SURREY HEARTLANDS
Health and Care Partnership

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SURREY COUNTY COUNCIL

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Welcome to our Lunch and Learn on:

Clozapine

Housekeeping

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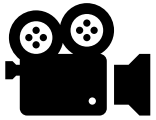
- This is a Teams call, so please mute yourself unless you are the designated speaker

- Please use the chat function to ask any questions and feel free to ‘like’ any questions you’d also like answered

- We’ll answer questions during our designated Q&A slot, and you are welcome to raise your ‘hand’ and speak at those times



- This event will be recorded, and we’ll share the recording and slides afterwards

Agenda

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Item	Speaker
Welcome	**Simon Whitfield**, Chief Pharmacist
Background and Why It Is Important	**Dr Sajad Yousuf**, Consultant Psychiatrist and Medical Lead East Place
Patient Journey: Good Practice and Lessons Learnt from Incidents across Surrey Heartlands	**Alison Marshall**, Medicines Safety Officer, Pharmacist for Safety and Quality **Karen Duckenfield**, Service Manager **Kate Clarke**, Lead Primary Care Medicines Safety Pharmacist
Panel Questions	**Simon Whitfield**, Chief Pharmacist **Nikki Smith**, Head of Medicines Safety / Patient Safety Specialist **Alison Marshall**, Medicines Safety Officer, Pharmacist for Safety and Quality **Karen Duckenfield**, Service Manager **Dr Sajad Yousuf**, Consultant Psychiatrist and Medical Lead East Place
Closing Remarks	**Simon Whitfield**, Chief Pharmacist

Clozapine

Sajad Yousuf, Consultant Psychiatrist Home Treatment Team East and Mid Surrey

Objectives

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- Introduction about Clozapine
- Indications
- Initiation
- Side effects

Introduction

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- Originally introduced in 1961, withdrawn in 1975 after serious hematological side effects
- Following a study by Kane in 1988, it was found to be effective in schizophrenia unresponsive to other antipsychotics
- 1990 reintroduced in UK with stringent monitoring requirements
- First atypical antipsychotic, licensed for treatment of resistant schizophrenia

Mechanism of action

- Clozapine exerts its effects involves the blocking of 5-HT_{2A}/5-HT_{2C} serotonin receptors and the D1-4 dopamine receptors, with the highest affinity for the D_4 dopamine receptor.
- As a serotonin and D_4 dopamine antagonist, clozapine is able to elicit its antipsychotic effects without inducing many of the extrapyramidal motor effects associated with D_2 dopamine receptor antagonists

Indications

- Failure to respond to two or more antipsychotics when given at an adequate dose for at least 6 -8 weeks.

- 20-30% of patients diagnosed with Schizophrenia are considered as Treatment Resistant.

- Psychosis during the course of Parkinson's disease

Haematological contraindications to Clozapine

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- Patients unable to undergo regular blood tests
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis
- History of Clozaril-induced agranulocytosis
- Impaired bone marrow function

Initiation of Clozapine

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- Full Medical history and physical examination
- Give verbal and written information to patients
- Opportunity to discuss clozapine treatment
- Patients must be informed about the need for regular blood testing and possible side effects.
- Patient should be informed of the initiation process and options of community or inpatient.
- Ensure consent has been obtained and documented

Prior to initiation

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- Baseline FBC
- Patient registration (by the treating consultant)
- Confirmation of “**Green**” blood result
- Treatment must commence within **10 days** of the baseline blood test or it will have to be repeated.

Monitoring frequency for initial 72 hours of titration period

Day 1	Temperature, Pulse, BP prior to first dose Then hourly Temperature, Pulse, BP for next 6 hours
Day 2	Temperature, Pulse, BP prior to dose Then 2, 4 and 6 hours after the dose
Day 3	Temperature, Pulse, BP prior to dose Then 3 and 6 hours after the dose

Trust Titration Chart

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CLOZAPINE STANDARD TITRATION PRESCRIPTION CHART
(Attach to Inpatient Prescription Chart)

IF NOT PRESCRIBING STANDARD DOSES USE NON-STANDARD CHART

Patient name:	DOB:
Ward:	Consultant:
NHS no:	CPMS no:
Care co-ordinator:	Contact no:

If patient previously on clozapine, date stopped:

If clozapine is omitted for greater than 48 hours, it is essential to restart clozapine from initial starting doses. However, according to tolerance, upward dose titration may be faster than on first exposure. A separate non-standard titration chart is also available.

