Chapter 4: CENTRAL NERVOUS SYSTEM
Updated: March 2018

Drugs and driving
From March 2015 a new driving offence of driving with certain medicines above specified limits in the blood was enforced in England & Wales. See MHRA drug safety update, February 2015 for details.

The following prescribing guidelines are relevant to the Central Nervous System chapter and can be found here
- Antipsychotics - Clozapine (GP information)
- Antipsychotics - recommended physical monitoring
- Dementia – managing behavioural problems in patients with dementia
- Dementia – management of dementia in primary care
- Depression and the use of antidepressants
- Domperidone - off licence use
- Melatonin - for the treatment of sleep disorders in children with neurodevelopment disorders
- Metoclopramide use in gastro-paresis
- Midazolam- the management of emergency rescue medication
- Pain- Nefopam positional statement
- Pain – neuropathic pain in primary care
- Pain – non-malignant chronic pain in primary care
- Pain – opioids - choice of strong opioids for cancer pain
- Smoking cessation- Nicotine replacement therapy formulary
- Smoking cessation – varenicline prescribing advice

Relevant Resources
- Anticholinergic drugs/ burden- Modified anticholinergic risk scales; drugs on the ACB scale
- Resource & signposting for the management of opioid & alcohol misuse
- Stopping over medication of people with learning disabilities

4.1.1 Hypnotics
Zopiclone tabs 3.75mg, 7.5mg

1. NICE TA77 recommends hypnotics to be prescribed for up to two weeks only, after non-drug measures have failed and the patient’s insomnia is severe, disabling or causing the patient extreme distress. This is due to concerns over hypnotic dependence.

2. Melatonin (Circadin MR) 2mg is BROWN after consultant/specialist initiation: Circadin MR classified as a specialist initiation drug for off licence use in children with neurodevelopment disorders and CAMHS patients. It remains BROWN not recommended except in exceptional circumstances for its licensed indication in patients over 55. Unlicensed preparations of melatonin have been classified as RED.

3. MHRA May 2014 zolpidem reminder of the risk of impaired driving ability the next day.

4. Sodium oxybate is classified as BLACK for treatment of narcolepsy with cataplexy in adult and RED in line with NHSE commissioning policy for symptom control of narcolepsy with cataplexy in children.

4.1.2 Anxiolytics
Diazepam tabs 2mg, 5mg
Chlordiazepoxide caps 5mg, 10mg (For alcohol withdrawal only usually under specialised services or GPs with a specialist interest)

1. CSM advice:
   - Benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe, disabling or subjecting the individual to unacceptable distress (occurring alone or in association with insomnia or short-term psychosomatic, organic or psychotic illness); not for short-term ‘mild’ anxiety.
   - Hypnotics should be used to treat insomnia only when severe, disabling or subjecting the individual to extreme distress. Only for short-term prescribing (2-3 weeks) in strict accordance with their licensed indications.
2. **NICE CG 113** - Do not offer a benzodiazepine for the treatment of GAD except as a short-term measure during crises; Benzodiazepines are associated with a less good outcome in the long term and should not be prescribed for the treatment of individuals with panic disorder.

3. Hypnotics to be prescribed at the lowest effective dose that can treat the patient’s symptoms.

4. Hypnotics should be avoided in the elderly who are at greater risk of becoming ataxic and confused, leading to falls and injury.

5. Lorazepam can be used acutely on a ‘when required’ basis for challenging behaviour associated with delirium usually on the advice of a specialist.

### 4.2 Drugs used in psychoses and related disorders

There is compelling evidence and a growing concern that a significant number of people with intellectual disabilities are prescribed psychotropic medication that, at best, is not helping them. For more information please see [Psychotropic drug prescribing for people with intellectual disability, mental health problems and/or behaviours that challenge: practice guidelines](#).

#### 4.2.1 Antipsychotic drugs

- **Haloperidol** caps 500mcg, tabs 1.5mg, 5mg, 10mg, 20mg, liquid SF 2mg/ml
- **Amisulpride** tabs 50mg, 100mg, 200mg, solution 100mg/ml
- **Risperidone** tabs 500mcg, 1mg, 2mg, 3mg, 4mg, 6mg, liquid 1mg/ml
- **Trifluoperazine** tabs 1mg, 5mg, liquid 1mg/5ml
- **Sulpiride** tabs 200mg 400mg liquid 200mg/5ml

**GREEN after consultant/specialist recommendation**

- **Olanzapine** tabs 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg
- **Quetiapine** tabs 25mg, 100mg, 150mg, 200mg, 300mg
- **Aripiprazole** tabs 5mg, 10mg, 15mg, 30mg

