सत्यमेव जयते

Clozapine Masterclass: Tackling the toughest drug in Psychiatry

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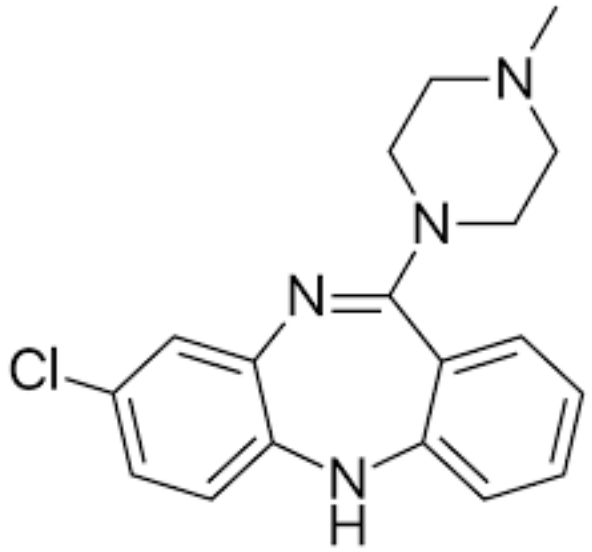
Clozapine

- Unique antipsychotic
- D1, D2, D4 antagonism [low D2 affinity]
- 5-HT2A inverse agonism



The road to clozapine

- In 1958, HF-1854 was discovered by Wander AG [A Swiss Company]
- Initial claim to fame – Multi-receptor activity and low EPS [Defective/ Atypical profile by Janssen's neuroleptic dogma]
- 1962 – First open clinical trials conducted at 160 mg TID [n=19]
- 1960s – Used Across Europe for patients unresponsive/ intolerant to typical antipsychotics.
- Noted to have improvement in both positive and negative symptom dimensions

Meyer, J. M. and Leckband, S. G. (2013). A history of clozapine and concepts of atypicality. In E. F.Domino (Ed.), History of Psychopharmacology, vol. 2 (pp. 95–106).

The fateful eight from Finland

› Acta Psychiatr Scand. 1977 Oct;56(4):241-8. doi: 10.1111/j.1600-0447.1977.tb00224.x.

Agranulocytosis in patients treated with clozapine. A study of the Finnish epidemic

H A Amsler, L Teerenhovi, E Barth, K Harjula, P Vuopio

PMID: 920225 DOI: 10.1111/j.1600-0447.1977.tb00224.x

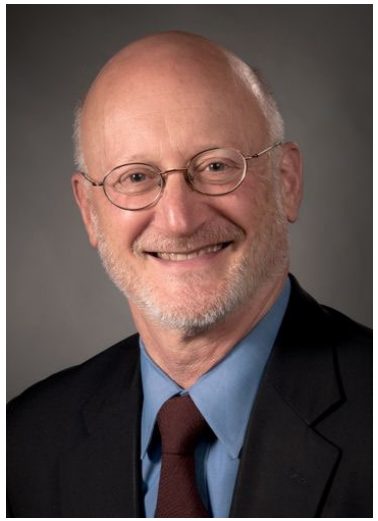
The lost years of 1970s and early 1980s

- Clozapine trials and use suspended
- Persons on clozapine started experiencing relapse
- German Psychiatrists pushed back
- Use limited to highly monitored research settings / compassionate use
- Dopamine theory of schizophrenia evolved

Prelude to Kane Study

- Anecdotal Signals in resistant patients
- No robust controlled evidence
- Sandoz took over Wander AG
- There was a demand for re-examining clozapine in a high stakes clean experiment
- NIMH + Sandoz + Kane (and colleagues) all came together with a purpose

37 years since Kane et al.



