NHS
Essex Partnership University
NHS Foundation Trust

SECTION 21: HIGH RISK MEDICINES

Formulary and Prescribing Guidelines

There are many medicines which can be classed as high risk due to the number of potentially harmful medication incidents that have been reported through the National Reporting and Learning Services (NRLS) and NHS Improvement. This document aims to highlight those medicines and highlight the issues involved.

The medicine classes included are:

Anticoagulants

Insulin

Lithium

Valproate

Methotrexate

Midazolam

Oral bowel cleansing preparations

Paraffin based skin products and emollients

Antimicrobials

Injectable phenytoin

Opioids

Steroids

21.1 Anticoagulants

Anticoagulants are one of the classes of medicines most frequently identified as causing preventable harm and admission to hospital.[1]

Medicines included in the category are:

Older oral anticoagulants	Novel oral anticoagulants	Parenteral anticoagulants
Warfarin	Dabigatran	Heparin
Phenindione	Apixaban	Enoxaparin
Acenocoumarol	Rivaoxaban	Dalteparin
	Edoxaban	Tinzaparin
		Fondaparinux

For further information on the use of these medicines see Chapter 14 Anticoagulants and CG83 Clinical Guideline for the management of patients on anticoagulants in inpatient units.

References:

1. National Patient Safety Agency. NPSA /2007/18. Actions that can make anticoagulant therapy safer: Alert and other information March 2007. Accessed via http://www.nrls.npsa.nhs.uk

21.2 Insulin

Errors in the administration of insulin are common and may cause severe harm or death. In order to ensure that the correct dose is administered it is essential that where possible insulin pen devices are used. If a syringe has to be used it should be an insulin syringe marked in units and not mls. Intravenous syringes should never be used.

When prescriptions for insulin are written, prescribers should ensure that the word “unit” is used and not “U” or “IU”

Insulin preparations are available in increasingly high strengths. Where these are available in pen devices they are calibrated so that the correct dose is administered to the patient. Insulin should **never** be withdrawn from these devices using a syringe.

Many patients are competent at managing their own insulin and many use carbohydrate counting to adjust the dose that is administered. Every effort should be made to ensure that patients are allowed to continue with this wherever possible. If it is felt that this is not possible for reasons of patient safety there should be a discussion with the patient and/or their family regarding the best solution to the management of insulin administration.

All patients should carry an insulin passport. This will normally be issued by the clinic where the insulin is initiated, but they are available from pharmacy if it is discovered that the patient does not have one.

Cutaneous amyloidosis at the injection site has been reported[5] in patients using insulin and this may affect glycaemic control. Remind patients to rotate injection sites within the same body region.

Advice for healthcare professionals[5]:

- injection of insulin (all types) can lead to deposits of amyloid protein under the skin (cutaneous amyloidosis) at the injection site
- cutaneous amyloidosis interferes with insulin absorption, and administration of insulin at an affected site can affect glycaemic control
- remind patients to rotate injection sites within the same body region to reduce or prevent the risk of cutaneous amyloidosis and other skin reactions (for example, lipodystrophy)
- consider cutaneous amyloidosis as a differential diagnosis to lipodystrophy when a patient presents with subcutaneous lumps at an insulin injection site
- advise patients:
    - that insulin may not work very well if they inject into an affected ‘lumpy’ area
    - to contact their doctor if they are currently injecting insulin into a ‘lumpy’ area before changing injection site since a sudden change may result in hypoglycaemia
    - to monitor carefully blood glucose after a change in injection site and that dose adjustment of insulin or other antidiabetic medication may be needed
- report serious adverse drug reactions associated with insulin to the Yellow Card Scheme

References:

1. National Patient Safety Agency. NPSA/2010/RRR013 Safer administration of insulin June 2010. Accessed via http://www.nrls.npsa.nhs.uk
2. National Patient Safety Agency. NPSA/2011/PSA003. The adult's passport to safer use of insulin March 2011. Accessed via http://www.nrls.npsa.nhs.uk
3. NHS Improvement: NHS/PSA/W/2016/011 Risk of severe harm and death due to withdrawing insulin from pen devices. Accessed via Patient Safety Alert Withdrawing insulin from pen devices
4. CLPG13 Procedures for the Safe and Secure Handling of Medicines July 2017.
5. Drug Safety Update volume 14, issue 2: September 2020: 5.

21.3 Lithium

Some patients taking Lithium have been harmed because they have not had their dosage adjusted based on the results of recommended blood tests.

For information on how to initiate Lithium and monitor ongoing treatment refer to Section 3 of the Formulary and Prescribing Guidelines.

As Lithium can be extremely toxic when not used at the correct dose, no patient who is being admitted to the Trust should receive a dose until the results of a valid blood test have been received.

All patients prescribed Lithium should be issued with a Lithium Therapy pack. This contains information for patients, a booklet where blood test results can be recorded and a Lithium alert card.

If patients are admitted to the Trust already being treated with Lithium should have a Lithium Therapy pack that has been completed with details of previous blood tests. If this is not the case the current booklet should be updated by prescribers with previous results and if there is no pack a new one should be issued.

Lithium Therapy packs can be obtained from the Trust Pharmacy department.

