

Chapter 4: CENTRAL NERVOUS SYSTEM

Updated: March 2020

Drugs and driving

It is an offence to drive with certain medicines above specified limits in the blood. 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 – management in primary care
- Dementia – managing behavioural problems
- Depression and the use of antidepressants
- Domperidone – off licence use
- Lithium carbonate (Priadel) update - switching paused
- Low back pain and sciatica
- Melatonin – for the treatment of sleep disorders in children
- Metoclopramide use in gastro-paresis
- Midazolam – management of convulsive seizures in the community
- Pain – Nefopam position 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
- Stopping over medication of people with learning disabilities
- Valproate- Pregnancy Prevention Programme pathway; DCHS PIL/ workbook
- SPS- How can nausea and vomiting be treated during pregnancy?

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 **GREY** 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 **GREY** 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 **RED** for treatment of narcolepsy with cataplexy. CCG commissioned for adult patients as per the RMOC criteria through the specialist sleep centres; and NHSE commissioned in line with commissioning policy for symptom control 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*)

- 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.
- [MHRA March 2020](#)- Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression. Only prescribe together if there is no alternative and closely monitor patients for signs of respiratory depression.
- [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.
- Hypnotics to be prescribed at the lowest effective dose that can treat the patient's symptoms.
- Hypnotics should be avoided in the elderly who are at greater risk of becoming ataxic and confused, leading to falls and injury.
- 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 see [Psychotropic drug prescribing for people with intellectual disability, mental health problems and/or behaviours that challenge: practice guidelines](#).

4.2.1 Antipsychotic drugs

Amisulpride tabs 50mg, 100mg, 200mg, oral solution SF 100mg/ml

Aripiprazole tabs 5mg, 10mg, 15mg, 30mg *consultant/specialist recommendation*

Haloperidol tabs 1.5mg, 5mg, 10mg, oral solution SF 10mg/5ml, 5mg/5ml

Olanzapine tabs 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg *consultant/specialist recommendation*

Quetiapine tabs 25mg, 100mg, 150mg, 200mg, 300mg *consultant/specialist recommendation*

Risperidone tabs 500microg, 1mg, 2mg, 3mg, 4mg, oral solution SF 1mg/ml

Sulpiride tabs 200mg 400mg, oral solution SF 200mg/5ml

Trifluoperazine tabs 1mg, 5mg, oral solution SF 5mg/5ml

- Orodispersible tablets are significantly more expensive compared to plain tablets.
- Amisulpride 400mg strength significantly more expensive- use combination of lower strength instead.
- Aripiprazole oral for treating moderate to severe manic episodes in [adolescents](#) with bipolar I disorder (NICE TA292) and aripiprazole injection and depot injection are classified as **RED**.
- 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.
- Quetiapine MR (preferred brand Brancico XL or Sondate XL) is more expensive than standard formulation and has been classified as **GREY**. Prescribe under exceptional circumstances only for:
 - patients who have discontinued their treatment with quetiapine and currently have to re-titrate 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

Haloperidol decanoate inj 50mg/ml, 100mg/ml

Zuclopenthixol decanoate inj 200mg/ml, 500mg/ml

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

4.2.3. Antimanic drugs

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

Carbamazepine

Sodium Valproate (see NICE CG38 on bipolar disorder)

Lithium is **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/> 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 \(MHRA 2018\)](#) 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](#).

4.3 Antidepressants

See antidepressants guidelines. Note not recommended for mild depression.

