly with regard to parkinsonian symptoms
Promethazine
Betahistine – chronic use Meniere's disease

MHRA Drug Safety Updates:

- Domperidone carries risk of serious ventricular arrhythmia and sudden cardiac death particularly for patients older than 60 years and patients who receive daily oral doses of more than 30 mg. It is contra-indicated in patients with underlying cardiac conditions and with other risk factors, including receiving other medications known to prolong QT interval or potent CYP3A4 inhibitors. MHRA Drug Safety Update May 2014
- Domperidone for nausea and vomiting: lack of efficacy in children; reminder of contraindications in adults and adolescents MHRA Drug Safety Update Dec 2019

- Metoclopramide has a risk of short-term extrapyramidal disorders and tardive dyskinesia. Caution in the elderly and in children with regard to parkinsonian symptoms. Note – restricted indication in children over 1 year to 18 years as a second line option for prevention of delayed chemotherapy-induced nausea and vomiting, and for treatment of established postoperative nausea and vomiting. MHRA Drug Safety Update – August 2013.

4.7 Analgesics

NICE NG193 Chronic pain (primary and secondary) in over 16s:

- **For chronic primary pain:** consider prescribing a low dose of an antidepressant, either amitriptyline, citalopram, duloxetine, fluoxetine, paroxetine or sertraline, after a full discussion of the benefits and harms. Do not initiate paracetamol, an opioid, benzodiazepine or gabapentinoid.
- **For chronic secondary pain:** see relevant NICE guidance. Can be accessed via NICE Visual Summary

Further relevant NICE guidance see under opioid analgesics

Local prescribing guidelines**:** DFM resources

- Prescribing in Chronic Non-Malignant Pain in Adults
- Neuropathic pain – Primary care Pharmacological Management in Adults
- Migraine pathway in Primary Care and Primary Care Pathway – Headaches in Children

Chronic pain signposting: DFM resources

- Sheffield Aches and Pains
- NHS Sheffield Talking Therapies – Living well with pain
- Patient resources to help with Chronic Pain

Palliative care:

- Sheffield Palliative Care Formulary,

- Pre-emptive prescribing (EoL algorithms),

4.7.1 Non-opioid analgesics

Self-care with over the counter (OTC) preparations is advised for short term use.

Paracetamol

There is little evidence that combinations containing low doses of opioid (e.g. 8mg codeine) with aspirin or paracetamol are more effective than aspirin or paracetamol alone.
Soluble preparations have a high sodium content compared with standard formulations and are up to 3 times more expensive.

Some adult patients may be at increased risk of experiencing toxicity from paracetamol at therapeutic doses, particularly those with a body weight under 50 kg and those with risk factors for hepatotoxicity. Clinical judgement should be used to adjust the dose of paracetamol in these patients. See Paracetamol: oral dosing for adults with low body weight

Sheffield APG does not support the routine prescribing of nefopam tablets in primary
care -Nefopam position statement.

Link to: South Yorkshire Self-Care Guidance

4.7.2 Opioid analgesics

NICE guidance:

- NICE NG193: Chronic pain (primary and secondary) in over 16s – for more information see under analgesics
- NICE NG215: Medicines associated with dependence or withdrawal symptoms: safe prescribing and withdrawal management for adults.
- NICE NG225: Self-harm: assessment, management and preventing recurrence supports safer prescribing.
- NICE CG140: Palliative care for adults: strong opioids for pain relief

Opioid resources for chronic non-cancer pain:DFM resource

- See section 4.7 (Analgesics): local guidelines and chronic pain signposting
- Faculty of Pain Medicine - Opioids aware
- Opioids and chronic pain patient leaflet - Do you take medication for chronic pain?, Opioid prescription agreement and Opioid tapering resource

MHRA Drug Safety Updates:

- Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression MHRA Drug Safety Update Mar 2020
- Opioids: risk of dependence and addiction MHRA Drug Safety Update Sep 2020

Weak opioids

Codeine phosphate– consider laxative if constipation is a problem.

If codeine and paracetamol are required, it is preferable to prescribe the two separately rather than as a combined preparation. This allows titration of the codeine dose to reduce opioid side effects.

Codeine should only be used to relieve acute moderate pain in children older than 12 years and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen alone. MHRA Drug Safety Update Jul 2013

Note: If patients respond poorly to codeine, this may be due to being poor metabolisers of codeine to morphine. Consider **dihydrocodeine** as an alternative.