References:

1. National Patient Safety Agency. NPSA/2009/PSA005 Safer Lithium Therapy December 2009. Accessed via http://www.nrls.npsa.nhs.uk

21.4 Valproate

Valproate is an effective medicine used to treat epilepsy and bipolar disorder.
Unborn babies exposed to valproate during pregnancy are at very high risk of neurodevelopment disability e.g. lower intelligence and autistic spectrum disorders.
In girls and women of a childbearing potential, valproate should be initiated and supervised by a specialist and **only** when other medicines have not been tolerated or have been proved to be ineffective.
The Medicines and Healthcare products Regulatory Agency (MHRA) has published a valproate toolkit providing sets of resources for patients, GPs, pharmacists and specialists.

Valproate medicines must not be used in women or girls of childbearing potential unless a Pregnancy Prevention Programme is in place[1] and the conditions met, and only if other treatments are ineffective or not tolerated, as judged by an experienced specialist. Ensure all women and girls (and their parent, caregiver, or responsible person, if necessary) are fully informed of the risks and the need to avoid exposure to valproate medicines in pregnancy. Specialists must book in review appointments at least annually with women and girls under the Pregnancy Prevention Programme, check they are on highly effective contraception (taken without interruption), and re-evaluate treatment as necessary; explain clearly the conditions as outlined in the supporting materials (the "toolkit")[2] ;provide a "Patient Guide"[2] to girls (of any age) and women of childbearing potential (or their parent/caregiver/responsible person) who are started on or are continuing to use valproate medicines; and complete and sign the Annual Risk Acknowledgement Forms[2] (Annex 1)—a copy of the form must be filed in the patient's record, a copy given to the patient or patient/caregiver/responsible person, and a copy sent to their GP.

As with all teratogenic medicines, pregnancy should be excluded before initiation on valproate medicines, with a negative plasma pregnancy test, confirmed by a healthcare professional. Women and girls of childbearing potential must use highly effective contraception if they are able to become pregnant (see guidance from Faculty of Sexual and Reproductive Health [FSRH] https://www.fsrh.org/news/fsrh-ceu-statement-on-contraception-for-women-using-known/). Methods of contraception considered 'highly effective' in this context include the long-acting reversible contraceptives (LARC): copper intrauterine device (Cu-IUD), levonorgestrel intrauterine system (LNG-IUS), and progestogen-only implant (IMP), and male and female sterilisation, all of which have a failure rate of less than 1% with typical use (see guidance from FSRH for more about user-independent methods and failure rates). If a user-independent form is not used, two complementary forms of contraception including a barrier method should be used and regular pregnancy testing considered. Individual circumstances should be, in each case, evaluated when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures.[1]

If the patient becomes pregnant on valproate, consideration should be given to tapering the valproate down carefully, while introducing suitable alternative drug treatment. Treatment of BPAD in children & adolescents and antenatal & postnatal services users is discussed in F&PG section 12 and section 20 respectively. Additional information regarding prescribing in older adults can also be found in section 11.

References:

1. Drug Safety Update. Valproate medicines (Epilim▼, Depakote▼): contraindicated in women and girls of childbearing potential unless conditions of Pregnancy Prevention Programme are met. Medicines and Healthcare products Regulatory Agency. Published 24 April 2018. Accessed 23/5/2018. https://www.gov.uk/drug-safety-update/valproate-medicines-epilim-depakote-contraindicated-in-women-and-girls-of-childbearing-potential-unless-conditions-of-pregnancy-prevention-programme-are-met
2. Guidance. Valproate use by women and girls. Information about the risks of taking valproate medicines during pregnancy. Toolkit. Medicines and Healthcare products Regulatory Agency. Last updated 9 April 2019. Accessed 23/5/2019. https://www.gov.uk/guidance/valproate-use-by-women-and-girls

21.5 Methotrexate

Oral methotrexate is used in low doses (up to 25mg weekly) for the treatment of rheumatoid arthritis and psoriasis.

Prescribers will not be asked to initiate methotrexate treatment, but may be responsible for maintaining therapy and monitoring patients.

Methotrexate should only be prescribed by healthcare professionals who are fully aware of the benefits and risks of treatment and who have all necessary prescribing competence.

Written confirmation of the dose should be sought before prescribing, including the dosage and frequency of taking, plus the day of the week when methotrexate is normally taken. This should be done through the medicines reconciliation process. Additional information may be available in a patient held record book.

Confirmation of the frequency of monitoring should also be clarified with the original prescriber.

Prescribers should ensure that only one route of administration for methotrexate is prescribed.

Only the 2.5mg tablets will be issued by the pharmacy department.
If folic acid is prescribed alongside methotrexate, it is not usually given on the same day as methotrexate.

Monitoring of methotrexate therapy is to specifically look for adverse toxic effects. Blood tests for renal and liver function in addition to full blood counts are monitored at baseline, then 1-2 weekly until stable, at the clinic, then every 2-3 months.

Liver and renal function tests and FBCs should be done on admission for all patients. If they are abnormal the information should be shared with the initiating clinic.

If the patient is on the ward-unit for longer than 3 months the tests should be repeated. Patients on methotrexate are considered to be immunosuppressed and should not receive live vaccines.

Methotrexate interacts with some commonly prescribed medicines including non-steroidal anti-inflammatories (NSAIDs) such as ibuprofen and aspirin, as well as antibiotics such as trimethoprim which can be fatal if prescribed together.

Healthcare professionals must be aware of potentially toxic adverse effects of methotrexate including blood dyscrasias – often found through symptoms of infection or unexplained bruising or bleeding, liver cirrhosis - picked up through blood tests or symptoms of jaundice, and also pulmonary toxicity – manifested as shortness of breath or dry persistent cough.