Day	Date	Time	Clozapine Dose	Prescriber's Signature	Given By	*Date Blood Test Due
1 morning	-		12.5mg			
2 morning			12.5mg			
evening			12.5mg			
3 morning			12.5mg			
evening			25mg			
4 morning			25mg			
evening			25mg			
5 morning			25mg			
evening			50mg			
6 morning			25mg			
evening			50mg			
7						

Focus is to monitor for :

- Hypotension
- Excessive drowsiness
- Tachycardia
- Hyperthermia
- The most likely time for this to occur is during the first six hours after the initial dose

Blood Test frequency

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- Weekly for the 1st 18 weeks
- Every 2 weeks for the next 34 weeks
- Every 4 weeks thereafter
- Only the CPMS can decide if the result is “green”.

Management of FBC results

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RESULT	ACTION
GREEN White Blood Count X 10^9 / L > 3.5 Neutrophil Count X 10^9 / L > 2.0	Satisfactory
AMBER White Blood Count X 10^9 / L 3.0 – 3.5 Neutrophil Count X 10^9 / L 1.5 – 2.0	Either White Blood Count or Neutrophil Counts are below acceptable levels. Blood count should be repeated twice weekly until the count stabilises or increases. Advice should be sought from the monitoring service
RED White Blood Count X 10^9 / L < 3.0 Neutrophil Count X 10^9 / L < 1.5 Platelet Count X 10^9 / L < 50	Immediate cessation of treatment. Blood sampling should be done daily until the patient recovers. Advice should be sought from the monitoring service

Regular Physical Health Monitoring

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	Baseline	1 Month	3 Months	6 Months	9 Months	12 Months & Annually
Weight & BMI	X		X	X	X	X
Lipids (fasting if possible)	X		X	X	X	X
HbA1C (& fasting glucose if possible)	X	X (fasting glucose only)	X	X		X **complete every 6 months**
Troponin T or I	X	**If myocarditis suspected check at that point in time**				
C Reactive Protein	X	**If myocarditis suspected check at that point in time**				
LFTs	X					X
Echocardiogram		Clozapine may cause cardiomyopathies and myocarditis. Plasma troponin and CRP should be checked if suspected. An echocardiogram can be useful. Consult with a cardiologist.				

Regular monitoring 2

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	Baseline	1 Month	3 Months	6 Months	9 Months	12 Months & Annually
ECG (especially important to check if on multiple drugs that increase QTc)	X	Clozapine may cause cardiomyopathies and myocarditis. Plasma CRP and troponin should be checked if suspected. Use QTc as marker for Torsades des Points				
U&Es	X					X
FBC	As per clozapine protocol. Weekly for 18 weeks, fortnightly up to 1 year and then 4 weekly. Additional monitoring may be required if appropriate.					
TFTs	X					
Prolactin	Clinical signs of possible hyperprolactinaemia include menstrual disturbance, galactorrhoea, gynaecomastia, sexual dysfunction and risk of osteoporosis. Consider other causes.					
Side-effect Rating Scale	X	X	X	X	X	X
BP and Pulse	Daily during titration. See Trust Clozapine initiation.	X	X	X		X
Smoking Habits	X					X
Serum Level Clozapine	Always at end of initial titration. Additionally Clozapine levels should be completed if the requirements laid out below are met					

Plasma Level results

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Alert the consultant as a matter of urgency if:

- The clozapine plasma level is below 0.25mg/L as may not be adequate to maintain response.
- The clozapine plasma level is above 0.6mg/L may be related to an increased risk of adverse effects such as seizures.
- There is any unexpected or concerning change in plasma levels