Article

September 1988

Clozapine for the Treatment-Resistant Schizophrenic

A Double-blind Comparison With Chlorpromazine

John Kane, MD; Gilbert Honigfeld, PhD; Jack Singer, MD; et al

» Author Affiliations

Arch Gen Psychiatry. 1988;45(9):789-796. doi:10.1001/archpsyc.1988.01800330013001

Kane trial – High-stakes, clean experiment

- Needed to define TRS scientifically and as objectively as possible
- Design an ethical RCT with inclusion of only truly resistant patients
- Avoid heterogeneity [schizophrenias] and placebo effects
- Manage Safety fears around agranulocytosis

Kane’s Criteria

Landmark/ Original

Domain	Criterion	Details
I. Historical (Past Treatment Failures)	Number of Antipsychotic Trials	Failed response to **≥3 antipsychotic trials**
	Chemical Classes	At least **2 trials from different chemical classes**
	Dose Adequacy	Minimum dose: **≥1000 mg/day chlorpromazine equivalents**
	Duration of Each Trial	Each trial of **≥6 weeks** duration
	Long-Term Course	No period of good functioning in the past **5 years**
II. Actual (Cross-Sectional Symptom Severity at Entry)	BPRS Total Score	≥ **45**
	Core Symptom Severity	Score of **≥4 on 2 of 4 core BPRS items**:- Conceptual disorganization- Suspiciousness- Hallucinatory behavior- Unusual thought content
	Clinical Global Impression (CGI)	**≥4 (moderately ill or worse)**
III. Prospective (Prospective Treatment Failure)	Prospective Haloperidol Trial	Failed **6-week haloperidol trial** (target 60 mg/day, or maximally tolerated ≥20 mg/day)
	Definition of Non-Response	Failure to achieve BOTH:- ≥20% reduction in BPRS score- Post-treatment CGI score ≤3 *or* BPRS ≤35

Clozapine

- Extensively studied during residency
- Underutilized in schizophrenia
- Feared molecule[1,2]

1 -Sultan, R. S., Olfson, M., Correll, C. U., et al. (2017). Evaluating the effect of the changes in FDA guidelines for clozapine monitoring. Journal of Clinical Psychiatry, 78, e933–e939.
2 - Cohen, D. (2014). Prescribers fear as a major side-effect of clozapine. Acta Psychiatrica Scandinavica, 130, 154–155.

How do we optimize use of Clozapine?

- Establishing expertise centers on use of clozapine
- Educational outreach to mental health professionals through lectures, publications and written summaries.
- Up to date with treatment guidelines
- Surveillance systems
- Psychoeducation of patients and family members
- Evidence based practice

1 - Carruthers, J., Radigan, M., Erlich, M. D., et al. (2016). An initiative to improve clozapine prescribing in New York State. Psychiatric Services, 67(4), 369–371.
2 - Cohen, D. (2014). Prescribers fear as a major side-effect of clozapine. Acta Psychiatrica Scandinavica, 130, 154–155.

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Up to date with treatment guidelines

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Clozapine adverse effects

Common adverse effects		Serious adverse effects [FDA black box]
Sedation	Weight gain	Agranulocytosis
Hypersalivation	Fever	Seizures
Constipation	Nausea	Orthostatic hypotension, bradycardia, syncope
Hypotension	Nocturnal enuresis	Myocarditis and cardiomyopathy
Hypertension	GERD	Increased risk of death in elderly especially those with dementia-related psychosis
Tachycardia	Dyslipidemia/ Hyperglycemia	

Constipation
[First 4 months – usually persists]

Muscarinic antagonism

Weak antagonism at 5 HT3

Antihistaminergic

Sedentary life style

Constipation

- Prevalence is 30-60%
- Fatality rate of paralytic ileus is 15-27 %[1] [contrast to that of severe neutropenia 2.2 to 4.2%]
- Increases the colonic transit time from 23 hours up to 100+ hours [2]
- Median time to ileus – 1528 days[3]

1 - Cohen, D. (2017). Clozapine and gastrointestinal hypomotility. CNS Drugs, 31, 1083–1091.
2 -Clozapine-treated patients have marked gastrointestinal hypomotility, the probable basis of life-threatening gastrointestinal complications: A cross sectional study. EBioMedicine, 5, 125–134.
3 - Nielsen, J. and Meyer, J. M. (2012). Risk factors for ileus in patients with schizophrenia. Schizophrenia Bulletin, 38, 592–598

Rome IV criteria – [Opioid] 2 or more of a-f

a. Straining during more than one-fourth (25%) of defecations

b. Lumpy or hard stools (Bristol Stool Form Scale 1–2) more than one-fourth (25%) of defecations

c. Sensation of incomplete evacuation more than one-fourth (25%) of defecations

d. Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations

e. Manual maneuvers to facilitate more than one-fourth (25%) of defecations (e.g. digital evacuation, support of the pelvic floor)

f. Fewer than three spontaneous bowel movements per week

Lacy, B. E., Mearin, F., Chang, L., et al. (2016). Bowel disorders. Gastroenterology, 150, 1393–1407