Persistent nausea and vomiting poses additional risks for patients on methotrexate as the risk of toxicity increases if dehydration occurs. These symptoms could also be indicative of intolerance to oral methotrexate.

In September 2020, MHRA published further advice to reduce risk of fatal overdose due to inadvertent daily instead of weekly dosing, for autoimmune diseases and some cancer therapy. These new measures have been implemented to prompt healthcare professionals to record the day of the week for intake and to remind patients of the dosing schedule and the risks of overdose.

Advice for prescribers:

• before prescribing methotrexate, make sure that the patient is able to understand and comply with once-weekly dosing
• confirm with the patient which day of the week they take their methotrexate
• remind the patient and their caregivers of the potentially fatal risk of accidental overdose if methotrexate is taken more frequently than once a week; specifically, that it should not be taken daily
• advise patients of the need to promptly seek medical advice if they think they have taken too much

References:

1. National Patient Safety Agency. Towards the safer use of oral methotrexate. NPSA 2004 Accessed via http://www.nrls.npsa.nhs.uk on 15/12/2013

2. National Patient Safety Agency 2006. Oral methotrexate patient information leaflet & dosage record booklet

3. National Patient Safety Agency. NPSA/2006/13. Improving compliance with oral methotrexate guidelines - Patient Safety Alert 2006. Accessed via http://www.nrls.npsa.nhs.uk

4. Drug Safety Update volume 14, issue 2: September 2020: 5.

21.6 Midazolam

Buccal midazolam can be prescribed to treat prolonged epileptic seizures in adults and children. It is available as pre-filled oral syringes and a multidose bottle. Care must be taken to ensure that only the oral syringes provided by the manufacturer should be used and never a syringe that is designed to administer injectable preparations.

The solution should be administered into the buccal cavity (the space between the gum and the cheek). If necessary, half should be given on the left and half on the right side of the mouth. The full contents of the syringe should be given. The dose should only be repeated in accordance with the patient's careplan.

These preparations are intended for oromucosal use only, and must never be injected.

Intravenous midazolam for conscious sedation should only be used during electro-convulsive therapy (ECT) under the direct supervision of an anaesthetist experienced in this area. Only the high strength midazolam (10mg in 2mL) ampoules are kept in the Trust, and only on the ECT suite.
Subcutaneous midazolam may be prescribed and supplied for named patients for subcutaneous use

References:

1. National Patient Safety Agency. Prevention of Harm with Buccal Midazolam | Signal 2012. Accessed via http://www.nrls.npsa.nhs.uk
2. National Patient Safety Agency. Reducing risk of overdose with midazolam injection in adults NPSA/2008/RRR011. Accessed via http://www.nrls.npsa.nhs.uk

21.7 Oral Bowel Cleansing Preparations

Oral bowel cleansing preparations are used before certain investigational or medical procedures. These preparations have been highlighted as hazardous due to electrolyte

imbalances, dehydration or other problems associated with their use, particularly in vulnerable patient groups such as elderly, frail and children. Service users may need to use these preparations before undergoing surgery or investigations for physical health problems, and therefore staff must understand how and when they are to be used.
It is usual procedure that a clinician at the acute hospital will advise use of an oral bowel cleansing preparation, and they usually supply it directly.

It is the responsibility of the clinician authorising the surgery or investigative procedure to ensure that there is no contraindication (e.g. clinical condition such as diverticulitis) or risks (e.g. concurrent medication such as diuretics) from the use of a bowel cleansing solution. The same clinician authorising the use of the oral bowel cleansing preparation must also ensure that adequate information is given to the patient and/or carer.
For inpatients, staff must ensure that the preparation is prescribed on the patient's Prescription and Administration chart, and that the information on when to take it and how much fluid to drink is strictly adhered to.

Staff must contact the authorising clinician if there are any questions or concerns around the use of an oral bowel cleansing preparation.

References:
National Patient Safety Agency. NPSA/2009/RRR012. Reducing risk of harm from oral bowel cleansing solutions. Accessed via http://www.nrls.npsa.nhs.uk

21.8 Paraffin Based Skin Products, and Emollients

There is a risk of severe and fatal burns with all emollients, not just paraffin based products [1,2,3].

Emollients include skin cream, ointment, lotion, gel, spray, bath oil or soap substitute.

Emollients can transfer from the skin onto clothing, bedding, dressings, and other fabric. Once there, they can dry onto the fabric and build up over time. In the presence of a naked flame, fabric with emollient dried on is easily ignited.

Although emollients are not flammable in themselves or when on the skin, when dried on to fabric they act as an accelerant, increasing the speed of ignition and intensity of the fire. This accelerant effect significantly reduces the time available to act to put out a clothing or bedding fire before serious and fatal burns are sustained.

This applies to all emollients, whether they contain paraffin or not.

Pharmacy will apply a "fire hazard" label to any emollients, plus a patient information leaflet for the product.

All staff should be aware of the potential risk of fire if any open flames (including cigarettes) are used near the emollient, or any sites where it has been applied to.

A check should be made that the patient understands these risks.
If, against advice, a hospitalised patient intends to leave the ward to smoke, they should be informed of the risk and advised to wear a thick outer covering that has not been contaminated with emollients.

Resources [3] have been published by MHRA (August 2020) to support the safe use of these products.

