

MANAGEMENT OF ADVERSE EFFECTS OF CLOZAPINE

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Acknowledgement

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Program

Why should we use clozapine – balancing the risks vs benefits?

Management of adverse effects?

Agranulocytosis

Sedation

Constipation

Hypersalivation

Epilepsy

Pneumonia

Clozapine-greatest mismatch between efficacy and utilization in clinical practice

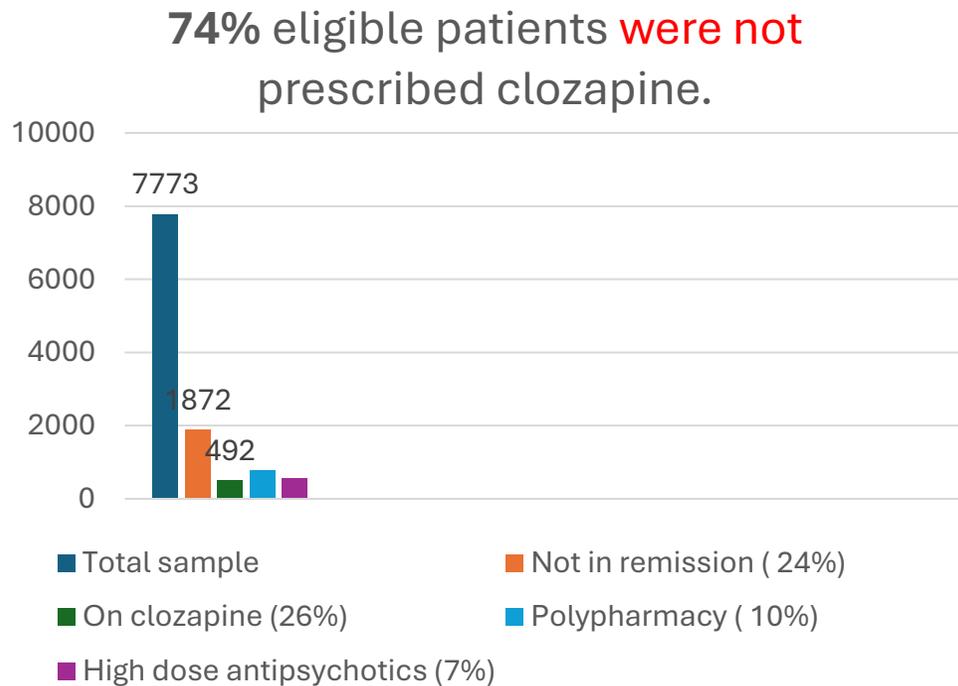
- Significantly **more effective** than antipsychotic drug in TRS (NNT – about 2)
- **Only medication** licensed for Treatment Resistant Schizophrenia.
- **Added benefit** – reduced suicide risk, alcohol and drug use, violent behavior.
- **Most important Clozapine reduces all cause mortality (incl. suicide)**
- Between 1991-1993, in the US, 67,000 patients received clozapine*
 - All-cause mortality rate was 54% lower vs discontinued
 - Suicide rate was 83% lower vs discontinued
- Between 1996-2006, in Finland, 66,881 cases of severe mental illness**
 - Clozapine had the lowest mortality risk (HR 0.74)
 - Quetiapine had the highest (HR 1.41)
- Clozapine does have many adverse effects including fatal adverse effects.

Walker AM, et al. Mortality in current and former users of clozapine. *Epidemiology*. 1997 ;8(6):671-6777

Tiihonen J, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet*. 2009 : 22;374:620-7

What happens in real life ?