Treatment

- Any other medications worsening constipation?
- Lifestyle modifications?
- Polyethylene glycol [Osmotic laxative] 17 grams OD to BID
- Lactulose [Osmotic laxative] 30 ml OD to BID
- Bisacodyl [Stimulant laxative] 5 mg OD to 15 mg BID
- Secretagogues and prucalopride
- Bethanechol [Cholinergic agonist] 10 mg TID

Steps in Porirua protocol – go to next step after 48 hours of persistent constipation

1. Docusate 100 mg + Senna 16 mg at night
2. Increase doses to maximum of 200 and 32 mg respectively
3. Enemas or disimpaction to be considered if stools are impacted. If not add PEG 13.125 grams twice daily
4. Gastroenterology or surgery liaison

Every-Palmer, S., Ellis, P. M., Nowitz, M., et al. (2017). The Porirua Protocol in the treatment of clozapine-induced gastrointestinal hypomotility and constipation: A pre- and post-treatment study. CNS Drugs, 31, 75–85.

Intestinal secretagogues - Newer drugs for constipation

- Lubiprostone [PgE1 analogue]
- Linaclotide [Guanylate cyclase-C agonist]
- Plecanatide [Guanylate cyclase-C agonist]

Ileus

1. Moderate to severe abdominal pain discomfort lasting for more than 1 hour
2. At least one of the following:

a. Vomiting (especially feculent vomitus)
b. Distension
c. Absent or high-pitched bowel sounds
d. Diarrhea (especially bloody)
e. Hemodynamic instability or other signs of sepsis

Cohen, D. (2017). Clozapine and gastrointestinal hypomotility. CNS Drugs, 31, 1083–1091

Sedation

[First few months; decreases with time, may persist]

Histaminergic blockade

Muscarinic blockade

Sedation

- Probably the most common adverse effect of clozapine. [44%][1]
- Reduce dose [5% every 4 weeks] or give smaller dose in morning or prefer HS dosing[2]
- Interventions[1,2] – Modafinil, Aripiprazole, ? Betahistine

1 - Citrome, L., McEvoy, J. P. and Saklad, S. R. (2016). Guide to the management of clozapine related tolerability and safety concerns. Clinical Schizophrenia & Related Psychoses, 10, 163–177.
2 - Perdigues, S. R., Quecuti, R. S., Mane, A., et al. (2016). An observational study of clozapine induced sedation and its pharmacological management. European Neuropsychopharmacology, 26, 156–161.

Orthostatic hypotension, Syncope

[Onset within couple of weeks; decreases with time, tolerance over 6 weeks]

Alpha 1 adrenergic antagonism

Non pharmacologic management

- Psychoeducation: warning patients about hypotension and reassurance it will improve with time.
- Counseling to move slowly when rising from lying or seated position.
- Warning about the seriousness of falls risk.
- Encourage adequate fluid intake to prevent dehydration which may worsen orthostasis.

1- The Clozapine Handbook: Stephen Stahl 2018
2 - Nielsen, J., Correll, C. U., Manu, P., et al. (2013). Termination of clozapine treatment due to medical reasons: When is it warranted and how can it be avoided? Journal of Clinical Psychiatry, 74, 603–613.

Pharmacologic management

- Slower up-titration
- Other antihypertensives – the culprit?
- Fludrocortisone [0.1 mg/day PO in combination with high salt diet and adequate fluid intake; may be increased in increments of 0.1 mg/wk; not to exceed 1 mg/day][1]
- Continuous malignant syncope – termination as last resort[2]

1- The Clozapine Handbook: Stephen Stahl 2018
2 - Nielsen, J., Correll, C. U., Manu, P., et al. (2013). Termination of clozapine treatment due to medical reasons: When is it warranted and how can it be avoided? Journal of Clinical Psychiatry, 74, 603–613.

