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Supporting prescribing excellence - informing colleagues in primary and secondary care

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How smoking status affects clozapine dosing

Did you know smokers need a higher dose of clozapine to maintain similar plasma levels than if they were a non-smoker?[1] This is due to polycyclic aromatic hydrocarbons found in tobacco, that induce the major isoenzyme (predominantly CYP1A2) involved in the metabolism of clozapine resulting in a lower clozapine concentration and requirement for a higher dose[2].

Sudden reduction in smoking or smoking cessation can result in clozapine related side effects or toxicity. Adverse effects occur, even if nicotine replacement therapy (NRT) or e-cigarettes (also known as vaping) are used as they do not affect CYP1A2 induction[1,2].

When specialists are initiating clozapine it is preferable that patients stop smoking first however, where this is not an option and starting clozapine is a priority, any changes to a smoking habit should be accompanied with monitoring for typical adverse effects of clozapine.

Key points

- check smoking status at reviews or during hospital admissions
- in the case of temporary smoking cessation, for example, due to an acute hospital stay, first check for any cautioned or contraindicated clinical features when using clozapine. If there are no issues then dose adjustments are not usually necessary for temporary smoking cessation because it takes approximately one week for the effect of the induction of CYP1A2 to diminish[3]
- long term changes to smoking habits and/or the presence of cautions or contraindications should be referred to the patient's CPN for advice and links with their psychiatrist.

For further information and advice -

Healthcare professionals:
intranet.lothian.scot.nhs.uk/Directory/MedicinesManagement/MentalHealth/Guidelines/NRT%20Practical%20Guidance%20on%20the%20use%20of%20NRT%20products.pdf Note Section 3.3.1

Specific advice for clozapine patients:
www.choiceandmedication.org/nhs24/generate/handyfactsheetsmokingandclozapine.pdf

References

1. NHS Lothian Clozapine Handbook. Version 7. November 2020. Department of Pharmacy, Royal Edinburgh Hospital. intranet.lothian.scot.nhs.uk/Directory/MedicinesManagement/MentalHealth/Documents/Section%206.%20Management%20of%20Side%20Effects%20and%20Drug%20Interactions.pdf.

2. Stockley's Drug Interactions www.medicinescomplete.com/#/content/stockley/x19-4029.

3. NHS Lothian Guidance for the Prescribing and Administration of Nicotine Replacement Therapy for Nicotine Withdrawal Symptoms. Version 4. December 2021. Royal Edinburgh and Associated Services. intranet.lothian.scot.nhs.uk/Directory/MedicinesManagement/MentalHealth/Guidelines/NRT%20Symptomatic%20Prescribing%20Guidance.pdf.

Thanks to Paulina Mlawa, Specialist Clinical Pharmacist, REH and Alexis Rumbles, NHS Lothian Tobacco Control Project Manager (Acute Sites) who contributed to this article.

Safe prescribing of anticoagulants and antiplatelets for patients with non-valvular atrial fibrillation

Direct Oral Anticoagulants (DOACs) are licensed for a variety of indications. The East Region Formulary recommends edoxaban or apixaban for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors. Warfarin is within the formulary pathway for both non-valvular and valvular AF[1]. Anticoagulation treatment is not without its risks and there are key considerations that should be taken into account when prescribing DOACs.

Choice of Anticoagulation Warfarin remains the only licensed treatment for patients with mechanical prosthetic heart valves or in patients who have moderate or severe mitral stenosis. In July 2021, there was a national patient safety alert regarding patients with mechanical heart valves being inappropriately switched from warfarin to a DOAC. Supporting information is available for clinicians and advice from secondary care should be sought if there are any outstanding enquiries regarding this group of patients[2,3].

Prescribing guidance for NVAF

Safe switching of anticoagulants – the summaries of product characteristics (SPC) for both apixaban and edoxaban give robust advice on how to safely switch from a vitamin K antagonist (VKA) like warfarin, to a DOAC as well as how to switch from a DOAC to a VKA[4,5].

Dosing and frequency for DOACs in NVAF - it is often reported that there are instances when prescribing apixaban or edoxaban; for example the incorrect dose and/or frequency is prescribed for the individual patient. It is recommended that the information within the SPC be followed when initiating a DOAC, and when reviewing repeat prescriptions, because there may be a need to change doses or stop the medication based on a clinical reason. Optimal dosing is based on age, weight and renal function. Dosing frequency may influence a prescribers choice of DOAC but care should be taken to consider all of the clinical particulars before making a decision.