Strong opioids oral

Morphine sulphate slow release (Zomorph® capsules)
Morphine sulphate solution 10mg/5ml

Strong opioids
Oral morphine should be considered the first-choice strong opioid for severe pain. Oxycodone, transdermal fentanyl and buprenorphine should be considered second line. **Zomorph®** is the preferred brand for modified release morphine. The lowest strength of Zomorph® is 10mg. For 5mg strength prescribe MST®.

Morphine orodispersible tablets (Actimorph®) are GREEN on TLDL only as an option for use in vulnerable patient groups, to reduce the risk of accidental or intentional overdose; or where there are dexterity issues.

Transdermal opioids: see here

Tramadol:
Now classified as a strong opioid in the BNF. Used as an alternative to weak opioids at STH when the alternatives are not tolerated or effective. Caution is recommended when considering prescribing Tramadol to patients already receiving SSRI's, SNRI's or tricylic antidepressants and also to patients who are epileptic.

Tramadol 50mg capsules are more cost effective than modified-release preparations. If prescribing as modified release the preferred brand to use in Sheffield is a twice daily preparation Tramulief®.

Oxycodone:
Sheffield Oxycodone Prescribing Guidance. Oxypro® is the preferred brand of oxycodone modified release tablet to use in Sheffield and Shortec® for oxycodone immediate release capsule.

Fentanyl immediate-release (tablets, lozenges and spray): BLACK on TLDL – see Sheffield STOP list for full details and note circumstances where prescribing may be appropriate. Only licensed for cancer pain – see SPC.

Strong opioids transdermal (TD)

Buprenorphine 7-day patch: (Bunov®) 5,10, or 20 microgram/hour)
Note: Bunov® is not available as a 15 microgram/hour patch. Prescribe as either Butec® 15microgram/hour or Bunov® requiring application of a 5 microgram/hour and a 10 microgram/hour patch.

Transdermal opioid patches DFM resources

Sheffield Guidelines on the use of Transdermal (TD) Opioid (fentanyl and buprenorphine) in a primary care setting:

Fentanyl is a potent opioid – a 12 microgram/hour fentanyl patch equates to daily doses of oral morphine of up to 45mg a day. Do not use fentanyl patches in opioid-naive patients (see MHRA Drug Safety Updates). Only initiate fentanyl patches for chronic non-cancer pain if supported with advice from a Specialist Pain or Palliative Care Service.

If using opioid patches for chronic non-cancer pain and no significant improvement of pain with oral morphine equivalent 60mg/day (fentanyl 25 micrograms/hour or buprenorphine 20 micrograms/hour) refer to pain clinic for further recommendation. Do not increase dose further without specialist advice.

- Patient information leaflet: Opioid patches- Information to keep you safe
- SPS advice: Using transdermal patches safely in healthcare settings and Brand name prescribing is recommended to reduce the risk of confusion and error in dispensing and administration

Fentanyl 72-hour patch: (Mezolar® is the preferred brand to use in Sheffield) 12, 25, *37.5, 50, 75 or 100 micrograms/hour. **This strength is unique to Mezolar®*

Buprenorphine 3- or 4- day patch: (Consider prescribing as a cost-effective 4-day patch e.g Bupeaze®) 35, 52.5 or 75 microgram/hour.

MHRA Drug Safety Updates:

- Fentanyl is a potent opioid – a 12 microgram/hour fentanyl patch equates to daily doses of oral morphine of up to 45mg a day. Do not use fentanyl patches in opioid-naive patients. MHRA Drug Safety Update Sep 2020
- TD fentanyl "patches": reminder of potential for life-threatening harm from accidental exposure, particularly in children MHRA Drug Safety Update Jul 2014
- Serious and fatal overdose of fentanyl patches MHRA Drug Safety Update Dec 2014

4.7.3 Neuropathic pain

Trigeminal Neuralgia

Carbamazepine Modified Release carbamazepine is associated with a risk of foetal malformations and can impair the effectiveness of hormonal contraceptives (See further advice below).

Neuropathic pain

Amitriptyline

Gabapentin (capsules), pregabalin or duloxetine are alternatives to amitriptyline.

NICE CG173 (Neuropathic pain in adults: pharmacological management in non-specialist settings) and NICE NG215 (Medicines associated with dependence or withdrawal symptoms).