When to check Plasma Clozapine level

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- Obtain baseline for future comparison
- If smoking habit changes
- If adherence may be a problem
- If the patient experiences troublesome adverse effects
- When someone is prescribed a dose greater than 600mg per day
- If on new medications that could interact with clozapine
- If a patient has pneumonia or other serious infection
- If poor (reduced) clozapine metabolism is suspected
- If Toxicity/overdose is suspected
- If someone hasn't had their plasma level monitored for several years, bearing in mind that age is one of the determinants of clozapine levels
- If information is lacking as to the consistency of the above factors since last level

Common Side effects usually dose dependent

- Sedation
- Hypersalivation
- Constipation
- Reduced seizure threshold
- Hypotension and hypertension
- Tachycardia
- Pyrexia
- Weight gain
- Glucose intolerance and diabetes mellitus
- Nocturnal enuresis
- QTc prolongation

Rare serious side effects:

Idiosyncratic and non-dose-independent

- Neutropenia
- Agranulocytosis
- Thromboembolism
- Cardiomyopathy
- Myocarditis
- Aspiration pneumonia

Constipation

- High doses → constipation → slowed gastric transit → increased levels → worsened constipation
- Can be fatal leading to gastrointestinal obstruction and paralytic ileus
- Caution if receiving medications known to cause constipation
  - anticholinergic drugs
  - opioids
  - antipsychotics
  - antidepressants
  - antiparkinsonian treatments
- Caution - colonic disease or a history of lower abdominal surgery
- Important to recognise early and treat actively
- Consider prophylactic laxatives – stimulant laxatives 1ST line

Tachycardia

- Heart rate greater than 100 bpm
- Often occurs if dose escalation is too rapid.
- If pulse is persistently above 100bpm, consider cardiology referral.
- If persistent at rest, associated with fever, hypotension or chest pain may indicate myocarditis – seek cardiology referral.
- If accompanied by chest pain or shortness of breath seek immediate medical assessment.

Management of a Red Result

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- If a patient's WBC is less than 3.0 x 10^9/L and/or the neutrophil count is less than 1.5 x 10^9/L this is known as a **RED ALERT**
- **STOP CLOZAPINE TREATMENT IMMEDIATELY**
- Check the patient for any signs of infection and contact the Clozapine monitoring service as soon as possible.
- If the red alert is confirmed **THE PATIENT MUST NOT RESTART CLOZAPINE TREATMENT**
- **Continue FBC until Green results**
- Observed closely for signs of infection e.g. sore throat, fever
- The patient should be given clear instructions on what to look out for that should prompt them to seek immediate medical attention eg if they become febrile or unwell.
- Transfer any patients with signs of sepsis to A&E immediately to avoid a delay in treatment

Smoking and Clozapine

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- Smoking induces CYP1A2
- Therefore, higher doses of clozapine are needed in smokers
- Stopping smoking will result in a rise in levels
- Nicotine products will NOT interact
- It’s the hydrocarbons in tobacco smoke that interact

Caffeine

- Changes in caffeine intake can alter clozapine levels possibly through caffeine inhibiting CYP1A2
- Whilst small changes are unlikely to have a huge impact big changes in caffeine intake may affect clozapine levels
- Patients should be advised to avoid sudden changes and products with very high caffeine levels e.g. caffeine tablets or energy drinks

Break in Treatment

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Medication Dose

- Any breaks less than 48 hours, patient continue on regular dose
- Any break of >48 hours requires re-titration

Blood Monitoring Changes

Any break of 3 days or more requires adjustment of monitoring frequency

- If 2-weekly or 4-weekly, and break 3-28 days weekly monitoring for 6 weeks
- If 2-weekly or 4 weekly, and break >28 days weekly monitoring for 18 weeks restarted

References

- Maudsley guidelines
- CPMS website
- *BrJClinPharm Vol 3 Jan 11 18-21 R Flanagan Clozapine therapeutic drug monitoring: why is it important.*
- SABP clozapine guidelines
- https://www.gov.uk/drug-safety-update/clozapine-and-other-antipsychotics-monitoring-blood-concentrations-for-toxicity
- Nucifora FC, Mihaljevic M, Lee BJ, Sawa A. Clozapine as a Model for Antipsychotic Development. Neurotherapeutics. 2017;14(3):750-761
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019758s062lbl.pdf. Published 2018. Accessed November 30, 2018.