Edoxaban is taken **once a day**. Edoxaban dose recommendations may change based on **one or more clinical factors.** You should note that the manufacturers give specific advice on an interaction with p-glycoprotein inhibitors. Prescribers should also conduct an interaction check for each patient[4].

Edoxaban - Summary guide for dosing[4]		
Recommended dose		60mg edoxaban once daily
Dose recommendation for patients with **one or more** of the following clinical factors:		
Renal impairment	*Moderate or severe (CrCl 15–50mL/min)*	30mg edoxaban once daily
Low body weight	*≤60kg*	
P-gp inhibitors	*Ciclosporin, dronedarone, erythromycin, ketoconazole*	

Apixaban is taken **twice a day**. Apixaban dose recommendations for NVAF may change based on **two or** more clinical factors and patient characteristics[5].

Apixaban - Summary guide for dosing[5]		
Recommended dose Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)		5mg apixaban twice a day
Dose recommendation for patients with **two or more** of the following clinical factors:		
Age	*≥80 years*	2.5mg apixaban twice a day
Renal impairment	*Serum creatinine ≥1.5mg/dL (133micromole/L)*	
Low body weight	*≤60kg*	

My patient has developed new AF and is suitable for anticoagulation. Current weight is 138kg (BM >40kg/m^2) - can I still use a DOAC?

There is no specific dosing recommendation from the manufacturer of edoxaban for high body weight. Apixaban exposure in patients >120kg compared with those between 65 to 85kg was associated with an approximate 30% lower exposure. There are studies ongoing in patients who are >120kg, however this has not yet been included in guidelines and summaries of product characteristics but may be used by specialists when making recommendations.

My patient is already on an antiplatelet (aspirin or clopidogrel) because of ischaemic heart disease (IHD) or a previous stroke and has now developed NVAF. If it is deemed appropriate to initiate a DOAC – should the patient continue the antiplatelet?

The combined prescription of an antiplatelet and anticoagulant increases the bleeding risk. When the antiplatelet is prescribed for primary prevention, or due to IHD or previous stroke, the antiplatelet should be reviewed with the view of discontinuing if a DOAC is to be prescribed for NVAF. If there are concerns regarding stopping the antiplatelet agent, cardiology or stroke advice should be sought[6].

My patient has NVAF and is currently prescribed apixaban. They had an ST-elevation myocardial infarction (STEMI) and were admitted to hospital. On review of their discharge letter, they have been discharged on apixaban, aspirin and clopidogrel 'triple therapy' – is this correct?

Yes, if a patient with NVAF has had a primary coronary intervention (PCI) and stent inserted, there will be a requirement to be on 'triple therapy' for a set duration of time. The duration of this should be stated on the discharge letter. If not, it should be confirmed with the cardiology team. The typical duration would be a DOAC with dual antiplatelet therapy (DAPT) for one month, followed by a single antiplatelet and DOAC for a further six months then DOAC monotherapy long term. This should always be confirmed in a letter or with the specialist team. If for any reason the patient stops their long-term anticoagulation, they will need long term antiplatelet monotherapy to prevent stent thrombosis.

My patient is currently prescribed edoxaban 30mg once daily (body weight 50kg) and has been started on erythromycin. I note the SPC states to dose reduce – do I need to reduce the dose to edoxaban 15mg daily?

No, if the patient is already on a lower dose due to low body weight or reduced renal function, there is no further dose reduction required. The patient can remain on 30mg daily.

My patient is on a DOAC and wants to get pregnant – what should I do?

Within NHS Lothian, refer to haematology for counselling prior to conception for women on a DOAC. If the patient is already pregnant, urgently phone the haematology consultant on call apps.nhslothian.scot/refhelp/guidelines/adviceforwomenonwarfarinordoacs/.

Are there any patients that should not be prescribed DOACs in NVAF?

Reference should be made to the SPC for a full list of advice on clinical particulars including contraindications; special warnings and precautions for use; interactions and fertility, pregnancy and lactation[4,5].

Do I have to calculate the creatinine clearance (CrCl) when prescribing DOACs?