Pregabalin and gabapentin can lead to dependence and may be misused or diverted See: Advice for prescribers on the risk of the misuse of pregabalin and gabapentin, PHE & NHSE Dec 14.

Local prescribing guidelines and resources:

- Neuropathic Pain - Primary Care Pharmacological Management in Adults
- Sheffield Gabapentinoid deprescribing guidance: DFM resources Includes indications for reduction/withdrawal e.g., following a period of stability after 2-3 months or at annual review if an attempt has not been made in the last 12 months).
- Patient leaflets: when used for treating nerve pain pregabalin and gabapentin
- Patient leaflets: when used for treating nerve pain How to stop gabapentin safely and How to stop pregabalin safely .

MHRA Drug safety updates:

- Antiepileptic drugs in pregnancy: updated advice following comprehensive safety review MHRA Drug Safety Update Jan 2021.

  Carbamazepine: Highly effective contraception is required during treatment and for at least two weeks after stopping treatment. Carbamazepine can potentially reduce the efficacy of hormonal contraception. Acceptable forms of contraception include:
  - intrauterine method (Cu-ICD or LNG-IUS), or
  - Medroxyprogesterone acetate depot injection PLUS a barrier method.

  Use of combined hormonal contraception, progestogen-only pills and the etonogestrel implant is not recommended. See local guidance: Medicines with teratogenic potential.

- Pregabalin and gabapentin have both been associated with reports of respiratory depression, in some cases without concomitant opioid treatment. Consider whether adjustments in dose or dosing regimen are necessary for patients at higher risk of respiratory depression (this includes people: with respiratory or neurological disease, renal impairment, taking other CNS depressants (including opioids), aged older than 65 years: Gabapentin MHRA Drug Safety Update Oct 2017 and Pregabalin MHRA Drug Safety Update Feb 2021.

- Pregabalin may slightly increase the risk of major congenital malformations if used in pregnancy. Patients should continue to use effective contraception during treatment and avoid use in pregnancy unless clearly necessary. MHRA Drug Safety Update Apr 2022.

4.7.4 Antimigraine drugs

Local Migraine pathway for adults in primary care

4.7.4.1 Treatment of acute migraine attack

Self-care with over the counter (OTC) preparations is advised for short term use of infrequent migraine

Aspirin*, ibuprofen or paracetamol (available as soluble if required).

Sumatriptan first line triptan

Rizatriptan orodispersible

Metoclopramide - only licensed for > 18 years for nausea and vomiting associated with acute migraine. Maximum treatment duration is 5 days.

*Aspirin should not be used in children under 16 years.
People with migraine are advised to take combination therapy with a triptan and either a NSAID or paracetamol Link NICE quality standards (QS42).
Sumatriptan nasal spray should be considered for 12 to 17 years.
Triptans are not licensed for people aged over 65 years.
NICE CG150:

- Do not offer opioids for acute treatment of tension headache or migraine.
- Suggests riboflavin at a dose of 400mg daily may be effective in reducing migraine frequency and intensity for some patients. This recommendation refers to self-purchase only.

4.7.4.2 Prophylaxis of migraine

Propranolol – see safety information below

Topiramate tablets - topiramate is associated with a risk of foetal malformations and can impair the effectiveness of hormonal contraceptives. Contraindicated in pregnancy and in women of childbearing potential unless unless the conditions of the Pregnancy Prevention Programme (PPP) are fulfilled (see further advice below).

Amitriptyline - Consider amitriptyline for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. For patients already having treatment with another form of prophylaxis such as amitriptyline, and whose migraine is well controlled, continue the current treatment as required.

NICE CG150 (Headaches in over 12s)
Medicines Overuse Headache: Is best treated by withdrawing overused medication. Advise people to stop taking all overused acute headache medications for at least 1 month and to stop abruptly rather than gradually. Advise people that headache symptoms are likely to get worse in the short term before they improve and that there may be associated withdrawal symptoms and provide them with close follow-up and support according to their needs.

For advice in children - Primary Care Pathway – Headaches in Children

Propranolol: People with depression and migraine could be at an increased risk of using propranolol for self-harm. Use caution when prescribing propranolol, in line

with the Healthcare Safety Investigation Branch's report on the under-recognised risk of harm from propranolol.