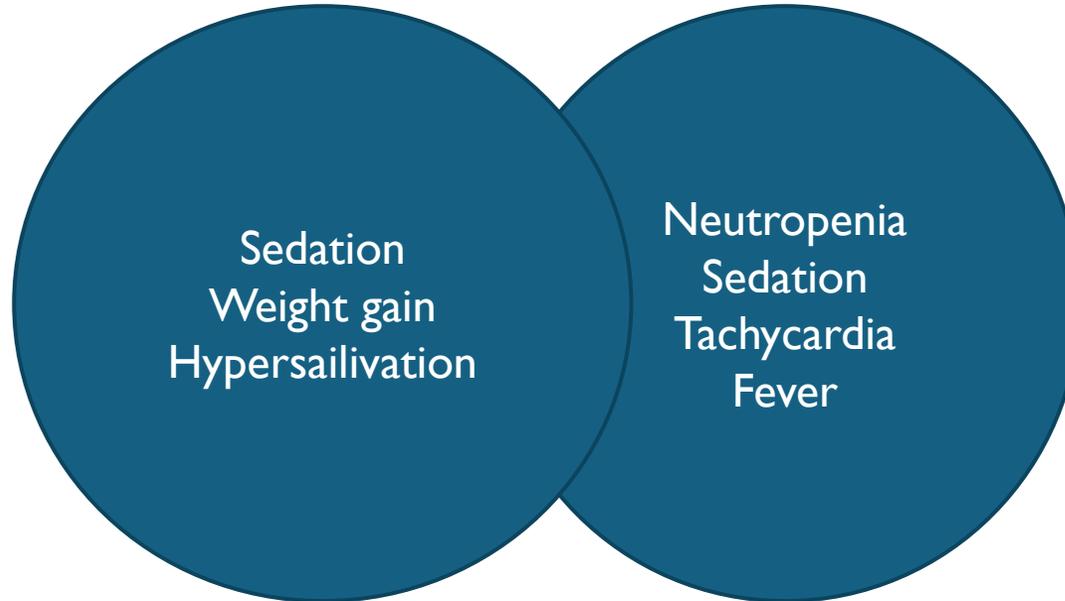
- National Clinical Audit of Psychosis (2017)



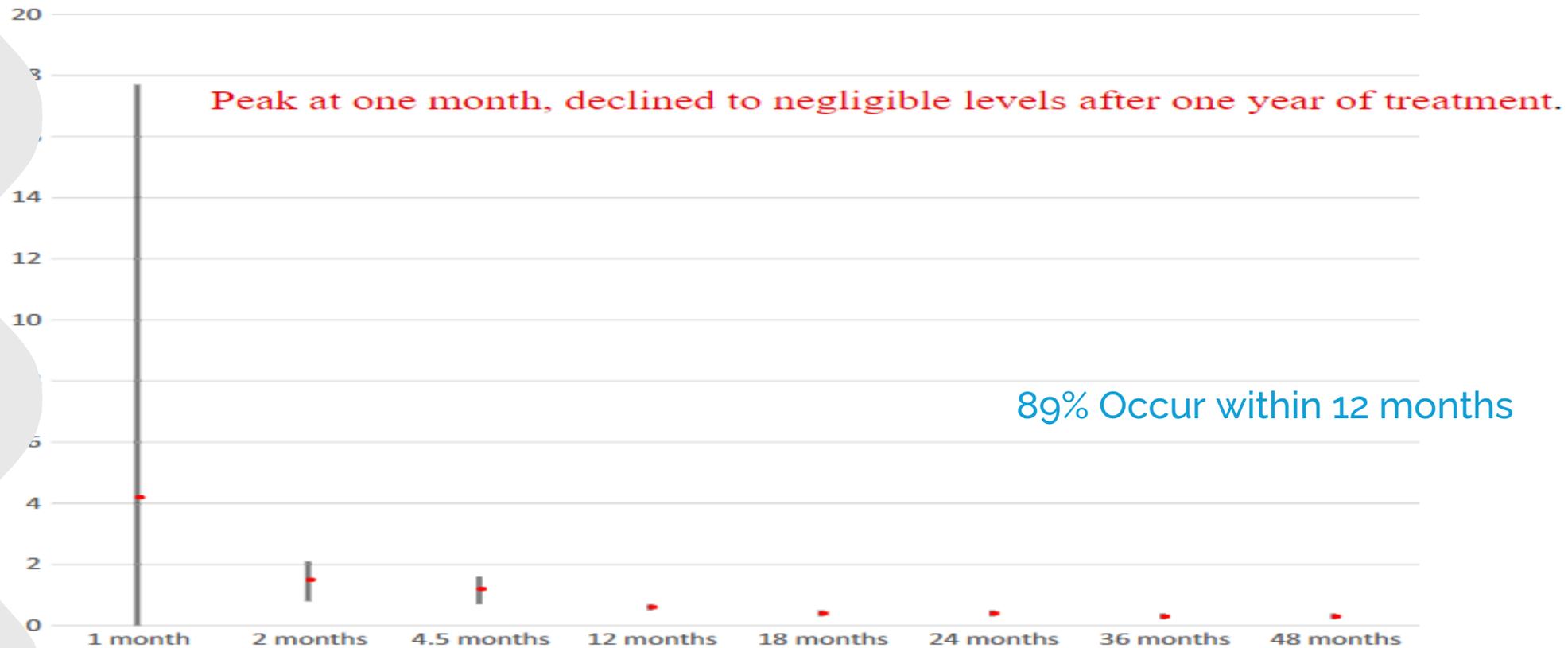
Common reason provided for not using clozapine (1380 patients)	
Offered but refused by patients	240 (17%)
Discontinued due to poor response or adverse effects	152 (11%)
Medically contraindicated	75 (5%)
No reason documented*	372 (27%)
Fear of poor compliance*	372 (27%)
Fear of alcohol or drug abuse*	114 (8%)
Lack of services for community initiation / waiting of admission*	11 (1.1%)