References:

1. National Patient Safety Agency. RRR/2007/4. Fire hazard with paraffin-based skin products November 2007. Accessed via http://www.nrls.npsa.nhs.uk
2. Drug Safety Update volume 12, issue 5: December 2018: 3. Emollients: new information about risk of severe and fatal burns with paraffin-containing and paraffin-free emollients. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/765896/PDF-Dec-2018.pdf
3. MHRA. Emollients and risk of severe and fatal burns: new resources available. Published 26/8/2020. https://www.gov.uk/drug-safety-update/emollients-and-risk-of-severe-and-fatal-burns-new-resources-available

21.9 Antimicrobials

Antimicrobial resistance (AMR) is a major global threat to public health and has risen alarmingly over the last 40 years. Very few novel antimicrobials have been developed meaning that existing antibiotics are under extreme pressure and inappropriate use of these antibiotics has increased the risk to patients of colonisation with resistant organisms, which can subsequently be transmitted to other patients. Antibiotics selected for prescribing should therefore be the narrowest spectrum for the identified condition and broad spectrum antibiotics such as co-amoxiclav, fluoroquinolones and cephalosporins should be avoided unless indicated. Prescribers should use the following principles to guide antibiotic selection, thereby promoting safe, effective and economic use and minimising the emergence of antibacterial resistance:

- Ensure you document all your decisions
- Use local guidance based on clinical evidence in conjunction with professional judgement and taking patients' wishes/clinical condition into account
- Take a thorough allergy history
- Initiate treatment within one hour of diagnosis in life threatening infection and severe sepsis
- Ensure the presence of viral infection has been excluded before prescribing
- Do not prescribe during a telephone consultation except in exceptional circumstances
- Ensure the indication, dose and route are recorded on both the drug chart and in the patients' record
- Prescribe the shortest appropriate duration (broad spectrum antibiotics taken for protracted periods can promote resistance) and ensure a review/stop date is documented
- Avoid topical antibiotics unless indicated (this can promote resistance)
- Take cultures prior to commencing treatment (where appropriate) but do not delay initiation in the absence of cultures
- Contact your local microbiologist for advice in cases of recurrent or resistant infection

Patients and their carers should be advised that if an antibiotic is prescribed, it should be taken exactly as directed even if the patient is feeling better. There are numerous pieces of legislation, guidance and reviews, both national and local, to guide clinicians and provide background information.

References:

1. Department of Health. UK 5 Year Antimicrobial Resistance Strategy 2013 to 2018. September 2013. Available at: https://www.gov.uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018
2. Public Health England. Management of infection guidance for primary care for consultation & local adaptation. May 2016. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/586766/managing_common_infections.pdf
3. Public Health England. Start Smart - Then Focus: Antimicrobial Stewardship Toolkit for English Hospitals. March 2015. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/417032/Start_Smart_Then_Focus_FINAL.PDF
4. South Essex Partnership University NHS Foundation Trust. Protocol for Antimicrobial Stewardship. April 2014.
5. Annual Report of the Chief Medical Officer: Volume Two, 2011. Infections and the rise of antimicrobial resistance (published 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/138331/CMO_Annual_Report_Volume_2_2011.pdf
6. Cochrane Library. Interventions to improve antibiotic prescribing practices for hospital inpatients (updated protocol). May 2014. Available at: http://www.cochrane.org/CD011236/EPOC_interventions-to-improve-antibiotic-prescribing-practices-for-hospital-inpatients-updated-protocol
7. Public Health England. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report. October 2014. Available at: https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report
8. Department of Health. The Health and Social Care Act 2008: code of practice on the prevention and control of infections and related guidance. July 2015. Available at: https://www.gov.uk/government/publications/the-health-and-social-care-act-2008-code-of-practice-on-the-prevention-and-control-of-infections-and-related-guidance
9. Review on Antimicrobial Resistance. Tackling drug-resistant infections globally: Final report and recommendations. May 2016. Available at: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf
10. National Institute for Health and Care Excellence. Antimicrobial stewardship: systems and processes for effective antimicrobial medicines use (NG 15). August 2015. Available at: https://www.nice.org.uk/guidance/ng15
11. National Institute for Health and Care Excellence. Antimicrobial stewardship (QS121). April 2016. Available at: https://www.nice.org.uk/guidance/qs121
12. National Institute for Health and Care Excellence. Changing risk-related behaviours in the general population (NG63). January 2017. Available at: https://www.nice.org.uk/guidance/ng63

21.10 Injectable Phenytoin

Injectable phenytoin is used to slow and stabilise erratic electrical brain activity in for example, status epilepticus, which is a life threatening medical emergency. Phenytoin is a particularly complicated drug to use. It is unlikely that injectable phenytoin will be used in this Trust, but if prescribing is considered the pharmacy department should be contacted for advice.

References:

1. NHS Improvement. Patient Safety Alert: Risk of death and severe harm with injectable phenytoin NHS/PSA/W/2016/010. Risk of error with injectable phenytoin

21.11 Opioids

Good practice in prescribing opioid medicines for pain should reflect fundamental principles in prescribing generally. The decision to prescribe is underpinned by applying best professional practice; understanding the condition, the patient and their context, and understanding the clinical use of the drug.

Initiating, tapering or stopping opioid medicines should be managed in agreement with the patient and all members of their healthcare team.