1. Note Orodispersible tablets are significantly more expensive compared to plain tablets.
2. Amisulpiride 400mg strength significantly more expensive - use combination of lower strength instead.
3. **Aripiprazole RED**: Oral. NICE TA292: for treating moderate to severe manic episodes in adolescents with bipolar I disorder. Injection (7.5mg) and depot injection is
4. Clozapine is a **RED** drug but an information sheet for GPs is provided for filing in the patient primary care notes (see [here](#)). **MHRA Oct 2017** Clozapine: potentially fatal risk of intestinal obstruction, faecal impaction, and paralytic ileus. It is vital that constipation is recognised and actively treated. Advise patients to report constipation immediately.
5. **Quetiapine MR** (preferred brand Brancico XL) is more expensive than standard formulation and has been classified as **BROWN**. Prescribe under exceptional circumstances only for:
   - patients who have discontinued their treatment with quetiapine and currently have to re-titrated over the period of a week and;
   - patients who require once daily administration but are unable to tolerate titration to the therapeutic dose with once daily plain tablets.

Specialists should document the exceptionality when communicating with the primary care prescriber.

#### 4.2.2 Antipsychotic depot injections

*Follow consultant advice* (GREEN after consultant/specialist recommendation)

- **Flupentixol decanoate** inj. 20mg/ml, 100mg/ml, 200mg/ml
- **Fluphenazine decanoate** inj. 25mg/ml, 100mg/ml, 0.5ml & 1ml amp
- **Haloperidol decanoate** inj 50mg/ml, 100mg/ml
- **Zuclopenthixol decanoate** inj 200mg/ml, 500mg/ml

1. Risperidone depot injection and olanzapine LA injection have been classified as **RED** drugs.

#### 4.2.3. Antimanic drugs

*Follow consultant advice* (GREEN after consultant/specialist recommendation)

- **Carbamazepine**
- **Sodium Valproate** (see NICE CG38 on bipolar disorder)

**AMBER** - see [shared care guideline](#)

- **Lithium carbonate m/r** tabs (Priadel, Camcolit, Liskonum)
- **Lithium Citrate Liquid** 5.4mmol/5ml (Priadel, Li-Liquid) (5.4mmol is equivalent to 200mg lithium carbonate)
1. **Lithium**
   - **Prescribe lithium by brand name.**
   - Sampling should be 12 hours post dose. To facilitate this dose should routinely be taken at night.
   - All patients on lithium should have the “purple book” as recommended by the NPSA. These can be obtained from Primary Care Support England (PCSE) through the following link [http://pcse.england.nhs.uk/](http://pcse.england.nhs.uk/) using your practice log in details.

2. **Sodium Valproate**
   - **EMA March 2018** recommends a ban on the use of valproate-containing medicines for migraine or bipolar disorder during pregnancy, and a ban on treating epilepsy during pregnancy unless there is no other effective treatment available. Valproate-containing medicines must not be used in any woman or girl able to have children unless the conditions of a new pregnancy prevention programme are met. These include:
     - an assessment of each patient’s potential for becoming pregnant
     - pregnancy tests before starting and during treatment as needed
     - counselling about the risks of valproate treatment and the need for effective contraception throughout treatment
     - a review of ongoing treatment by a specialist at least annually
     - introduction of a new risk acknowledgement form that patients and prescribers will go through at each such annual review to confirm that appropriate advice has been given and understood.
   - **MHRA February 2016** - children exposed to valproate in utero are at high risk of developmental disorders and congenital malformations. A [toolkit](http://pcse.england.nhs.uk/) to help understanding of the risks of valproate and pregnancy has been launched to ensure female patients are better informed about the risks of taking valproate medicines during pregnancy. See also [MHRA January 2015](http://pcse.england.nhs.uk/).

### 4.3 Antidepressants

See antidepressants guidelines. Note not recommended for mild depression.

#### 4.3.1 Tricyclic and related antidepressant drugs

**Lofepramine** tabs 70mg

**Amitriptyline** tabs 10mg, 25mg, 50mg.

1. Amitriptyline use in neuropathic pain [see local guideline](http://pcse.england.nhs.uk/).
2. The role of pregabalin (prescribed generically) for generalised anxiety disorder (GAD) is restricted as per NICE CG 133. Pregabalin is **GREEN after specialist initiation** for GAD, where SSRIs or venlafaxine are ineffective, poorly tolerated or considered clinically inappropriate.
3. Nortriptyline is **BROWN** for use as second line to amitriptyline and also as an adjunct in treatment resistant depression. Amitriptyline and Imipramine are cost effective choices compared to nortriptyline.
4. Dosulepin is **BLACK** not recommended/commissioned for new patients. It is particularly dangerous in over dosage and not recommended for depression. Existing patients on treatment should not have their medication stopped abruptly. Careful review is required which may require specialist input.
5. Doxepin is **BROWN** after consultant/specialist initiation for use in dermatology patients after a trial of conventional antihistamines.