Patient Journey: Good Practice and Lessons Learned from Incidents across Surrey Heartlands

Alison Marshall, Medicines Safety Officer, Pharmacist for Safety and Quality
Karen Duckenfield, Service Manager
Kate Clarke, Lead Primary Care Medicines Safety Pharmacist

Patient Stories

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- An individual was taking clozapine regularly with no concerns
- They were admitted to an acute hospital, where their clozapine was not prescribed
- Because the break in treatment was >48 hours they required retitration
- Their mental health deteriorated and they required transfer to the mental health hospital and an inpatient stay of 8-10 weeks

How could the outcome have been different?

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- A full medication history should be available – including items prescribed by secondary care

- Empowering patients to highlight to professionals that they are taking clozapine

Patient Stories

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- A person was due to start treatment with clozapine, and all the required blood tests were undertaken

- There were then delays in starting treatment, and the blood test validity expired

- The team then started treatment without a valid blood test as medication had been supplied for the individual based on the initial planned starting date.

- It is a requirement that people taking clozapine have full blood counts (FBC) (particularly white cell count, neutrophils, and platelets) monitored by the manufacturer. This is because clozapine can rarely cause fatal agranulocytosis, neutropenia, and thrombocytopenia.

How could the outcome have been different?

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- Staff should be aware of the schedule of blood tests for each person under their care

- No-one should receive medication without confirmation of their valid blood test

Patient Stories

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- A person was unable to collect their medication during the working week from the CMHRS Team base

- They ran out of medication on Saturday, and called the crisis line and 111

- A prescription was issued by the 111 service and the person tried a number of pharmacies but was unable to source the medication

How could the outcome have been different?

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- The SABP Pharmacy can supply against a valid prescription.
  - This can include people admitted to our acute hospitals who are under SABP care.

- If necessary, such as in this case, we can make a professional judgement to supply sufficient until the CMHRS is able to provide the medication previously supplied.

- In an emergency the person's registration with their usual supplying pharmacy can be transferred to the SABP pharmacy. We can then dispense against a valid prescription

Surrey Heartlands ICB. Primary care audit – recording hospital prescribed clozapine on GP system.

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- **Aim**: To improve safety across the interface by ensuring the safe recording of clozapine prescribed by Surrey and Borders Partnership NHS Foundation Trust (SABP) on primary care patient records
- **Measure 1**: Has the clozapine prescribed by SABP been added to the GP clinical system, as a hospital only medication in line with guidance on PAD for adding 'Non-GP Prescribed Medications'? (Yes – 53%, no 46%)
- **Measure 2**: Is it clear that clozapine is prescribed by SABP and should not be issued by the practice? (Yes 35%, No 61%)
- **Measure 3**: Is Clozapine linked to a problem? (Yes 19%, No 80%)
- **Following audit:** 141 hospital issued clozapine items added to GP records (53% of those not initially added) and 171 patients/ 298 meet measures 1-3 (57% compared to 10% before audit).
- **Next steps identified**
- Guidelines : Recording non GP prescribed medications New updated version to be uploaded - Nov 2024.

Panel Questions

Simon Whitfield, Chief Pharmacist

Nikki Smith, Head of Medicines Safety / Patient Safety Specialist

Alison Marshall, Medicines Safety Officer, Pharmacist for Safety and Quality

Karen Duckenfield, Service Manager

Dr Sajad Yousuf, Consultant Psychiatrist and Medical Lead East Place

Thank you for joining us!

The presentation and recording will be shared in due course.