4.3.1 Tricyclic and related antidepressant drugs

Lofepamine tabs 70mg

Amitriptyline tabs 10mg, 25mg, 50mg

1. Amitriptyline use in neuropathic pain [see local guideline](#).
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. Pregabalin is reclassified as Schedule 3 controlled drugs from 1 April 2019. See NHS England [briefing note](#) and [MHRA February 2021](#). Pregabalin (Lyrica): reports of severe respiratory depression.
3. Nortriptyline is **GREY** 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 **Do Not Prescribe (DNP)** 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 **GREY** 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](#) and UKMi [Medicines Q&A](#) 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 **GREY** 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 **GREY** after consultant/specialist initiation - 2nd line as per NICE
6. Vortioxetine has been classified 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](#)
8. SSRI/SNRI antidepressants- small increased risk of postpartum haemorrhage [MHRA January 2021](#). SSRIs and SNRIs (venlafaxine) are known to increase the bleeding risk; observational data suggest that the use of some antidepressants in the last month before delivery may increase the risk of postpartum haemorrhage. Continue to consider the benefits and risks for use of antidepressants during pregnancy, and the risks of untreated depression in pregnancy.

4.3.4 Other antidepressants drugs

Mirtazapine tabs 15mg, 30mg, 45mg

Venlafaxine caps 37.5mg m/r, 75mg m/r, 150mg m/r

1. The most cost effective strength of venlafaxine should be prescribed.
2. 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.
3. Mirtazapine oral solution is **GREY**. 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 **Do Not Prescribe (DNP)**.
2. [MHRA November 2020](#):- Modafinil: increased risk of congenital malformations if used during pregnancy
 - Modafinil should not be used during pregnancy and women of childbearing potential must use effective contraception during treatment and for 2 months after stopping modafinil.
 - Modafinil may reduce the effectiveness of steroidal contraceptives, including oral contraceptives, through the induction of CYP3A4/5. Alternative or concomitant methods of contraception are required.

The following drugs are classified as **AMBER** -see [shared care guideline](#)

Methylphenidate	Atomoxetine
Lisdexamfetamine	Guanfacine
Dexamfetamine	

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, oral solution SF 5mg/5ml

Domperidone tabs 10mg, oral suspension SF 1mg/ml

Cyclizine tab 50mg

Prochlorperazine tabs 5mg, oral solution 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.
 - 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
 - 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.

[MHRA advice](#) (2019)- Domperidone is no longer licensed for children under 12 years of age due to lack of efficacy. Where it is used outside of its authorised indications in children for gastrokinetic effects in conditions other than nausea and vomiting, specialist input is required.
3. For use in gastroparesis and other gastric outlet physiological impairment, metoclopramide and domperidone are classified as **GREY** 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.
6. [NICE NG201 Antenatal care](#) gives advice on treatment of nausea and vomiting in pregnancy
 - Reassure women that mild to moderate nausea and vomiting are common in pregnancy and likely to resolve before 16-20 weeks.
 - For pregnant women with mild-to-moderate nausea and vomiting who prefer a non-pharmacological option, suggest that they try ginger.
 - When considering pharmacological treatments for nausea and vomiting in pregnancy, discuss the advantages and disadvantages of different antiemetics with the woman. Take into account her preferences and her experience with treatments in previous pregnancies.
 - For pregnant women with nausea and vomiting who choose a pharmacological treatment, offer an antiemetic. See [NICE table 1](#) on the advantages and disadvantages of different pharmacological treatments for nausea and vomiting in pregnancy.

7. For further information on nausea & vomiting in pregnancy see SPS - [How can nausea and vomiting be treated during pregnancy](#)

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-dydramol 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 **GREY**.
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)

>50 kg	500mg-1g every 4-6 hours, Maximum 4g daily
40 - ≤50 kg	500mg-1g every 4-6 hours, Maximum 3g daily
30-39 kg	Dose reduction required

5. The prescribing of Co-proxamol is not supported and clinicians should move patients to suitable alternatives. Its use has been linked to death by fatal poisoning. Co-proxamol is unlicensed and has been classified locally as **Do Not Prescribe (DNP)**.
6. JAPC has classified nefopam as **Do Not Prescribe (DNP)**. 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-dydramol: prescribe and dispense by strength to minimise risk of medication error. Previously co-dydramol (dihydrocodeine/paracetamol) was available only in the ratio 1:50 (co-dydramol 10/500 mg). Two products are now available with a higher strength of dihydrocodeine (co-dydramol 20/500 mg and 30/500 mg tablets). It is therefore important that co-dydramol products are prescribed and dispensed by strength to minimise dispensing errors and the risk of accidental opioid overdose.