#### 4.3.2 Monoamine-oxidase inhibitors

**Moclobemide** tabs 150mg, 300mg

1. Moclobemide poses little dietary restrictions and few interactions.

#### 4.3.3 Selective serotonin re-uptake inhibitors

**Citalopram** tabs 10mg, 20mg, 40mg, 40mg/ml oral drops

**Fluoxetine** caps 20mg

**Sertraline** tabs 50mg, 100mg

1. The SSRI of choice is dependent on the patient presenting, for example sertraline is the preferred SSRI in breast-feeding women
2. There is an association between the use of SSRIs and upper GI bleeds. The use of SSRIs with concomitant NSAIDs increases the risk of upper GI bleeding further. If an SSRI is required in a patient at high risk of an upper GI bleed then the use of a gastro-protective agent could be considered. See local [PPI guidance](http://pcse.england.nhs.uk/) and UKMi [Medicines Q&A](http://pcse.england.nhs.uk/) for further detail.
3. Citalopram
   - Maximum dose is 40mg daily in adults; 20mg in elderly (>65 years of age) and those with reduced hepatic function
   - Contraindicated in patients with known QT interval prolongation or congenital long QT syndrome; or use with other medicines known to prolong QT interval
   - Use is cautioned in patients at higher risk of developing Torsade de Pointes, including those with congestive heart failure, recent myocardial infarction, bradyarrhythmias, or a predisposition to hypokalaemia or hypomagnesaemia due to illness or drug therapy.
   - The dose for citalopram oral drops should be stated in drops, not in millilitres to avoid confusion for patients and also for ease of administration
   - Use in children is BROWN after consultant/specialist initiation - 2nd line as per NICE

4. Fluoxetine is GREEN after consultant/specialist initiation when used in children and adolescents in primary care at the licensed dose. This group of patients will be initiated with treatment by the Children Adolescent Mental Health Services (CAMHS) and prescribing handed over to primary care under patient specific management plans. Fluoxetine 20mg dispersible tablets are a cost-effective option for patients with swallowing difficulties.

5. Sertraline use in children is BROWN after consultant/specialist initiation - 2nd line as per NICE

6. Vortioxetine has been classified locally as RED for treating major depressive episodes as per NICE TA367

7. Switching and withdrawal of antidepressants - A quick-reference guide can be found here

4.3.4 Other antidepressants drugs

Mirtazapine orodispersible tabs, tabs 15mg, 30mg, 45mg
Venlafaxine tabs 37.5mg, 75mg, tabs

1. Venlafaxine should be avoided in those with pre-existing heart disease and in anyone who has uncontrolled or untreated hypertension. Consider ECG for patients at risk of heart disease. Review blood pressure after initiation, dose increase, and annually - if raised, only continue venlafaxine if BP under control and alternative antidepressant not suitable.

2. Venlafaxine MR is BROWN and significantly more expensive than standard release formulation. This should be reserved for patients with compliance issues.

3. Mirtazapine oral solution is BROWN. Use mirtazapine orodispersible tablet instead.

4. Duloxetine has limited place in therapy see full traffic light classification for further details.

4.4 CNS stimulants and drugs used for attention deficit hyperactivity disorder

Modafinil tabs 100mg, 200mg

1. Modafinil is GREEN after specialist initiation to treat narcolepsy and narcolepsy secondary to Parkinson’s disease. For other indications it is BLACK.

4.5 Drugs used in the treatment of obesity

Orlistat caps 120mg

1. NICE clinical guideline_189 (guidance on the prevention of overweight and obesity in adults and children) must be strictly adhered to.