*May be considered inappropriate

Reason for Discontinuation (45% in first two years)



Risk of agranulocytosis



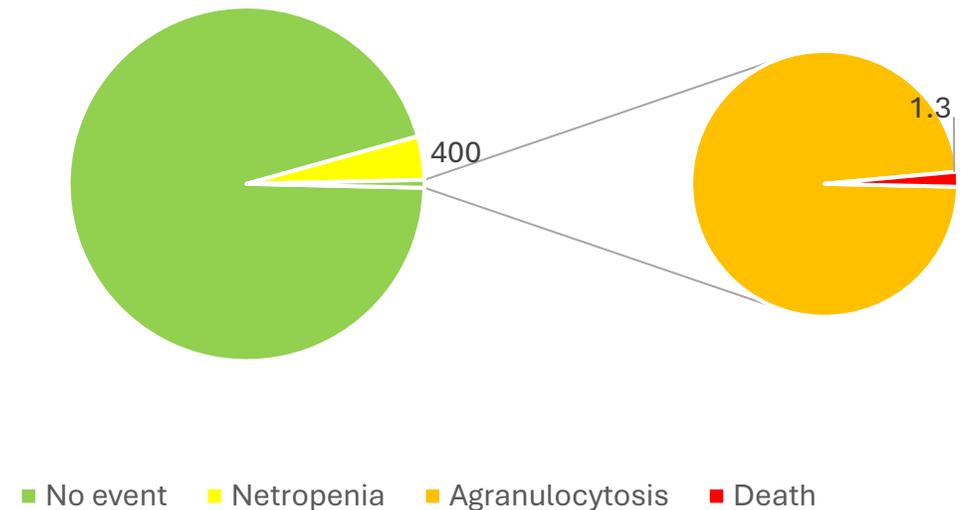
- Myle N. et al. Meta-analysis examining the epidemiology of clozapine-associated neutropenia Acta Psychiatr Scand. 2018 Aug; 138(2): 101-109

Clinical significance of neutropenia

1 / 8000

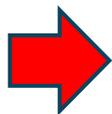
Risk and consequence of neutropenia due to Clozapine			
Mild (red result)	1000–1499 /mm ³	3.9%	75% of will not progress
Moderate	500–999/mm ³	0.9-1.3	
Severe (agranulocytosis)	<500 /mm ³	0.9%	2.1% fatality

The risks of neutropenia ,agranulocytosis and death in 10,000 patient



Clozapine monitoring requirement- REMS (USA)- 2015

Zone	WBC mm ³ (/l)	ANC mm ³ (/l)	ANC mm ³ (/l) under BEN criteria	Guidance
Green	3500	>2000	>1500	Continue
Amber	3000-3500	1500 -2000	1000-1500	Continue – monitor twice weekly
Red	<3000	<1500	<1000	STOP
FDA 2015*		<1000	<500	STOP- clinician can override, if benefit> risk



[*Guidelines for prescribing clozapine in schizophrenia – UpToDate 2021](#)

Management of agranulocytosis-key points

- 1. Red results might not indicate a serious pathological process.**
- 2. Most cases with a red result would not develop agranulocytosis.**
- 3. The risk of agranulocytosis after a year of initiation is minimal and probably equivalent to other antipsychotic drugs.**
- 4. Late-onset neutropenia might not be related to clozapine.**
- 5. Most patients with CIN, can be successfully rechallenged on clozapine, the support of lithium and CGSF.**
- 6. Rechallenge can also be considered in patients with CIA, with the support of lithium and Neutrophil stimulating growth factor.**

Agranulocytosis- take home points

- Agranulocytosis (severe neutropenia) is **an uncommon side effect**.
- When a monitoring service is not used, evidence suggests a mortality rate from agranulocytosis of 0.3% . This is compared to a mortality rate when Clozaril is used in conjunction with the Clozaril Patient Monitoring Service, of 0.01%.
- **The UK national pharmacovigilance has identified eight clozapine related blood dyscrasia deaths to date .**
- **VERY ROBUST SYSTEM IS IN PLACE, WITH STRICT GUIDELINES**
- **Comprehensively document** if a patient has to stop Clozapine due to the red result – retrieval is permitted (off license) – with success rate of about 80%
- Maudsley has decided to keep three monthly monitoring for patients on long-term clozapine.