Topiramate: Contraindicated for migraine prophylaxis in pregnancy. It is also contraindicated in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme (PPP) are fulfilled.
From June 2024, an **Annual Risk Awareness Form for Migraine** must be completed with all female patients of childbearing potential receiving topiramate (or their responsible person). For support to review existing patients in line with the PPP, see the Topiramate Flowcharts. For more information see Migraine Management in Primary Care and the MHRA Drug Safety Update (June 2024).

Note: Topiramate can potentially reduce the efficacy of hormonal contraception.
Acceptable forms of contraception include:

- Intrauterine method (Cu-ICD or LNG-IUS), or
- Medroxyprogesterone acetate depot injection PLUS a barrier method.

Use of combined hormonal contraception, progestogen-only pills and the etonogestrel implant is not recommended.
For more information see FSRH Clinical Guidance: Drug Interactions with Hormonal Contraception and local guidance: Medicines with teratogenic potential.

4.8 Antiepileptic drugs

4.8.1 Control of epilepsy

All drugs in this section are **specialist initiated**. Clinicians may undertake prescribing in accordance with shared care arrangements

Link to shared care protocol for Epilepsy in Adults
Link to shared care protocol for The Management of Epilepsies in Children - (under review)
Information on branded prescribing of antiepileptic medication is available here.

Valproate
From January 2024, **all new requests** to prescribe valproate in patients younger than 55 years should be accompanied by a completed Risk Acknowledgement Form (female or male), signed by two specialists.
Valproate is contraindicated in women and girls of childbearing potential unless there is a Pregnancy Prevention Programme (PPP) in place. In pregnancy valproate is contraindicated for bipolar disorder and must only be used for epilepsy if there is no suitable alternative treatment.
There is a possible increased risk of neurodevelopmental disorders in children born to men treated with valproate in the 3 months prior to conception.

Further details can be found in SY Valproate Guidance in Primary Care and MHRA Valproate safety measures.

Topiramate
From June 2024, an Annual Risk Awareness Form for Epilepsy must be completed with all female patients of childbearing potential receiving topiramate.

Topiramate is contraindicated for epilepsy in pregnancy unless there is no other suitable treatment. It is also contraindicated in women and girls of childbearing potential unless the conditions of the Pregnancy Prevention Programme (PPP) are fulfilled.
For support to review existing patients in line with the PPP, see the Topiramate Flowcharts. For more information see the MHRA Drug Safety Update (June 2024).
Note: Topiramate can potentially reduce the efficacy of hormonal contraception.
Acceptable forms of contraception include:

- Intrauterine method (Cu-ICD or LNG-IUS), or
- Medroxyprogesterone acetate depot injection PLUS a barrier method.

Use of combined hormonal contraception, progestogen-only pills and the etonogestrel implant is not recommended.

For all antiepileptic drugs, see FSRH Clinical Guidance: Drug Interactions with Hormonal Contraception and local guidance: Medicines with teratogenic potential.

4.8.2 Drugs used in status epilepticus

Diazepam – rectal
Midazolam – buccal

Prescribers need to be aware that there are two different strengths of buccal midazolam in common use in Sheffield.
Epistatus® (which is licensed aged 10 to less than 18 years of age) Midazolam 10mg in 1ml Buccal Liquid and
Buccolam® Midazolam 5mg in 1ml Buccal Liquid which is currently licensed for use from 3 months to 18 years of age and is the preferred brand for children. Note, counsel patients to ensure the red and translucent cap are both removed prior to administration. See MHRA advice for details. Link to Patient Information Leaflet.

4.9 Drugs used in parkinsonism and related disorders

All drugs in this section are **specialist initiated**. Clinicians may undertake prescribing in accordance with shared care arrangements
Link to Shared Care Protocol for Parkinson's Disease

4.10 Drugs used in substance dependence

4.10.1 Alcohol dependence

Primary care clinicians are advised to refer to Sheffield Alcohol Service – Likewise who will prescribe detox medication and coordinate psychosocial support. After initiation by the alcohol service, ongoing relapse prevention medication (acamprosate, disulfiram and naltrexone) may be prescribed in primary care.

4.10.2 Nicotine dependence

Nicotine replacement therapy, bupropion hydrochloride and varenicline are all red on the TLDL for clients over 12 years and non-pregnant women. Primary care clinicians should refer this cohort of patients to use Yorkshire-Smoke-Free Service. Patients with addiction to e-cigarettes can also be referred to the service for quitting, note however e-cigarettes will not be provided by the service.