4.6 Drugs used in nausea and vertigo

Metoclopramide tabs 10mg, syrup 5mg/5ml
Domperidone tabs 10mg, suspension 5mg/5ml, suppositories 30mg
Prochlorperazine tabs 5mg, syrup 5mg/5ml, injection 12.5mg/ml
Cinnarizine tabs 15mg
Betahistine tabs 8mg, 16mg

1. Metoclopramide – MHRA advice (2013) risk of neurological adverse effect:
   - For adults, the maximum dose in 24 hours is 30mg (or 0.5mg per kg bodyweight). The usual dose is 10mg three times a day and should only be prescribed for short-term use (up to 5 days)
   - Off label use of metoclopramide is recognised as standard practice in palliative medicine. JAPC recognises that long term use of metoclopramide may be appropriate in some patients given orally/parentally
   - Use in patients under 20 years of age is restricted and likely to cause dystonic reactions

2. Domperidone – MHRA advice (2014)
• Domperidone may be associated with a small increased risk of serious ventricular arrhythmia or sudden cardiac death. These risks may be higher in patients older than 60 years and in patients who receive daily oral doses of more than 30 mg.

• Domperidone is preferred in patients where the risk of dystonic reactions is high i.e. young women, children, the elderly, and those with Parkinson’s disease.

• For adults the maximum dose in 24 hours is 30mg.

• The duration of treatment should not usually exceeded one week- see local position statement for exceptions

3. For use in gastroparesis and other gastric outlet physiological impairment, metoclopramide and domperidone are classified as BROWN after consultant/specialist initiation – see the JAPC local position statement. Advice on use of domperidone for ‘off-licence’ indications (babies and children, nursing mothers) is also included in this statement.

4. Prochlorperazine is useful in the treatment of vertigo but should be avoided in the elderly if possible because of extrapyramidal effects.

5. Haloperidol is recommended for the control of opiate induced vomiting in a dose of 1.5mg orally once or twice daily or 2.5mg IM to stop active vomiting.

4.7 Analgesics

4.7.1 Non-opioid analgesics

For treatments of minor, short-term medical conditions such as mild toothache, headaches, period pain, mild fever and back pain, patients are encouraged to self-care with over-the-counter painkillers and lifestyle changes.

Paracetamol tabs 500mg, suspension 120mg/5ml, 250mg/5ml

Compound analgesic preparations

Co-Codamol tabs 30/500

1. Paracetamol is the simple analgesic of choice. Co-codamol 8/500, 15/500 and co-dydrarnol 10/500 are listed by the BNF as less suitable for prescribing and are both now removed in the local traffic light formulary. There is a lack of efficacy from trial data over paracetamol but may be considered for patients unresponsive to full licensed doses of paracetamol alone before using more potent and costly analgesia.

2. Prescribing of combination analgesics with a high dose of codeine or dihydrocodeine does not allow flexibility of dosing.

3. Avoid effervescent products (unless genuine swallowing difficulties) as they have high sodium content and are associated with significantly increased odds of adverse cardiovascular events compared with standard formulations of those same drugs. These preparations should be prescribed with caution only if the perceived benefits outweigh these risks and should be avoided if possible. (This does not apply to aspirin 75mg dispersible which contains very low levels of sodium). Paracetamol soluble and co-codamol effervescent tablets are BROWN.

4. Some patients may be at increased risk of experiencing toxicity at therapeutic doses, particularly those with a body-weight under 50kg and those with risk factors for hepatotoxicity (e.g. malnourishment, long-term treatment with liver enzyme-inducing drugs such as carbamazepine). Clinical judgement should be used to adjust the dose of oral paracetamol in these patients. Example of dosing for these patients adopted from DTHFT: (Final dose to be determined on individual basis)

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Paracetamol Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50 kg</td>
<td>500mg-1g every 4-6 hours, Maximum 4g daily</td>
</tr>
<tr>
<td>40 - ≤50 kg</td>
<td>500mg-1g every 4-6 hours, Maximum 3g daily</td>
</tr>
<tr>
<td>30-39 kg</td>
<td>Dose reduction required</td>
</tr>
</tbody>
</table>

5. The prescribing of Co-proxamol is not supported and clinicians should support patients to suitable alternatives. Its use has been linked to death by fatal poisoning. Co-proxamol is unlicensed and has been classified locally as BLACK.

6. JAPC has classified nefopam as BLACK. Patients already on treatment should be able to continue treatment until their next medication review where their NHS clinician might consider it appropriate to switch or stop treatment.

7. MHRA January 2018 Co-dydrarnol: prescribe and dispense by strength to minimise risk of medication error. Previously co-dydrarnol (dihydrocodeine/paracetamol) was available only in the ratio 1:50 (co-dydrarnol 10/500 mg). Two products are now available with a higher strength of dihydrocodeine (co-dydrarnol 20/500 mg and 30/500 mg tablets). It is therefore important that co-dydrarnol products are prescribed and dispensed by strength to minimise dispensing errors and the risk of accidental opioid overdose.
4.7.2 Opioid analgesics

**Codeine phosphate** 15mg, 30mg, 60mg tabs
**Dihydrocodeine** tabs 30mg
**Tramadol** caps 50mg

1. Following **MHRA July 2013 advice** codeine should only be taken 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.