The MHRA have advised that CrCl be used when prescribing particular medicines in patients with renal impairment[7]. The Edinburgh Renal Unit recommend using the online CrCl calculator link within the antimicrobial team intranet pages intranet.lothian.scot.nhs.uk/Directory/amt/Pages/Antimicrobial%20Management%20Home%0Page.aspx

Thanks to Seona Stalker, Lead Clinical Pharmacist Cardiology

References

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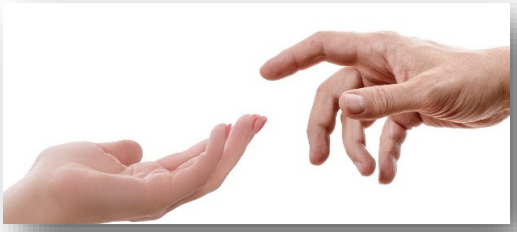
3. Inappropriate anticoagulation of patients with a mechanical heart valve, A National Patient Safety Alert, 14 July 2021 www.england.nhs.uk/wp-content/uploads/2021/07/NaPSA-DOAC-Heart-Valve-FINAL-v2.pdf.
4. Edoxaban, Lixiana Summary of product characteristics, March 2023, www.medicines.org.uk/emc/product/6905/smpc.
5. Apixaban, Eliquis Summary of product characteristics, March 2023, www.medicines.org.uk/emc/product/2878/smpc.
6. Atrial fibrillation: diagnosis and management, NICE guideline April 2021 www.nice.org.uk/guidance/ng196/resources/atrial-fibrillation-diagnosis-and-management-pdf-66142085507269.
7. MHRA Drug Safety Update, Prescribing medicines in renal impairment, October 2019 www.gov.uk/drug-safety-update/prescribing-medicines-in-renal-impairment-using-the-appropriate-estimate-of-renal-function-to-avoid-the-risk-of-adverse-drug-reactions.

Shared care update



Removal of Disease Modifying Anti-Rheumatic Drug (DMARD) blood monitoring changes during the pandemic

During the pandemic, the shared care agreements were revised and reductions were made to the monitoring requirements. These recommendations were based on a risk assessment of the potential for harm if monitoring were reduced, compared with the risk associated with exposure to COVID-19 in healthcare settings. Specialist services were consulted and advised accordingly.

The risk assessments were also influenced by the reduced capacity within the healthcare system to fulfil monitoring schedules during the pandemic.

In September 2022, the General Practice Prescribing Committee (GPPC) were advised by specialists that they would support reverting back to the pre-pandemic DMARD monitoring schedule in line with national guidance and product licensing. The committee agreed and the interim guidance has now been removed from the shared care pages of the formulary website.

The current versions of all the shared care agreements can be accessed at www.formulary.nhs.scot/east/help-and-support/for-healthcare-professionals/shared-care-of-medicines.

East Region Formulary Project update: website rebrand and paediatric chapter reviews

The East Region Formulary project is moving into its next phase of chapter reviews for paediatrics. This will also coincide with the rebranding of the website from the Lothian Joint Formulary to the East Region Formulary as our colleagues in NHS Borders and NHS Fife will begin to use the same webpages once the paediatric chapters are updated.

Drug safety update Volume 16 Issue 6 January 2023

Topical testosterone (Testogel): risk of harm to children following accidental exposure

Premature puberty and genital enlargement have been reported in children who were in close physical contact with an adult using topical testosterone and who were repeatedly accidentally exposed to this medicine. To reduce these risks, advise patients to wash their hands after application of topical testosterone, cover the application site with clothing once the product has dried, and wash the application site before physical contact with another adult or child.

KEY MESSAGES

- when prescribing topical testosterone, inform patients of the potential consequences if it is accidentally transferred to other people
- advise patients of the possible effects should accidental exposure occur in adult women (facial and/or body hair growth, deepening of voice, changes in menstrual cycle) or children (genital enlargement and premature puberty, including development of pubic hair)
- counsel patients on methods to reduce the risks of accidental exposure, for example washing their hands after application of topical testosterone, covering the application site with clothing once the product has dried, and washing the application area with soap and water before physical contact with another adult or child
- patients should seek medical advice if accidental exposure is suspected
- report suspected adverse drug reactions associated with topical testosterone on a Yellow Card yellowcard.mhra.gov.uk/.