The Faculty of Pain Medicine (FPM) in collaboration with Public Health England (PHE) provides information to support a safe and effective prescribing decision. The key principles from this information include:

- Opioids are very good analgesics for acute pain and for pain at the end of life but there is little evidence that they are helpful for long term pain
- A small proportion of people may obtain good pain relief with opioids in the long-term if the dose can be kept low and especially if their use is intermittent (however it is difficult to identify these people at the point of opioid initiation)
- The risk of harm increases substantially at doses above an oral morphine equivalent of 120mg/day, but there is no increased benefit: tapering or stopping high dose opioids needs careful planning and collaboration
- If a patient has pain that remains severe despite opioid treatment it means they are not working and should be stopped, even if no other treatment is available
- Chronic pain is very complex and if patients have refractory and disabling symptoms, particularly if they are on high opioid doses, a very detailed assessment of the many emotional influences on their pain experience is essential

MHRA published new recommendations[1] in 2020 following a review of the risks of dependence and addiction associated with prolonged use of opioid medicines for non-cancer pain. 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.

Advice for healthcare professionals:

- opioid medicines (opioids) provide relief from serious short-term pain; however long-term use in non-cancer pain (longer than 3 months) carries an increased risk of dependence and addiction
- discuss with patients that prolonged use of opioids may lead to drug dependence and addiction, even at therapeutic doses – warnings have been added to the labels (packaging) of UK opioid medicines to support patient awareness
- before starting treatment with opioids, agree with the patient a treatment strategy and plan for end of treatment
- explain the risks of tolerance and potentially fatal unintentional overdose, and counsel patients and caregivers on signs and symptoms of opioid overdose to be aware of (see opioids safety information leaflet [2])

- provide regular monitoring and support especially to individuals at increased risk, such as those with current or past history of substance use disorder (including alcohol misuse) or mental health disorder
- at the end of treatment, taper dosage slowly to reduce the risk of withdrawal effects associated with sudden cessation of opioids; tapering from a high dose may take weeks or months
- consider the possibility of hyperalgesia if a patient on long-term opioid therapy presents with increased sensitivity to pain
- consult the latest advice and warnings for opioids during pregnancy in the product information and in clinical resources
- report suspected dependence or addiction to any medicine, including to an opioid, via the Yellow Card scheme

A number of resources are available to guide opioid prescribing [3, 4].

Fentanyl patches

MHRA published recommendations [1] for fentanyl patches (September 2020), "Transdermal fentanyl patches for non-cancer pain: do not use in opioid-naive patients".

Following a review of the risks associated with use of opioid medicines for non-cancer pain, the Commission on Human Medicines has recommended that fentanyl transdermal patches are contraindicated in opioid-naive patients in the UK [1].

Advice for healthcare professionals:

- Fentanyl is a potent opioid – a 12 microgram per 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
- use other analgesics and other opioid medicines (opioids) for non-cancer pain before prescribing fentanyl patches
- if prescribing fentanyl patches, remind patients of the importance of:
    - not exceeding the prescribed dose
    - following the correct frequency of patch application, avoiding touching the adhesive side of patches, and washing hands after application
    - not cutting patches and avoiding exposure of patches to heat including via hot water (bath, shower)
    - ensuring that old patches are removed before applying a new one
    - following instructions for safe storage and properly disposing of used patches or patches that are not needed; it is particularly important to keep patches out of sight and reach of children at all times
- make patients and caregivers aware of the signs and symptoms of fentanyl overdose and advise them to seek medical attention immediately (by dialling 999 and requesting an ambulance) if overdose is suspected

- remind patients that long-term use of opioids in non-cancer pain (longer than 3 months) carries an increased risk of dependence and addiction, even at therapeutic doses; before starting treatment with opioids, agree with the patient a treatment strategy and plan for end of treatment

- report suspected adverse drug reactions, including dependence, accidental exposure, or overdose associated with fentanyl patches, via the Yellow Card scheme

References:

1. Drug Safety Update volume 14, issue 2: September 2020

2. Opioid medicines and the risk of addiction. Safety leaflet on opioid medicines to help patients and their families reduce the risks of harm. https://www.gov.uk/guidance/opioid-medicines-and-the-risk-of-addiction

3. Faculty of pain medicine of the Royal College of Anaesthetists. Terminology and prevalance. https://fpm.ac.uk/opioids-aware-opioids-addiction/terminology-and-prevalence

4. Management of chronic pain. Healthcare Improvement Scotland / SIGN. https://www.sign.ac.uk/our-guidelines/management-of-chronic-pain/

21.12 Steroids

Patients with primary adrenal insufficiency (AI), such as those with Addison's disease, congenital adrenal hyperplasia, and hypothalamo-pituitary damage from tumours or surgery, and some groups of patient's who take steroids are steroid dependent.

When steroids are omitted in patients who have adrenal insufficiency, this can lead to adrenal crisis, a medical emergency that can be fatal if left untreated. Adrenal crisis can also be the result of failing to take into account the need for increased steroid doses during periods of intercurrent illness or surgery.

National guidance promotes a new Adult Steroid Emergency Card to be issued. This should be held by patients at risk of adrenal crisis and helps healthcare staff to identify appropriate patients and provide emergency treatment if they are acutely ill, or experience trauma, surgery or other major stressors.