De la Chapelle A, et al. *Clozapine-induced agranulocytosis: a genetic and epidemiologic study*. Hum Genet, 1977. 37: p. 183-194.

Clozaril Patient Monitoring Service, data on file.

Interactive drug analysis profile: Clozapine [Internet]. MHRA. 2019. Available from: https://info.mhra.gov.uk/drug-analysis-profiles/dap.html?drug=UK_EXTERNAL/NONCOMBINED/UK_NON_000299949199.zip&agency=MHRA.

Sedation

- Common but significant variability amongst individuals (17-67%)
- Histamine receptor –H₃ agonist and H₁ antagonist effects
- ? Dose-related /tolerance develop – significant variability
- Half life (<24 hours) – ideally divided dosages
- One of the common reasons for the discontinuation by patients
- Might report the adverse effects during the maintenance phase
- Also interferes with activities of daily living and rehabilitation



Sedation-Take home points

- **Consider stopping other sedative drug/ giving higher dosages at nighttime or single nighttime dose.** A survey of Clozapine patients in North America showed that in clinical practice, up to 75% of patients were taking as a single night dose. (Takechi et al 2016)
- Clozapine dosages up to 500mg can be given as a single nighttime dose
- Consider gradually decreasing the dose (5% /month)
- **Other treatment options** (based on case reports and case series)
 - Modafinil
 - Methylphenidate – no worsening of psychotic symptoms
 - Betahistine.
 - Combining with Fluvoxamine- a reports suggest less sedation – probably due to increased nor-clozapine
 - Aripiprazole augmentation or single nighttime doses

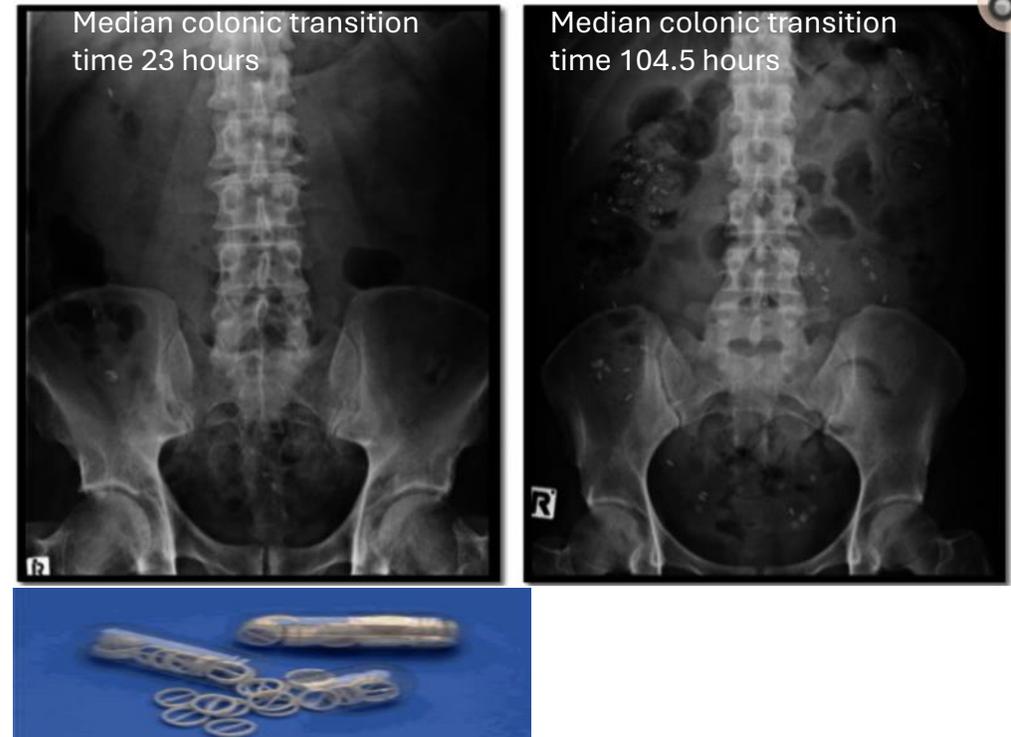
Constipation -

- Up to 60% patients suffer from constipation
- More often not reported by the patients - **unless asked**
- Fatal consequences – paralytic ileus, necrotizing colitis, intestinal obstruction
- Australian Therapeutic Goods Administration and New Zealand Pharmacovigilance Centre (1992-2013)- 160/43132 (37/10000)- 29 died (7/10,000-18% fatality).*
- One of the reasons for the noncompliance
- Dose related adverse effect