4.10.3 Opioid dependence

All drugs in this section are Red on the TLDL, primary care clinicians are advised to refer to Sheffield Likewise.

4.11 Drugs for dementia

Specialist initiation only – Shared Care Protocol for the prescribing of donepezil, galantamine, rivastigmine & memantine in the management of Alzheimer's disease.

NICE NG97 – Dementia (Revised March 2011)

If prescribing an AChE inhibitor (donepezil, galantamine or rivastigmine), treatment should normally be started with the drug with the lowest acquisition cost. Donepezil tablets are the lowest cost AChE inhibitor. See the Sheffield Dementia protocol [currently under review].

For patients with swallowing difficulties donepezil, galantamine and memantine tablets can be crushed and rivastigmine capsules can be opened (off-label use). Refer to NEWT guidance (subscription is required or contact Sheffield SY ICB Medicines Optimisation Team who have access to NEWT).

APPENDIX 1: ANTIPSYCHOTIC DRUGS AND DEPOT ANTIPSYCHOTIC DRUGS

General information:

There is little meaningful difference in efficacy of antipsychotics (other than clozapine) and response and tolerability to each antipsychotic differs. Side-effects caused by antipsychotic drugs are common and contribute significantly to non-adherence to therapy.

Antipsychotics can cause side effects such as:

- Extrapyramidal symptoms (Pseudo parkinsonism, akathisia, tardive dyskinesia, dystonia),
- Anticholinergic effects (Blurred vision, dry mouth, tachycardia, constipation),
- Weight gain,
- Elevated glucose, cholesterol, triglycerides and have been linked with the development or exacerbation of diabetes.

Different antipsychotics may be more likely to exhibit certain side effects:

- First generation or typical – Extrapyramidal symptoms.
- Second generation or atypical – Metabolic disorders such as diabetes.

Evidence suggests that choosing the most appropriate drug and formulation for an individual may be more important than the drug group. Individual patient factors including medication history, co-morbidities, degree of sedation required, presence of negative symptoms along with relative potential for side effects (extrapyramidal side effects, QTc prolongation must be considered individually).

As older adults are particularly sensitive to the side effects of antipsychotics, initial doses should be reduced (to half the adult dose or less, see BNF or individual SPC for dosing information), considering factors such as the patient's weight, co-morbidity, and concomitant medication.

Choice needs to be considered in the consultation between the patient and a psychiatrist.
NICE CG178 provide guidance on psychosis and schizophrenia in adults. More information is available here: psychosis and related disorders.

Asenapine, paliperidone and depot olanzapine are red on the drug traffic light list and should not be prescribed in primary care.

Dementia

Antipsychotic drugs should not be used in elderly patients with dementia to treat mild to moderate psychotic or behavioural symptoms. The balance of risks and benefit should be considered before prescribing antipsychotic drugs for elderly patients. Antipsychotics are associated with a small increased risk of mortality and an increased risk of stroke or transient ischaemic attack in elderly patients with dementia. Furthermore, elderly patients are particularly susceptible to postural hypotension and to hyper - and hypothermia in hot or cold weather. See MHRA Drug Safety Update for further information.

For advice and support on non-drug measures to help manage behaviour that challenges see Alzheimer's UK information.

If an antipsychotic is needed risperidone and haloperidol are the only antipsychotics licensed for short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others. Treatment with antipsychotic drugs should be started with a low dose and titrated upwards, with regular review. In patients who have dementia with Lewy bodies, careful monitoring for severe untoward reactions, such as neuroleptic sensitivity reactions, is recommended.

Stop Over Medication of People with Learning Disabilities, Autism, or both (STOMPwLD).
In July 2015, reports were published highlighting widespread inappropriate use of antipsychotics and other medicines used to treat mental illness in people with learning disabilities.
NHS England have produced a toolkit to support the review of patients with LD being prescribed psychotropic medication. For further information on non-pharmacological challenging behaviour support see here.

'Preparing to visit a doctor to talk about psychotropic medication leaflet'
This resource is a guide for a support worker or carer who is accompanying a person with a learning disability, autism, or both to a GP consultation appointment to talk about psychotropic medication.

An easy read patient information leaflet about STOMPwLD can be found here.