4.7.2 Opioid analgesics

[MHRA March 2020](#) - Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression. Only prescribe together if there is no alternative and closely monitor patients for signs of respiratory depression. At the end of treatment, taper dosage slowly to reduce the risk of withdrawal effects. Consider the possibility of hyperalgesia if a patient on long-term opioid therapy presents with increased sensitivity to pain.

[MHRA September 2020](#) - Opioids: long-term (>3months) use in non-cancer pain, even at therapeutic doses, carries an increased risk of dependence and addiction. Before prescribing opioids, discuss with the

patient the risks and features of tolerance, dependence, and addiction, and agree together a treatment strategy and plan for end of treatment. See [non-malignant chronic pain guideline](#) for further detail.

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 [here](#) for more information.
 - Tramadol MR is **GREY** and significantly more expensive than standard release formulation. (Preferred brand is Marol).

Strong opioids (see [choice of strong opioids for cancer pain](#))

1st line

Morphine Sulphate Modified release caps (Zomorph) 10mg, 30mg, 60mg, 100mg, 200mg

Immediate release tabs (Sevredol) 10mg, 20mg, 50mg

Oral solution 10mg/5ml

Injection 10mg/ml see [end of life pathway](#)

2nd line

Oxycodone Modified release tabs (Oxypro/ Oxeltra) 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. For non-cancer pain, JAPC advise that patients receiving opioid doses of >50mg/day morphine equivalent should be reviewed regularly (at least annually). Clinicians may seek specialist advice for doses >90mg/day morphine equivalent.
2. 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 **GREY**.
3. Prescribe laxatives when starting regular morphine and continue while on opioid. Consider anti-emetic if appropriate.
4. Onexila (once daily MR oxycodone) is **Do Not Prescribe (DNP)** due to the potential safety concerns and confusion over drug selection as already seen with immediate release and modified release formulations.
5. 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.
6. Diamorphine injections was previously a first line analgesia in palliative care. However, due to long-term and ongoing supply issue with 5 & 10mg strength commonly used in primary care and

associated increased cost, morphine injection is now recommended as first line. See [SPS memo](#) and local [end of life pathway](#).

Fentanyl

1. MHRA ([October 2018](#)) warns of the risk of serious and fatal overdose of fentanyl patches due to dosing errors, accidental exposure (particularly in children), and exposure of the patch to a heat. Remind patients (or caregivers) to:
 - Follow the correct frequency of patch application, avoiding touching the adhesive side of patches, and washing hands after application. Remove old patches before applying a new one.
 - Avoiding exposure of patches to heat including via hot water (bath, shower)
 - Follow instructions for safe storage and properly disposing of used patches or those which are not needed. After use, patches should be folded so that the adhesive side of the patch adheres to itself and then placed back into the original sachet.
 - Be aware of the signs and symptoms of fentanyl overdose (e.g. difficulty/ shallow breathing; tiredness; extreme sleepiness/ sedation; feeling faint, dizzy or confused) and seek medical attention immediately (by dialling 999 and requesting an ambulance) if overdose is suspected.
2. In patients who experience serious adverse events, remove patches immediately and monitor for up to 24 hours after patch removal.
3. 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 due to considerable risk of respiratory depression. ([MHRA September 2020](#))
4. Maximum titrated dose for fentanyl patches should not exceed >50microg/hour changed every three days. (12 microg per hour fentanyl patch equates to daily doses of oral morphine of up to 45mg a day) Seek specialist advice if increased dosing is required.
5. 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.
6. Patches exposed to external heat (e.g. a bath) could increase its absorption and possible side effects.
7. 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.”
8. All non-transdermal preparations (i.e. lozenges, tablets, buccal film and sublingual tablets) are classified as **GREY** after palliative care specialist initiation (to allow access in primary care if needed). Prescribe by brand to avoid confusion. These preparations require specialist initiation and titration. **Do Not Prescribe (DNP)** for all non-transdermal preparations initiated outside palliative care.