Patients in whom emergency steroid cards should be given:

- Patients with a suspected or established diagnosis of primary adrenal insufficiency.
- Patients with pituitary or hypothalamic disease known to be steroid dependant or for patients who have been advised to take steroids for intercurrent illness.
- Patients taking long-term glucocorticoids at a dose equivalent or higher than prednisolone 5mg (see Table 1)
- 3 or more short courses of high-dose oral glucocorticoids within the last 12 months, and for 12 months after stopping (see Table 2)
- 3 or more intra-articular/intramuscular glucocorticoid injections within the last 12 months, and for 12 months after stopping

- Inhaled steroids >1000mcg/day beclomethasone or >500mcg/day fluticasone (or equivalent), and for 12 months after stopping (see Table 3)
- Patients taking inhaled corticosteroids at doses together with any other form of glucocorticoid treatment (see Table 4)
- Nasal steroids >1000mcg/day
- Patients taking >40mg prednisolone or equivalent for longer than one week or repeated short courses of oral doses.
- Repeated courses of dexamethasone as an antiemetic in oncology regimens, and for 12 months after stopping
- Prolonged courses of dexamethasone (>10 days) for treatment of severe Covid-19
- Topical high-dose, potent or very potent glucocorticoids used across a large area of skin for 4 weeks or more, or factors increasing absorption assessed on a case by case basis, and for 12 months after stopping (see Table 5)
- Potent or very potent topical glucocorticoids applied to the rectal or genital areas and used at high dose (more than 30g per month) for more than 4 weeks, and for 12 months after stopping
- Patients prescribed any form of ongoing glucocorticoid treatment (except small amounts of a mild or moderate topical glucocorticoid which should be assessed on a case by case basis) in conjunction with medicines known to be potent CYP3A4 inhibitors (see Table 6).

Both Clinicians and Pharmacy need to be aware of 'at risk' patients that will need to be issued with a new NHS Steroid Emergency Card.

On admission to the service, the patient *identified at risk* must be issued a Steroid Emergency Card by the pharmacy team. **Supplies will be stocked at each local pharmacy team.**

They must also provide advice to patients regarding **'Sick day rules'** and when to seek urgent medical attention for signs and symptoms of adrenal crisis.

Patients should be made aware of the importance of carrying an NHS Emergency Steroid Card. In addition, they may wear a medic alert bracelet or necklace and use mobile phones to create a medical ID for use in an emergency

Patients can also register with their local ambulance trust so that they are 'red flagged' as potentially needing emergency parenteral hydrocortisone.

SICK DAY RULES

Steroid Emergency Card and "Sick day rules" advice

Advice regarding sick day rules will be provided to patients who are unwell outside of hospital and for patients who need education of this prior to discharge.

- Double the usual dose of oral glucocorticoid production if they are unwell with moderate intercurrent illness (e.g. fever, an infection requiring antibiotics) or for surgical procedures under local anaesthetic. Patients taking long-acting hydrocortisone preparations, such as Plenadren® should take the more rapidly absorbed hydrocortisone during intercurrent illness.

- Patients should be issued with intramuscular hydrocortisone for severe intercurrent illness (e.g. persistent vomiting), preparation for colonoscopy, acute trauma or

surgery (when clinically appropriate) and both patients and their families should be trained to self-administrate. If vomiting and diarrhoea persists, they should attend their local hospital urgently as they will require parenteral hydrocortisone and intravenous fluids without delay.

Table 1: Long-term oral glucocorticoids (4 weeks or longer)

Medicine	**Dose (*)**
Beclomethasone	625mcg per day or more
Betamethasone	750mcg per day or more
Budesonide	1.5mg per day or more***
Deflazacort	6mg per day or more
Dexamethasone	500mcg per day or more **
Hydrocortisone	15mg per day or more**
Methylprednisolone	4mg per day or more
Prednisolone	5mg per day or more

Table 2: Short-term oral glucocorticoids (one week course of longer and has been on long-term course within the last year or has regular need for repeated courses)

Medicine	**Dose**
Beclomethasone	5mg
Betamethasone	6mg per day or more
Budesonide	12mg (***)
Deflazacort	48mg per day or more
Dexamethasone	4mg per day or more (**)
Hydrocortisone	120mg per day or more (**)
Methylprednisolone	32mg per day or more
Prednisolone	40mg per day or more

Table 3: Inhaled glucocorticoid doses

Medicine	**Dose (*)**
Beclomethasone (as non-proprietary, Clenil, Easihaler or Soprobec)	More than 1000mcg per day
Beclomethasone (as Qvar, Kelhale or Fostair)	More than 500mcg per day (check if using combination inhaler and MART regimen)
Budesonide	More than 500mcg per day (check if using combination inhaler and MART regimen)
Ciclesonide	More than 480mcg per day (**)
Fluticasone	More than 500mcg per day
Momethasone	More than 800mcg per day (**)

Table 4: Inhaled glucocorticoid doses with any other form of glucocorticoid treatment

Medicine	**Dose (*)**
Beclomethasone (as non-proprietary, Clenil, Easihaler or Soprobec)	800-1000mcg per day
Beclomethasone (as Qvar, Kelhale or	400-500mcg per day (check if using

Fostair)	combination inhaler and MART regimen
Budesonide	400-500mcg per day (check if using combination inhaler and MART regimen
Ciclesonide	320-480mcg per day
Fluticasone	400-500mcg per day
Momethasone	400-800mcg per day or more

(*) dose equivalent from BNF except (**) where dose reflects that described in the guideline by Simpson et al (2020) and (***) best estimate