Constipation – slow transit constipation

- Due to antagonistic effect of M3 and serotonin receptor
- Other risk factors
 - Sedentary lifestyle, obesity, reduced fiber intake and dehydration
 - Negative symptoms and reduced sensitivity to prolonged pain



Every-palmer, s., Nowitz, m., Stanley, j., et al., 2016. clozapine-treated patients have marked gastrointestinal hypomotility, the probable basis of life-threatening gastrointestinal complications: a cross sectional study. *ebiomedicine* 5, 125–134

The Clozapine Handbook By Jonathan M. Meyer and Stephen M. Stahl Cambridge University Press. 2020.

Management

Life style and behavioral change-

- **Increasing fibre in diet** 30 gm/day--help increase stool weight and decrease gastric transit time .
- **Increasing fluid intake** to the usual recommendation of 1.5–2 litres a day- if increasing fibre intake, as increasing fibre without adequate fluid may lead to bowel obstruction
- **Decreasing sedentary lifestyle** and increasing active time to the recommended 150 min a week

Avoid bulk laxative and systemic anticholinergic drugs or opioids

Reduction of dose of Clozapine if possible

Laxative – single agent or in combination (from different class)

- Osmotic laxatives:** Lactulose, Macrogol (e.g., Movicol, Cosmocol, Laxido)
- Stimulant laxatives:** e.g. Senna, Bisacodyl
- Stool softeners:** e.g. Docusate
- Linaclotide (off-label) – specialist use only
- Prucalopride – specialist use only
- Herbal: e.g. Cascara
- Consider an enema for persistent constipation
- Develop a plan for ongoing individualized monitoring of patients with a known history of constipation