Buprenorphine

1. Buprenorphine patches are classified as **GREY** - the patches should be prescribed by brand as the frequency to be applied may vary between brands.
2. Buprenorphine patches at lower doses are broadly as effective as codeine or tramadol but much more expensive.
3. 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.
4. The preferred cost effective brand for low dose (7 day) patch is Reletrans
5. Higher strength patches are also available but the bioavailability and application varies between brands. Different brands are not interchangeable. Check individual SPC carefully.
6. The preferred cost effective high strength brand (replace after 96 hours) is Relevtec.

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, 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. Domperidone is an alternative anti-emetic and should only be used for a maximum of 7 days as per [JUCD headache pathway](#).
2. Patients should be warned about the risk of developing medication-overuse headache when starting acute treatment.
3. [SPS Summary](#): UK guidelines for the management of headaches advise that 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 as there is no licensed riboflavin product available in the UK, nor any cost effectiveness data to justify its use on NHS prescription.
4. 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.
 - if vomiting restricts oral treatment, consider a non-oral formulation (such as sumatriptan nasal spray or subcutaneous sumatriptan as per [JUCD headache pathway](#)).
5. Diclofenac 50mg or 100mg suppositories are useful if vomiting or severe nausea present as per [JUCD headache pathway](#)

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

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, e.g. 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) can be considered as a prophylactic treatment for patients with episodic or chronic migraine.
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

7. [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. See section 4.8.1 for more details.
8. Metoprolol at a dose of 100mg-200mg daily in divided doses is a suitable licensed alternative if propranolol cannot be tolerated; Nortriptyline is 2nd line option only to be used if amitriptyline is effective but patient unable to tolerate side effects, as per [JUCD headache pathway](#).
9. Verapamil is reserved as a 2nd line treatment option for cluster headaches. Prednisolone is reserved for use with verapamil for cluster headaches. See [JUCD headache pathway](#) for further details

4.8.1 Control of epilepsy

The following are classified as **GREEN** after specialist initiation

Clonazepam	Oxcarbazepone
Carbamazepine	Phenobarbital and other barbiturates
Ethosuximide	Phenytoin
Gabapentin	Pregabalin
Lacosamide	Sodium Valproate
Lamotrigine	Topiramate
Levetiracetam	Zonisamide

The following 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 neighbouring area prescribing [formularies](#)).

Eslicarbazepine	Perampanel
Retigabine	Rufinamide
Stiripentol	Tiagabine
Vigabatrin*	

*Vigabatrin is also classified as **AMBER**; [shared care](#) with Derby Hospitals NHS Foundation Trust ONLY for treating epilepsy in children.

[MHRA 2013](#) recommends that antiepileptics are divided into three risk based-categories

Category	Category 1: prescribers are advised that patients receiving treatment for epilepsy are maintained on the same manufacturer	Category 2: continuity of manufacturer is based on clinical judgement taking into account factors such as seizure frequency and treatment history	Category 3: it is usually unnecessary to ensure a specific manufacturer
Name of medicine	carbamazepine phenytoin phenobarbital primidone	clobazam clonazepam eslicarbazepine lamotrigine oxcarbazepine perampanel	retigabine rufinamide topiramate valproate zonisinamide
			ethosuximide gabapentin lacosamide levetiracetam pregabalin tiagabine vigabatrin