Table 5: Topical glucocorticoids

Topical Steroid treatments	**Potency**
Beclomethasone dipropionate 0.025%	Potent
Beclomethasone dipropionate 0.05% and higher [including Dalonev, Diprosone, Dovobet, Enstilar, in combination with Clotrimazole (incl Lotriderm) and salicylic acid (incl Diprosalic)]	Potent
Betamethasone valerate 0.1% and higher [incl Audovate, Betacap, Betesil, Betnovate, Betamousse, and in combination with clioquinol, Fusidic acid (incl. Fucibet, Xemacort) or neomycin]	Potent
Clobetasol propionate 0.05% and higher [incl Clarelux, Clobaderm, Dermovate, Etrivex and in combination with neomycin and nystatin]	Very potent
Diflucortolone valerate 0.1% [incl Nerisone]	Potent
Fluocinonide 0.05% [incl Metosyn]	Potent
Fluocinolone acetonide 0.025% [(incl Synalar) and in combination with clioquinol (incl Synalar C)]	Potent
Hydrocortisone Butyrate 0.1% [incl Locoid]	Potent
Fluticasone propionate 0.05% [incl Cutivate]	Potent
Mometasone 0.1% [incl Elocon]	Potent
Triamcinolone acetonide 0.1% [incl Aureocort]	Potent
Diflucortolone valerate 0.3% [incl Nerisone Forte]	Very potent

All other topical glucocorticoids available in the UK are either mild or moderate potency

Table 6:

CYP3A4 enzyme inhibitors increasing cortisol concentration and risk of HPA axis suppression

Patients prescribed any form of ongoing glucocorticoid treatment, at any dose, together with any of the medications below which are potent CYP3A4 inhibitors, should be issued with a Steroid Emergency Card.

Potent Protease Inhibitors	**Antifungals**	**Antibiotics**
Atazanavir	Itraconazole	Clarithromycin—long term courses only
Darunavir	Ketoconazole	
Fosamprenavir	Voriconazole	
Ritonavir (+/- Lopinavir)	Posaconazole	
Saquinavir		
Tipranavir		

References:

National Patient Safety Alert: *Steroid Emergency Card to support early recognition and treatment of adrenal crisis in adults*. Date of issue: 13th Aug 2020. Reference no: NatPSA/2020/005/NHSPS

Society for Endocrinology Clinical Committee and the Royal College of Physicians Patient Safety Committee (2020). *Guidance for the prevention and emergency management of patients with adrenal insufficiency* https://www.rcpjournals.org/content/clinmedicine/20/4/371

Society for Endocrinology; *Exogenous steroids, adrenal insufficiency and adrenal crisis-who is at risk and how should they be managed safely*. David Erskine, Helen Simpson

Annual Risk Acknowledgement Form
VALPROATE HAS RISKS IN PREGNANCY

Name of valproate user: **Date of Birth:**

Identification (NHS or hospital) number:

Name and role of specialist:

Signature of specialist and date:

Name of valproate user's GP:

Children exposed to valproate in utero have a very high risk for congenital malformations and neurodevelopmental disorders. Valproate is therefore contraindicated in women of childbearing potential unless the conditions of 'prevent', the pregnancy prevention programme are fulfilled.

The specialist must provide this form to girls and women of childbearing potential treated with valproate (Epilim, Depakote, Convulex, Episenta, Epival, Kentlim, Orlept, Syonell, Valpal) - or to their "responsible person": a parent/legal guardian or person capable of giving consent on behalf of patients who are minors or without the capacity to make an informed decision or person acknowledging that the treatment is in the best interests of the patient.

There are three steps needed to complete this form:

Step 1 – Decide if the patient needs to be on 'prevent' – the valproate pregnancy prevention programme

Step 2 – 'prevent' applies to this patient- she is of childbearing potential and at risk of pregnancy

Step 3 – Your patient needs to complete this section to confirm they understand the risks of valproate in pregnancy

WARNING: Prescribing valproate to a woman of childbearing potential without the pregnancy prevention programme conditions being fulfilled is contraindicated and represents an unlicensed use of the drug. Use of valproate during pregnancy for bipolar disorder, and during pregnancy for epilepsy (unless there is no suitable alternative treatment), are both unlicensed. This is the case even when treatment is based on an informed choice made by the patient.

Prescribers are expected to follow the General Medical Council's guidance in *"Good practice in prescribing and managing medicines and devices"*. You must document in the patient's clinical record your reason for unlicensed use, that you have informed the patient of the unlicensed use and its associated risk.

This form expires on_____(12 months after completion).

Complete a new form at each annual review.

More information can also be found online at www.medicines.org.uk by entering "valproate" in the search box and then clicking on "Risk Materials" next to any of the medicines that appear.

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Annual Risk Acknowledgement Form
VALPROATE HAS RISKS IN PREGNANCY

Step 1 – Decide if the patient needs to be on 'prevent' – the valproate pregnancy prevention programme

- Women of childbearing potential (from menarche to menopause) who are taking any medicine containing valproate, regardless of the indication, should fulfil all the requirements of **'prevent'**.
- The only exception is when you (the specialist) consider that there are compelling reasons to indicate that there is no risk of pregnancy.
- The absence of risk of pregnancy may be permanent (e.g., post-menopausal patients or those after hysterectomy) and in this case the risk does not need to be discussed in the next annual review and the requirements of **'prevent'** do not apply.
- If the absence of risk is subject to change (e.g., the patient is pre-menarchal), the date for the next annual discussion of the risks must be documented and the patient or the patient's family/carers asked to contact you rapidly if the situation changes before the next annual review in order to bring this review forward.
- Girls who have not yet reached menarche **DO NOT** need to be on **'prevent'**, but they and their responsible person need to be aware of the risks for the future. You should provide a copy of the Patient Guide, and remind the responsible person to contact the specialist or GP to arrange for review of treatment as soon as menarche occurs.