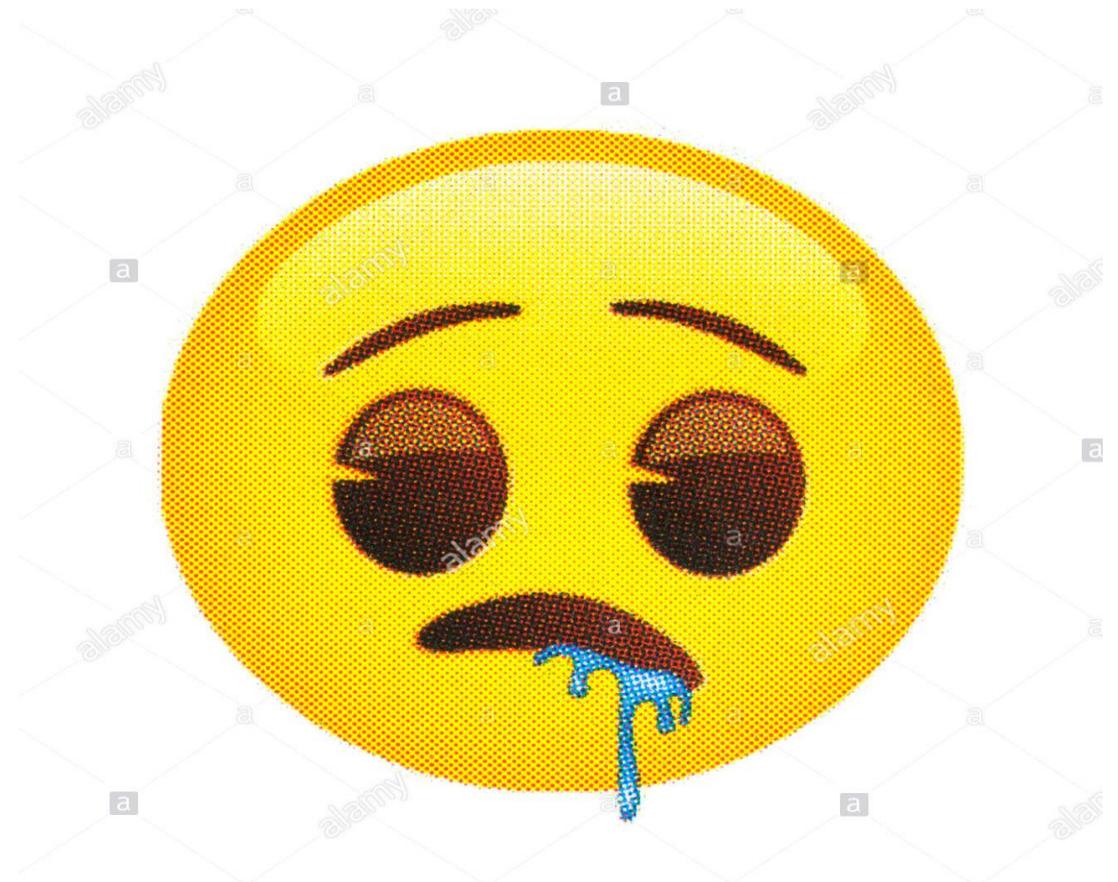
Constipation – Take home points

- **Routinely enquire** about it
- Inform patients about the **red warning symptoms and life style modification**
- Keep a low threshold to prescribe **laxative drugs**. There is a growing literature suggesting prophylactic use of laxative



Hypersalivation

- Common reported by 30-80%
- Pathophysiology of Clozapine-induced sialorrhea - remains elusive-agonist effect on M4 receptor, antagonist effects a adrenergic receptor and lastly diminished oesophageal motility
- Severity- nocturnal salivation to day time drooling
- Serious consequences – **aspiration pneumonia**
- Start soon after the initiation – **tolerance develops in long-run**
- Possibly a dose related adverse effect/ tolerance develops gradually
- One of the common reasons cited by the patient for discontinuing clozapine.
- Dose related adverse effect



Hypersalivation management

- Day time drooling- sugarless chewing gums
- Nighttime -covering the pillow with a towel, elevating the head and sleeping on the side



Hypersalivation management

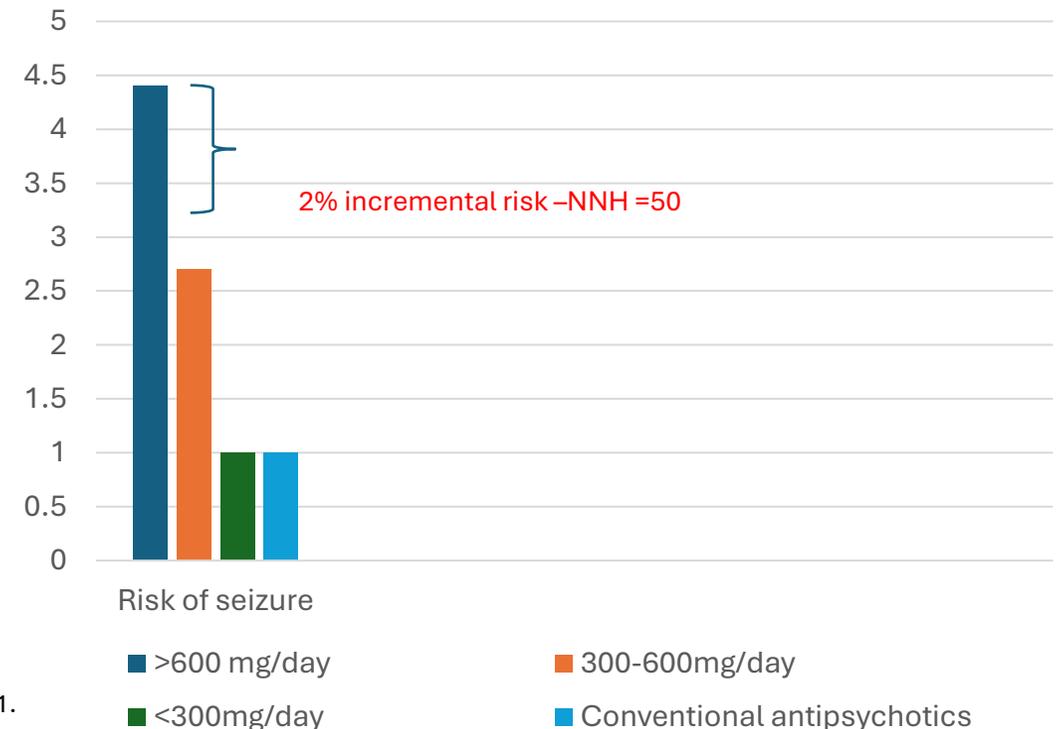
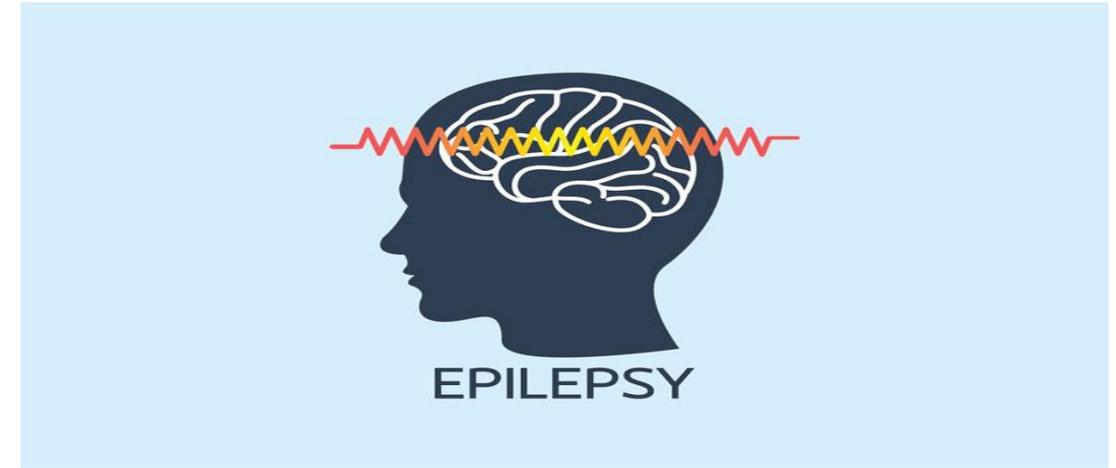
TABLE 1 Off-label pharmacological interventions for clozapine-induced sialorrhea