1. **Antiepileptic drugs in pregnancy**- a review of the risks of major congenital malformations and of adverse neurodevelopmental outcomes for antiepileptic drugs by the Commission on Human Medicines has confirmed that lamotrigine (Lamictal) and levetiracetam (Keppra) are the safer of the medicines reviewed during pregnancy. [MHRA January 2021](#)
 - Women using antiepileptic drugs who are planning to become pregnant should be offered folic acid 5mg daily before any possibility of pregnancy.
 - Urgently refer women who are planning to become pregnant for specialist advice on their antiepileptic treatment.
 - These are usually initiated by specialist. GPs using antiepileptic drugs for other indications must carefully consider the risk and benefit
2. All new antiepileptics will be considered to be **RED** in Derbyshire until formal classification at JAPC.
3. 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.

4. 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](#).

5. 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.

6. 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.
 - Phenytoin tablets although listed as generic medicines have significantly increased in price.
7. 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.
 8. Gabapentin and pregabalin are reclassified as Schedule 3 controlled drugs from 1 April 2019. See NHS England [briefing note](#).
 9. 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.
 10. Pregabalin has been associated with infrequent reports of severe respiratory depression, including some cases without the presence of concomitant opioid medicines. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment; those using concomitant CNS depressants; and people older than 65 years might be at higher risk of experiencing these events and adjustments in dose or dosing regimen may be necessary. See [MHRA February 2021](#).
 11. 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.
 12. Brivaracetam is **GREY** after consultant/specialist initiation and stabilisation of three months in patients that have responded to levetiracetam but unable to tolerate the adverse effects

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 **Do Not Prescribe (DNP)**. 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. Sinemet is currently the preferred cost effective brand of co-careldopa.
2. Ipinnia XL is the preferred cost effective brand for ropinirole.
3. Pramipexole MR preparation is 2nd line only (Pipexus is the cost effective brand)
4. Stanek and Sastravi are the cost effective choices of carbidopa/entacapone/levodopa combination
5. Kemadrin is the cost effective brand for procyclidine.

4.10 Drugs used in substance dependence

4.10.1 Alcohol dependence

The following are classified as **AMBER** see [shared care guidelines](#)

Acamprosate (For patients seen by/referred to the Derbyshire Recovery partnership)

Disulfiram (For patients seen by/referred to the Derbyshire Recovery partnership)

Naltrexone (For patients within services commissioned by appropriate body)

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. [MHRA Nov 2020](#): Bupropion: risk of serotonin syndrome with use with other serotonergic drugs
 - if concomitant prescribing with other serotonergic drugs is clinically warranted: do not exceed the recommended dose; remind patients of the milder symptoms of serotonin syndrome at initiation of treatment and at any change of dose and the importance of seeking medical advice if they occur
 - if serotonin syndrome is suspected, either decrease the dose of bupropion or withdraw therapy depending on the severity of the symptoms
4. 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

The following are classified as **AMBER** via Local Enhanced Service (LES) and GP with a special interest (GPSI). See [shared care guidelines](#)

Buprenorphine

Methadone

4.11 Drugs for dementia (see [local guidance](#))

These drugs are classified as **GREEN** after consultant/specialist initiation and stabilisation for 3 months based on the price drop, national consensus and growing experience in use of these drugs.

Donepezil tabs 5mg, 10mg	<i>1st line</i>
Galantamine tabs 8mg, 12mg; MR tabs 8mg, 16mg, 24mg	<i>Luventa XL is the preferred brand for MR tab</i>
Rivastigmine caps 1.5mg, 3mg	<i>Alzest is the preferred brand for patch</i>
Memantine tab 10mg, 20mg	

1. Rivastigmine is also **GREEN** for Parkinson's disease Dementia Complex (PDDC) - titration and dose stabilisation to be undertaken by consultant/specialist.
2. Rivastigmine 4.5mg and 6mg strength are significantly more expensive- use combination of lower strength instead.
3. Donepezil orodispersible is significantly more expensive than the standard tablet formulation.
4. **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.