2. **Tramadol**
   - Indicated for neuropathic pain and non-malignant chronic pain (see local guidelines).
   - It has a high incidence of ADRs and drug interactions. Locally it’s linked with hospital admissions.
   - It is a schedule 3 controlled drug. Prescription need to comply with CD requirements with the dose being stated, total quantity to be supplied given in both word and figures, also limits to validity of prescriptions and length of supply that can be provided. However it is not subject to storage in a CD cupboard. See the Derbyshire Medicines Management website for more information.
   - Tramadol MR is BROWN and significantly more expensive than standard release formulation. (Preferred brand is Marol).

**Strong opioids (see choice of strong opioids for cancer pain)**

**Morphine Sulphate**
- Modified release caps (Zomorph) 10mg, 30mg, 60mg, 100mg, 200mg
- Immediate release tabs (Sevredol) 10mg, 20mg, 50mg
- Oral solution 10mg/5ml
- Suppositories 15mg, 30mg

**Diamorphine**
- Injection 5mg, 10mg, 30mg, 100mg, 500mg For alternatives see end of life pathway

**Second line strong opioids**

**Oxycodone**
- Modified release tabs (Longtec) 5mg, 10mg, 20mg, 40mg, 80mg
- Immediate release caps (Shortec) 5mg, 10mg, 20mg
- Oral solution 5mg/5ml (Shortec)

**Fentanyl**
- Patch (Fencino, Matrifen or Mezolar) 12, 25, 50, 75, 100 microgram

1. Prescribe m/r morphine by brand name. Zomorph is the cost-effective option. To aid compliance the capsule can be opened and content sprinkled onto food. MXL (once daily MR morphine) is BROWN.

2. Prescribe laxatives when starting regular morphine and continue while on opioid. Consider anti-emetic if appropriate.

3. **Fentanyl**
   - Patches should only be considered for patients who are on a stable dose of an opioid and who are unable to swallow/ comply with oral medication. It should not be prescribed for opioid naïve patients.
   - Maximum titrated dose for fentanyl patches should not exceed >50mcg/hour changed every three days. Seek specialist advice if increased doing is required.
   - The CQC states that suitable systems should be in place to ensure the safe and effective use of transdermal fentanyl patches. This should include ongoing education of all staff involved in prescribing, dispensing, administering and disposing of transdermal fentanyl patches.
   - Patches exposed to external heat (e.g. a bath) could increase its absorption and possible side effects.
   - If required, fentanyl matrix patches only, may be cut in half. For accuracy the matrix patch should be cut diagonally; the other half should be disposed of, in the correct manner as for a controlled drug. N.B. cutting a fentanyl matrix patch renders the use of the drug as “off licence.”
   - All non-transdermal preparations (i.e. lozenges, tablets, buccal film and sublingual tablets) are classified as BROWN after palliative care specialist initiation (to allow access in primary care if needed). These preparations require specialist initiation and titration. BLACK for all non-transdermal preparations initiated outside palliative care.

4. **Buprenorphine patches** are classified as BROWN- the patches should be prescribed by brand as the frequency to be applied may vary between brands.
   - Buprenorphine patches at lower doses are broadly as effective as codeine or tramadol but much more expensive.
   - The patches are unsuitable in acute or unstable pain due to the need for slow titration of doses; it may take up to 72 hours to achieve a stable blood level after a change in dose.
   - The preferred cost effective brand for low dose (7 day) patch is Reletrans
• Higher strength patches are also available but the bioavailability and application varies between brands. Different brands are not interchangeable. Check individual SPC carefully.
• The preferred cost effective high strength brand (replace after 96 hours) is Relevtec.

5. Onexila (once daily MR oxycodone) is BLACK due to the potential safety concerns and confusion over drug selection as already seen with immediate release and modified release formulations.

6. Refer to NPSA/2008/RRR05 – reducing dosing errors with opioid medicines: When opioid medicines are prescribed, dispensed or administered, in anything other than acute emergencies, the healthcare practitioner concerned, or their clinical supervisor, should:
• Confirm any recent opioid dose, formulation, frequency of administration and any other analgesic medicines prescribed for the patient. This may be done for example through discussion with the patient or their representative (although not in the case of treatment for addiction), the prescriber or through medication records.
• Ensure where a dose increase is intended, that the calculated dose is safe for the patient (e.g. for oral morphine or oxycodone in adult patients, not normally more than 50% higher than the previous dose).
• Ensure they are familiar with the following characteristics of that medicine and formulation: usual starting dose, frequency of administration, standard dosing increments, symptoms of overdose, common side effects.