Drug	Dosage	Comments
Hyoscine hydrobromide oral tablet	300–900 µg/day Divided doses can be used for daytime hypersalivation	The tablet must be sucked or chewed for optimal effect Half-life is around 4 h Worsens anticholinergic adverse effects of clozapine
Hyoscine patches	1.5 mg/72 h	Easier to use than the tablet form
Atropine eye drops (sublingually) 1%	1–2 drops sublingually, initially at bedtime, and if needed up to three times a day Recommend that patients swish and spit to spread the medication around the mucosa	Less likely to cause systemic anticholinergic effects Short half-life and risk of rebound hypersalivation The bitter taste can be a limiting factor
Trihexyphenidyl	5–15 mg day	Worsening of anticholinergic adverse effects
Amitriptyline	10–100 mg at night	Additive anticholinergic adverse effects, postural hypotension and seizure
Ipratropium bromide nasal spray 0.03%	2 puffs sublingually at night or twice daily	Easier to use than sublingual atropine drops
Glycopyrrolate	2–4 mg at night Divided doses can be used for daytime hypersalivation	Longer-lasting effect than atropine and hyoscine Half-life is around 4 h Has no central anticholinergic effect but can increase peripheral anticholinergic effects Expensive
Pirenzepine	25–100 mg at night or divided dose	Mild diarrhoea; less likely to cause central anticholinergic adverse effects
Propantheline	30–120 mg at night or divided dose	Constipation, drowsiness and dry mouth
Diphenhydramine	100–200 mg at night	Sedation and dry mouth
Alpha-2 agonist, e.g. clonidine	Clonidine 100–500 µg/day	Sedation, dry mouth, depression and hypotension
Amisulpride	Up to 400 mg/day	May improve psychotic symptoms Likely to cause hyperprolactinemia

Q9
Q1

Seizure

- Almost all antipsychotics reduce seizure threshold – clozapine is worse amongst them
- Possible relationship with oral dose or plasma level \pm
- Possibly related to rise is plasma level
- 50% (34-42 days of initiation)
- Toxicity is associated with seizure



Seizure- Take home points

Devinsky et al (1991). recommended as one (but not the only) strategy that patients taking > 600 mg/day of clozapine be commenced on anticonvulsant therapy as a prophylaxis. **Maudsley guidelines also recommend it ,recent edition has mentioned other option as well.**

Recent literature advises against primary prophylaxis (Meyer and Stahl 2020 and Caetano 2014)

Secondary prophylaxis for seizure – review the possible reason, reduce the dose (by 50% or last seizure-free dose) and consider adding an AED

- Valproate – weight gain ,myocarditis and agranulocytosis
- Other medications-Lamotrigine, Topiramate, Gabapentin

Caetano D. Use of anticonvulsants as prophylaxis for seizures in patients on clozapine. *Australas Psychiatry*. 2014 Feb;22(1):78-83