Tachycardia

[usually seen in first 4 weeks; rarely may persist]

Alpha 1 Adrenergic blockade

Treatment

- Myocarditis
- Bisoprolol or atenolol
- Ivabradine
- Prolonged untreated tachycardia may itself cause cardiomopathy

Stryjer R et al. Beta adrenergic agonists for the treatment of clozapine induced tachycardia: a retrospective study. Clin J Neuropharmacol 2009

Sequential approach to Tachycardia

1. Is it due to orthostasis? [Acute or maintenance phase]
2. If in acute phase have you ruled out myocarditis?
3. Are there any other anticholinergic or adrenergic coprescribed medications? [taper]
4. Is there any evidence for pain, infection or inflammation?
5. If 1-4 is negative, consider pharmacological interventions with selective Beta 1 adrenergic antagonists

Stryjer R et al. Beta adrenergic agonists for the treatment of clozapine induced tachycardia: a retrospective study. Clin J Neuropharmacol 2009

Hypersalivation

[Most common adverse effect, first few months; decreases with time, may persist]

Muscarinic M1 and M4 agonism [norclozapine]

Alpha 2 adrenergic antagonism

Inhibition of swallowing reflex

Management strategies

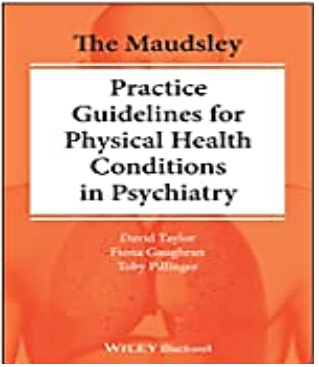
- Rating scales - Drooling Severity and Frequency Scale or Nocturnal Hypersalivation Rating Scale NHS
- Non-pharmacologic strategies
- Locally acting anti-cholinergics preferred
- Atropine eye drops – can be fatal if not taken correctly

1- The Clozapine Handbook: Stephen Stahl 2018
2 - Nielsen, J., Correll, C. U., Manu, P., et al. (2013). Termination of clozapine treatment due to medical reasons: When is it warranted and how can it be avoided? Journal of Clinical Psychiatry, 74, 603–613.

Second line

- Amisulpride [100-400 mg] and Clonidine [0.1 mg PO HS]
- Other –THP, Glycopyrrolate, Ipratropium, Guanfacine, Lofexidine, Amitriptyline
- Botulinum toxin B injections to the salivary glands
- Systemic anticholinergics are not preferred because of constipation

1- The Clozapine Handbook: Stephen Stahl 2018
2 - Nielsen, J., Correll, C. U., Manu, P., et al. (2013). Termination of clozapine treatment due to medical reasons: When is it warranted and how can it be avoided? Journal of Clinical Psychiatry, 74, 603–613.