4.7.3 Neuropathic pain
See local neuropathic pain guideline

4.7.4 Antimigraine drugs
4.7.4.1 Treatment of acute migraine
For treatments of minor short term conditions such as infrequent migraine patients are encouraged to self-care. Mild infrequent migraines can be adequately treated with over the counter pain killers and a number of combination medicines (contain both painkillers and anti-sickness medicines). Below recommendations are based on SIGN 155 Pharmacological management of migraine (Feb 2018)

Aspirin dispersible tabs 900mg
Ibuprofen tabs 400mg increase to 600mg if ineffective
Paracetamol tabs 1g in pregnancy or if unable to take other acute therapies
Sumatriptan tabs 50mg, 100mg 1st line triptan
Zolmitriptan tabs/ orodispersible tabs 2.5mg 2nd line triptan
(orodispersible reserved for patients who cannot manage other oral formulations)

1. Consider metoclopramide 10mg or prochlorperazine 10mg, especially for patients presenting with migraine-associated symptoms of nausea or vomiting.
2. Patients should be warned about the risk of developing medication-overuse headache when starting acute treatment.
3. Triptan:
• Should not be taken by people who have: Uncontrolled or severe hypertension; Cardiovascular disease, or are at high risk of cardiovascular disease; Coronary vasospasm (including Prinzmetal's angina).
• Frovatriptan has a substantially longer half-life (26 hours) than all other triptans, but this does not appear to translate into markedly lower relapse rates.
• For all triptans there is good evidence that a second dose is effective for relapse but very little to show that it is the most appropriate treatment. (BASH, diagnosis and management of migraine, 2010)
• All triptans except intranasal sumatriptan are unlicensed for use in children under 18. 5HT1 receptor agonists for children (aged 12-17) should be referred and initiated by a specialist. Sumatriptan and zolmitriptan oral formulations are treatment options (see BNF for children).
• Where triptans are indicated for acute migraine NICE CG150 recommends the use of combination therapy with a triptan and an NSAID, or a triptan and paracetamol, for first-line treatment of acute migraine with or without aura.

4.7.4.2 Prophylaxis of migraine
Propranolol 80–160 mg daily 1st line
Topiramate** 50–100mg daily 2nd line **SEE BELOW WARNING ON PREGNANCY
Amitriptyline 25–150mg daily 2nd line

The formulary lists the most clinically and cost effective choices for prescribing in primary care
1. For patients with migraine, maintaining a regular routine is important, including:
   - Encourage regular meals, adequate hydration with water, sleep and exercise
   - Avoid specific triggers if known
   - Consider activities that encourage relaxation such as mindfulness, yoga or meditation.

2. Consider prophylaxis if migraine is disabling and reducing quality of life, eg frequent attacks (>1 per week on average) or prolonged severe attacks. Start at low dose and gradually increase according to efficacy and tolerability.

3. If the patient responds well to prophylactic treatment a trial of gradual drug withdrawal should be considered after six months to one year.

4. Good response is a 50% reduction in severity and frequency of attacks; treatment failure is a lack of response to the highest tolerated dose used for 3 months.

5. SIGN 155: candesartan (16 mg daily) or sodium valproate (400–1500 mg daily) can be considered as a prophylactic treatment for patients with episodic or chronic migraine. SEE PAGE 9 WARNING ON PREGNANCY.

6. Topiramate
   - Advise women and girls of child bearing potential that topiramate is associated with a risk of fetal malformations and can impair the effectiveness of hormonal contraceptives. (NICE CG150) Pregnancy testing should be performed before initiating, and a highly effective contraceptive method advised. For advice on interactions between hormonal contraception and other drugs see FSRH guidance.
   - Prescribe tablets as capsules are more expensive

4.8.1 Control of epilepsy

JAPC formulary of anti-epileptics agreed as GREEN after specialist initiation

<table>
<thead>
<tr>
<th>Clonazepam</th>
<th>Oxcarbazepone</th>
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<tbody>
<tr>
<td>Carbamazepine</td>
<td>Phenobarbital and other barbiturates</td>
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<tr>
<td>Ethosuximide</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Pregabalin</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Sodium Valproate</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Zonisamide</td>
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</tbody>
</table>