When prescribing in generalised anxiety disorder (GAD), panic disorder, obsessive compulsive disorder (OCD) and body dysmorphic disorder (BDD) and borderline personality disorder:

- Do not offer an antipsychotic for the treatment of GAD in primary care (NICE CG113).
- Antipsychotics should not be prescribed for the treatment of panic disorder (NICE CG113).
- Antipsychotics as monotherapy should not normally be used for treating OCD or BDD. Prescribing in combination will be part of a multidisciplinary approach under a specialist (NICE CG31).
- Antipsychotic drugs should not be used for the medium and long-term treatment of borderline personality disorder (NICE CG 78)

Clozapine
Clozapine is red on the Sheffield Traffic Light Drug List; however, prescribers should be aware if patients are on clozapine and add this as a hospital only drug to the patient's record. By communicating between prescribing clinics and practices any interactions, side-effects or blood results can be recognised easier. As with all medication being prescribed by another provider it should be added to the patient's clinical records – see here for more guidance.

Clozapine (MHRA Drug Safety Update) has been associated with varying degrees of impairment of intestinal peristalsis; this effect can range from constipation, which is very common, to very rare intestinal obstruction, faecal impaction, and paralytic ileus. Prescribers are advised to:

- Exercise caution if co-prescribing medication that may cause constipation.
- Advise patients to report constipation immediately.
- Actively treat any constipation that occurs.

Clozapine can cause agranulocytosis and neutropenia. All patients taking clozapine should be managed by the secondary care team. Routine blood tests are needed, and this is the responsibility of the Michael Carlisle Centre clozapine blood clinic. For most patients the Michael Carlisle Centre clozapine blood clinic will issue blood test forms to the patient which states the dates they need to attend for their blood test.

Patients are advised to:

- Attend appointment with the prefilled form to ensure the results are returned to the Michael Carlisle Centre clozapine blood clinic.
- Attend either:
    - The Michael Carlisle Centre clozapine blood clinic or
    - The North or South SHSC clinics or
        (Recovery North, Northlands Community Health Centre
        Southey Hill, Sheffield, S5 8BE
        Phone: 0114 2716257

        Recovery South, East Glade Centre
        1 Eastglade Crescent, Sheffield, S12 4QN
        Phone: 0114 271 6451)
    - The Northern General Hospital phlebotomy service.

Note: For some patients the blood tests may be organised by a team such as the Learning Disability team; or another team within Sheffield Health Care Trust. This will be communicated to the GP and patient.

Although the majority of patients attend one of the options above some patients may choose to attend their GP surgery due to access / travel restrictions. Practices should discuss the above options with the patient but if access is a barrier practices can take the bloods, **but the bloods must be sent to the labs using the prefilled form from the Michael Carlisle Centre clozapine blood clinic**. If no form is presented, the Michael Carlisle Centre clozapine blood clinic should be contacted.

Michael Carlisle Centre Clozapine Blood Clinic
Pharmacy Department
Sheffield health and Social Care NHS Foundation Trust
75 Osbourne Road
Sheffield, S11 9BF
Phone: 01142718635 option 1

The responsibility for interpretation and on-going prescribing always remains with the specialist.

If the GP surgery performs an ad hoc blood test and inflammatory markers or immunosuppression is present the treating physician should be contacted immediately.

If any kind of infection begins to develop the GP surgery should perform a blood cell count and contact the treating physician immediately. Particular attention must be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia.

Particular attention must be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia.

There is a 48-hour window for missed doses before re-titration is necessary. In such circumstances contact urgently the psychiatrist or care coordinator to arrange a review.

Smoking

MHRA drug safety update:
Smoking causes a clinically significant interaction with clozapine and olanzapine, see Drug Safety Update October 2009. There needs to be a planned strategy for any patient on either of these agents who wants to stop smoking; liaison with health and social care is key.
For further information see SPS link.

Monitoring

Patients with severe mental illness or learning disabilities have a shorter life expectancy. The potential side effects of antipsychotic medication may increase the risk of premature death. As such, alongside any annual physical health check that may be needed, the following monitoring should be carried out once the patient has been stabilised on the treatment:

- Every 12 months: FBC, U&Es, LFTs, weight, lipids, prolactin, BP, fasting blood glucose. In addition, NICE CG178 recommends annual measurement of waist circumference, pulse and HbA1c.
- Consider if an ECG is needed:
- If patient experiences palpitations or any other symptoms that suggest cardiac disease.
- If specified by the SPC.

Other risk factors for QT prolongation. Wherever possibly, avoid co-prescribing other drugs that are known to prolong the QT interval (Refer to BNF drug interactions).