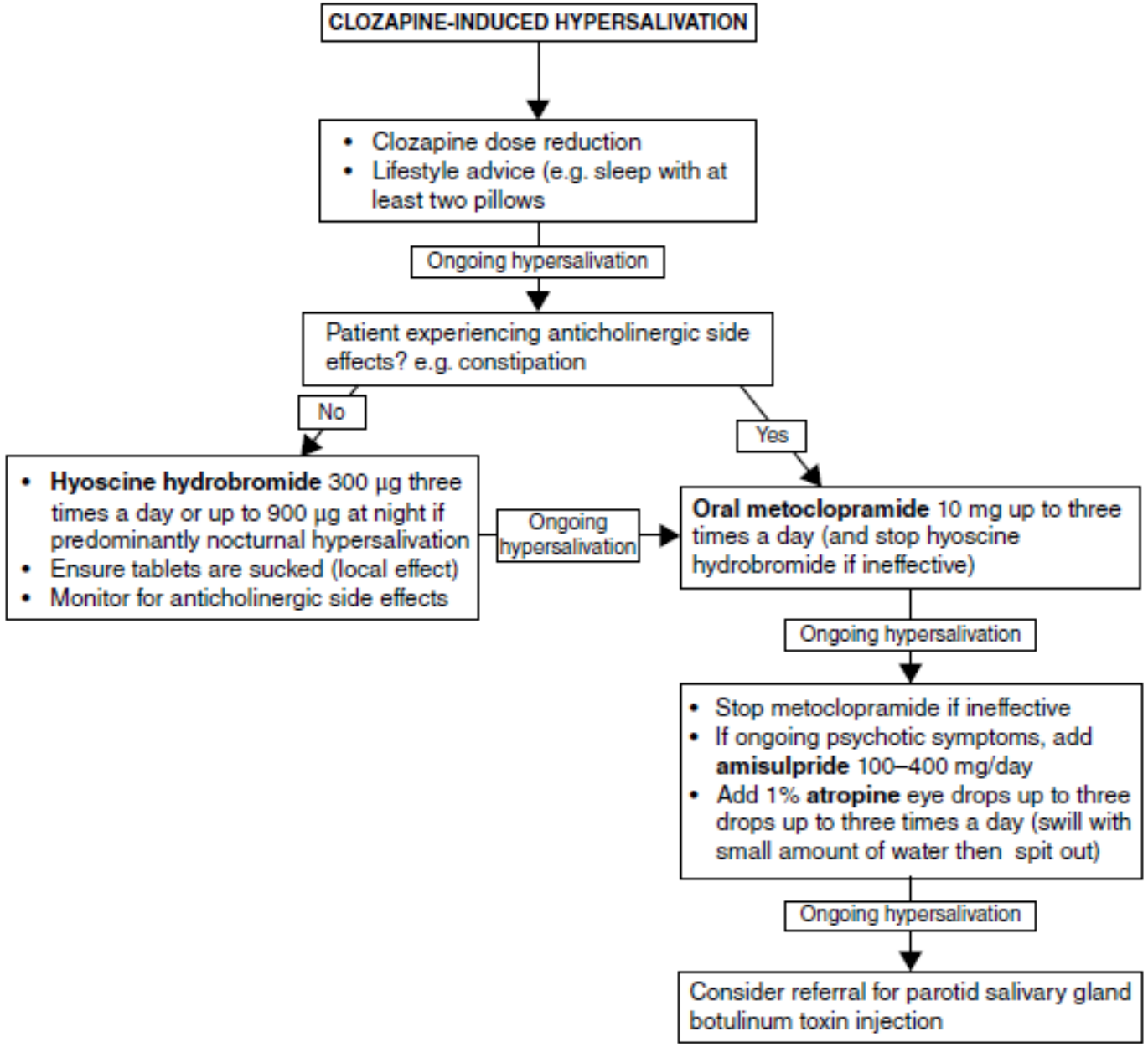


Figure 27.1 Suggested treatment algorithm for clozapine-induced hypersalivation.

Seizures

[Common adverse effect, cumulative incidence of 5% per year; low dose during uptitration and high dose maintainence]