The following anti-epileptic drugs are classified as RED for those patients referred to and /or under the care of a Derbyshire based specialist/Trust.
JAPC advises that request for these drugs from tertiary centres should be in line with the host area prescribing committee’s decision (see here for neighbouring area prescribing committee formularies). See also local detail aid for epilepsy management

<table>
<thead>
<tr>
<th>Eslicarbazepine</th>
<th>Retigabine</th>
</tr>
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<tbody>
<tr>
<td>Perampanel</td>
<td>Rufinamide</td>
</tr>
<tr>
<td>*Vigabatrin is also classified as AMBER; shared care with Derby Hospitals NHS Foundation Trust ONLY for treating epilepsy in children.</td>
<td></td>
</tr>
</tbody>
</table>

Brivaracetam is BROWN after consultant/specialist initiation and stabilisation of three months in patients that have responded to levetiracetam but unable to tolerate the adverse effects

GPs may find the following links provides a useful resource for management of epilepsy in primary care: Nice Bites; epilepsy management detail aid

MHRA 2013 recommends that antiepileptics are divided into three risk based-categories

<table>
<thead>
<tr>
<th>Category 1: prescribers are advised that patients receiving treatment for epilepsy are maintained on the same manufacturer</th>
<th>Category 2: continuity of manufacturer is based on clinical judgement taking into account factors such as seizure frequency and treatment history</th>
<th>Category 3: it is usually unnecessary to ensure a specific manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of medicine</td>
<td></td>
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</tr>
<tr>
<td>carbamazepine phenytoin phenobarbital primidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>clobazam clonazepam eslicarbazepine lamotrigine oxcarbazepine perampanel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>retigabine rufinamide topiramate valproate zonisamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ethosuximide gabapentin tiagabine lacosamide vigabatrin levetiracetam</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. All new antiepileptics will be considered to be RED in Derbyshire until formal classification at JAPC
2. There is an increased risk of teratogenicity associated with the use of antiepileptic drugs (reduced if treatment is limited to a single drug). Ensure adequate contraception. Those who wish to become pregnant or become pregnant should be referred to an appropriate specialist for advice.

3. **Valproate**
   - **EMA March 2018** recommends a ban on the use of valproate-containing medicines for migraine or bipolar disorder during pregnancy, and a ban on treating epilepsy during pregnancy unless there is no other effective treatment available. Valproate-containing medicines must not be used in any woman or girl able to have children unless the conditions of a new pregnancy prevention programme are met. These include:
     - an assessment of each patient’s potential for becoming pregnant
     - pregnancy tests before starting and during treatment as needed
     - counselling about the risks of valproate treatment and the need for effective contraception throughout treatment
     - a review of ongoing treatment by a specialist at least annually
     - introduction of a new risk acknowledgement form that patients and prescribers will go through at each such annual review to confirm that appropriate advice has been given and understood.
   - **MHRA February 2016** - children exposed to valproate in utero are at high risk of developmental disorders and congenital malformations. A toolkit to help understanding of the risks of valproate and pregnancy has been launched to ensure female patients are better informed about the risks of taking valproate medicines during pregnancy. See also **MHRA January 2015**.

4. **Topiramate**
   - Advise women and girls of child bearing potential that Topiramate is associated with a risk of fetal malformations and can impair the effectiveness of hormonal contraceptives. (NICE CG150)
   - Pregnancy testing should be performed before initiating, and a highly effective contraceptive method advised. For advice on interactions between hormonal contraception and other drugs see **FSRH guidance**.
   - Prescribe tablets as capsules are more expensive.

5. **Phenytoin**
   - Usually initiated with a loading dose. The use of loading doses of medicines can be complex and error prone. Incorrect use of loading doses or subsequent maintenance regimens may lead to severe harm or death. See [http://www.nrls.npsa.nhs.uk/resources/?EntryId45=92305](http://www.nrls.npsa.nhs.uk/resources/?EntryId45=92305)
   - Phenytoin tablets although listed as generic medicines have significantly increased in price.

6. In reference to NICE CG 137 JAPC decided that no conclusions can be drawn concerning the superiority of controlled release carbamazepine over immediate release with respect to reducing seizure frequency. Clinicians may consider the use of controlled release preparation if the patient is seizure-free but experiencing adverse reactions that compromise compliance.

7. Gabapentin has been associated with a rare risk of severe respiratory depression even without concomitant opioid medicines. See **MHRA October 2017**. Prescribe gabapentin as capsules - tablets are much more expensive.

8. **PHE issued advice** in 2014 for prescribers on the risk of misuse of pregabalin and gabapentin, and suggestions for a balanced and rational use of these medicines. See article for full details.