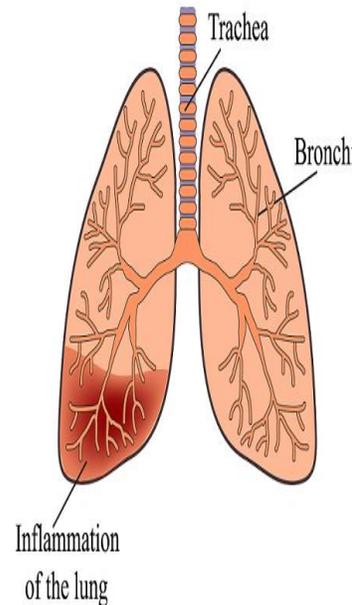
Devinsky O, Honigfeld G and Patin J. Clozapine-related seizures. *Neurology* 1991; 41: 369–731.

The Clozapine Handbook By Jonathan M. Meyer and Stephen M. Stahl Cambridge University Press. 2020.

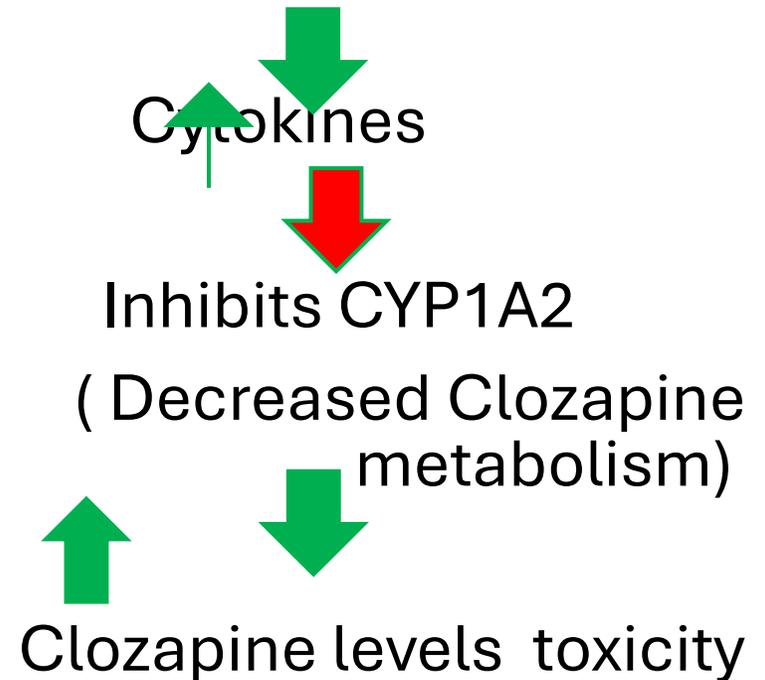
The information presented in this slide reflects the professional opinion of the speaker and does not reflect that of Viatrix' or equivalent.

Pneumonia

- High risk of pneumonia – with most antipsychotics
- Clozapine -Sedation, hypersalivation, difficulty in swallowing
- Fatality is significantly high with Clozapine



Severe infection or inflammation



Pneumonia - Take home points

- Pneumonia is one of the fatal adverse effects of Clozapine
- Informing patients and clinicians
- If suffering from severe respiratory infection (also with urinary infection)– if possible, reduce the dose of Clozapine by 50% /check for signs and symptoms of Clozapine toxicity (delirium, speech and gait disturbance, myoclonus or generalized seizures), reduce the dosages or stop Clozapine and arrange of plasma Clozapine levels

Clozapine and fatal adverse effects

- De-Leon et al (2020) reviewed the ADR reports sent from drug agencies all over the world to the World Health Organization (WHO)-
 - agranulocytosis - 550 deaths,
 - myocarditis – 539 deaths
 - seizures -308
 - pneumonia- 2077

Every-Palmer and Ellis (2017)- death due to GI adverse effects
7 in 10,000 patients.

Maudsley guidelines (2018) Risk of fatal agranulocytosis is less than 1 in 8000 patients /
fatal myocarditis or cardiomyopathy 1 in 1000.

Key learning points

- Most adverse effects appear early and can be effectively managed, discontinuation of Clozapine is rarely required (except agranulocytosis and myocarditis). We need to effectively communicate risks and benefits to patients/ carers to ensure increased acceptability and to avoid unnecessary discontinuation.
- Agranulocytosis is uncommon and rarely leads to a fatal outcome (most likely due to effective monitoring).
- Fatal outcomes are more likely due to constipation and secondary to pneumonia and clozapine toxicity
- Use validated rating scales such as GASS – Clozapine to screen adverse effects and actively managed those adverse effects.

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Questions and discussion