If you consider there is a compelling reason that indicates there is no risk of pregnancy, record this here. **If appropriate, you and your patient should still complete the rest of the form** so that your patient and/or their responsible person is aware of the risks if their situation were to change in the future.

To be completed by the specialist when they consider a Pregnancy Prevention Programme (PPP) is not needed
The requirements of **'prevent'**, the valproate pregnancy prevention programme, are not necessary because there are compelling reasons to indicate that there is no risk of pregnancy, because (*tick* which applies):
☐ the patient has not yet reached menarche. I have informed the patient and family to inform me if this changes before the next annual review which is due on *(insert date)*:
☐ the absence of pregnancy risk is permanent for the following reason *(insert reason)*:
☐ I consider that sexual activity that could lead to pregnancy will not occur before the next annual review because *(insert reason)*:
☐ I have given the patient or responsible person a copy of the Patient Guide
Signature of patient or responsible person to confirm:

More information can also be found online at www.medicines.org.uk by entering "valproate" in the search box and then clicking on "Risk Materials" next to any of the medicines that appear.

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Annual Risk Acknowledgement Form
VALPROATE HAS RISKS IN PREGNANCY

Step 2 – 'prevent' applies to this patient- she is of childbearing potential and at risk of pregnancy

This form confirms that you have discussed the risks with girls, women of childbearing potential and their responsible person (if applicable), and you are acting in compliance with the pregnancy prevention programme.

You need to:

- Explain the risks of valproate in pregnancy and ensure these are understood.
- Give your patient (or their responsible person) a copy of the Patient Guide.
- Complete all parts of this form, keep the original in the patient record and provide a copy to the patient, her responsible person (if appropriate), and to her GP.
- Arrange a follow-up appointment at least every year to review the need for continued treatment with valproate and compliance with **'prevent'**.

To be completed and initialled by the specialist	Initials
I confirm that the patient needs valproate because: • her condition does not respond adequately to other treatments, or • she does not tolerate other treatments, or • she is undergoing a treatment change from valproate	
I confirm I have discussed the following with the patient:	
Valproate must not be used during pregnancy (except in rare situations in epilepsy for patients who are resistant or intolerant to other treatments)	
The overall risks in children exposed to valproate during pregnancy are: • an approximately 10% chance of birth defects • a 30% to 40% chance of a wide range of early developmental problems that can lead to learning disabilities.	
The conditions of the pregnancy prevention programme must be fulfilled	
The need for regular (at least annual) review of the need to continue valproate treatment by a specialist	
The need for effective contraception, without interruption, throughout treatment with valproate	
The need to arrange an appointment with her specialist as soon as she is planning pregnancy to ensure timely discussion, and a timely switch to an alternative treatment before stopping contraception and conception occurring.	
The need to contact her GP immediately for an urgent review of her treatment in case of suspected or inadvertent pregnancy.	
The need for a negative (ideally serum) pregnancy test result at start and if needed thereafter	
I confirm I have given the patient or responsible person a copy of the Patient Guide	
In case of pregnancy, I confirm that:	
• We have discussed options for switching treatment	
• She is fully aware of the risks of pregnancy, and has had the opportunity for counselling about the risks	
• I have given the patient or responsible person a copy of the Patient Guide	

More information can also be found online at www.medicines.org.uk by entering "valproate" in the search box and then clicking on "Risk Materials" next to any of the medicines that appear.

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Annual Risk Acknowledgement Form
VALPROATE HAS RISKS IN PREGNANCY

Step 3 – Your patient needs to complete this section to confirm they understand the risks of valproate in pregnancy

If you use valproate while you are pregnant, your future child has significant risk of serious harm.

Completing this form confirms that you (or your responsible person) understand the risks of using valproate during pregnancy, and what method of contraception you will use to prevent becoming pregnant during treatment.

To be completed and signed by the patient or their responsible person	Initials
I have discussed the following with my specialist and I understand:	
√ Why I need valproate rather than another medicine	
√ That I should visit a specialist regularly (at least once a year) to review whether valproate remains the best option for me	
√ The risks in children whose mothers took valproate during pregnancy are: • 1 out of 10 children will have physical birth defects • 3 to 4 out of 10 children will have early developmental problems that can lead to significant learning disabilities	
√ That I have had a pregnancy test (if advised by my doctor/specialist)	
√ Why I must use effective contraception, without stopping or interruption, at all times while taking valproate	
√ The options for effective long-term contraception (or a consultation has been planned with a professional who can give me advice)	
√ The need to consult my specialist or GP as soon as I start thinking about becoming pregnant. This is to make sure I have time to switch to another treatment before I come off contraception	
√ That I should request an urgent GP appointment if I think I am pregnant	
√ I have been given a copy of the Valproate Patient Guide and know where to find more information	
In case of pregnancy, I confirm that: √ Options for switching treatment have been considered √ I am fully aware of the risks and have had the opportunity to have counselling about the risks	

Name of patient: _____

Name of responsible person (if applicable): _____

Signature of patient (or responsible person) and date: _____

Effective contraception is essential while taking valproate.

At least one highly effective method of contraception (preferably a user independent form such as an intrauterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case. When choosing the contraception method involve the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhoea she must follow all the advice on highly effective contraception.

More information can also be found online at www.medicines.org.uk by entering "valproate" in the search box and then clicking on "Risk Materials" next to any of the medicines that appear.

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