4.8.2 **Drugs used in status epilepticus**

   *Follow consultant advice (GREEN after consultant/specialist recommendation). See local guideline.*

   **Midazolam buccal (Buccolam)** pre-filled syringe 2.5mg/0.5ml, 5mg/1ml, 7.5mg/1.5ml, 10mg/2ml
   1. Derbyshire has moved to one preferred buccal midazolam product (Buccolam), for use in both adults (off-licence use) and children (licensed use).
   2. Epistatus (10mg/1ml) is classified as **BLACK**. Existing patients on epistatus should be reviewed by the specialist and switched to the recommended buccolam preparation at their next review and the patients care plan should be updated accordingly. Do not stop the epistatus abruptly, without the patient receiving training for the buccolam preparation. In line with NICE guidance diazepam rectal tubes 2.5, 5, 10mg are no longer recommended first line for seizure control.

4.9 **Drugs used in Parkinsonism and related disorders**

   *Follow consultant advice. See NICE bites Parkinson’s disease in adults.*

   1. Pramipexole MR preparation is 2nd line only (Pipexus is the cost effective brand)
   2. Stanek and Sastravi are the cost effective choices of carbidopa/entacapone/levodopa combination
   3. Kemadrin is the cost effective brand for procyclidine.

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The formulary lists the most clinically and cost effective choices for prescribing in primary care.
4.10 Drugs used in substance dependence
4.10.1 Alcohol dependence (see shared care guidelines)
Acamprosate
Disulfiram
Naltrexone (for Derbyshire County only)
1. These drugs should only be prescribed as part of a specialist service
2. For guidance on vitamin supplementation in alcohol misuse see here

4.10.2 Nicotine dependence
Nicotine replacement products (see nicotine replacement therapy formulary)
Bupropion tabs 150mg
Varenicline tabs 0.5mg, 1mg – see varenicline prescribing advice
1. To be prescribed in conjunction with specialist smoking cessation support.
2. Bupropion (CSM advice)
   - It is contra-indicated in patients with a history of seizures or of eating disorders, a CNS tumour, or who are experiencing acute symptoms of alcohol or benzodiazepine withdrawal. It should not be prescribed to patients with other risk factors for seizures unless the potential benefit of smoking cessation clearly outweighs the risk.
   - Factors that increase the risk of seizures include concomitant administration of drugs that can lower the seizure threshold, alcohol abuse, history of head trauma, diabetes, and use of stimulants and anorectics.
3. Varenicline
   - CSM advice - depression has been reported in patients using varenicline who are trying to stop smoking, and symptoms of depression may include suicidal thoughts and behaviour. Patients who are taking varenicline who develop suicidal thoughts should stop their treatment and contact their doctor immediately – see Drug safety update, July 2008.
   - Health care professionals are advised to weigh the risks of varenicline against the benefits of its use. Varenicline has been shown to have a higher occurrence of major adverse cardiovascular events (source FDA 2012)

4.10.3 Opioid dependence (see shared care guidelines)
Buprenorphine via specialist drug service (DS)
Methadone via Local Enhanced Service (LES) and GP with a special interest (GPSI)

4.11 Drugs for dementia (see local guidance)
Donepezil tabs 5mg, 10mg 1st line
Galantamine tabs 8mg, 12mg; MR tabs (Luventa XL) 8mg, 16mg, 24mg
Rivastigmine caps 1.5mg, 3mg (Alzest is the preferred brand for patch)
Memantine tab 10mg, 20mg
1. JAPC has re-classified these drugs as GREEN for dementia after consultant/specialist initiation and stabilisation for 3 months based on the price drop, national consensus and growing experience in use of these drugs.
2. Rivastigmine is also GREEN for Parkinson’s disease Dementia Complex (PDDC) - titration and dose stabilisation to be undertaken by consultant/specialist.
3. Rivastigmine 4.5mg and 6mg strength are significantly more expensive- use combination of lower strength instead.
4. Donepezil orodispersible is significantly more expensive than the standard tablet formulation
5. Aspirin and vascular dementia - Low-dose aspirin can improve the prognosis of heart disease and stroke, possibly by reducing clot formation within the blood vessels and helping to maintain or improve blood flow to the heart and brain. Many doctors assume that aspirin will also provide some benefit for people with vascular dementia. A Cochrane review, 2012, shows that there is no evidence to suggest that aspirin is useful for people with vascular dementia. It is possible that vascular dementia and stroke are caused by different pathological processes. Practitioners need to be aware of the risks of aspirin, such as haemorrhages, which can be fatal.