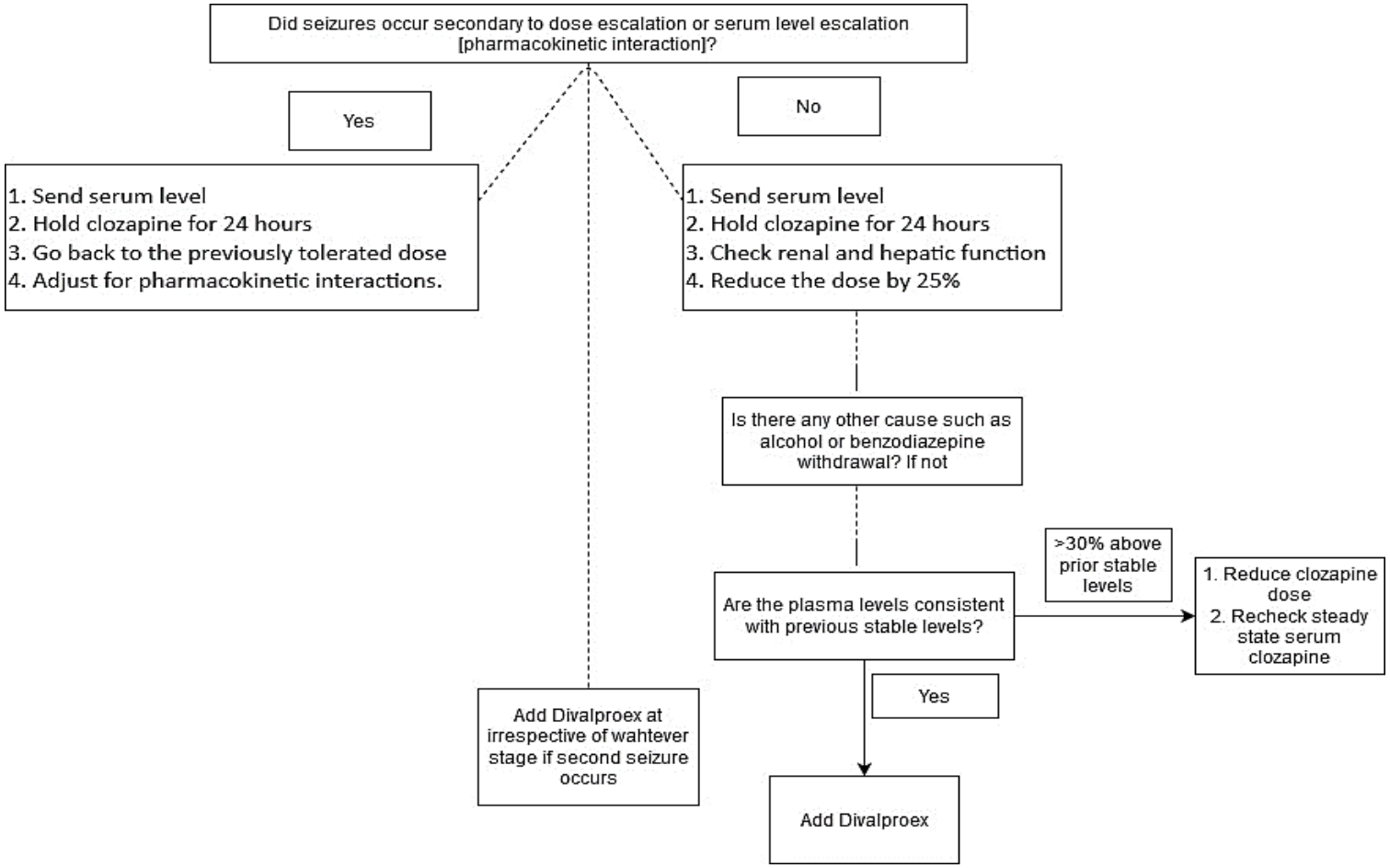
?

Seizures and clozapine

- EEG abnormalities are related to serum clozapine. [Not seizures][1]
- Routine EEG not recommended [1]
- Divalproex is the anticonvulsant of choice [1]
- Majority of seizures are GTCS [50%][1]
- Myoclonic (limbs/facial) and Atonic seizures [30%] [1]
- New onset stuttering and myoclonic jerks as predictors[2]

1 - Williams, A. M. and Park, S. H. (2015). Seizure associated with clozapine: Incidence, etiology, and management. CNS Drugs, 29, 101–111.
2 - Murphy, R., Gallagher, A., Sharma, K., et al. (2015). Clozapine-induced stuttering: An estimate of prevalence in the west of Ireland. Therapeutic Advances in Psychopharmacology, 5, 232–236.

Sequential approach to seizures



Conceptualized from - The Clozapine Handbook, Stephen Stahl 2018

Myocarditis

Cytokine induced hypersensitivity reaction

Course and evaluation

- First 6 weeks
- 3 % of patients
- Malaise, flu like symptoms, chest pain, fever [20% may not have fever]
- Troponin I/T more than twice the normal range
- CRP is elevated [> 100mg/l]
- DD - Interstitial nephritis [first 8 weeks], serositis and drug reaction with eosinophilia and systemic symptoms (DRESS)
- After chronic treatment – cardiomyopathy

1 - Kilian, J. G., Kerr, K., Lawrence, C., et al. (1999). Myocarditis and cardiomyopathy associated with clozapine. Lancet, 354, 1841–1845.
2 - Legge, S. E., Hamshere, M. L., Ripke, S., et al. (2017). Genome-wide common and rare variant analysis provides novel insights into clozapine-associated neutropenia. Molecular Psychiatry, 22, 1502–1508.

Australian & New Zealand Journal of Psychiatry

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A New Monitoring Protocol for Clozapine-Induced Myocarditis Based on an Analysis of 75 Cases and 94 Controls

Kathlyn J. Ronaldson, Paul B. Fitzgerald, Andrew J. Taylor, more...

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https://doi.org/10.3109/00048674.2011.572852

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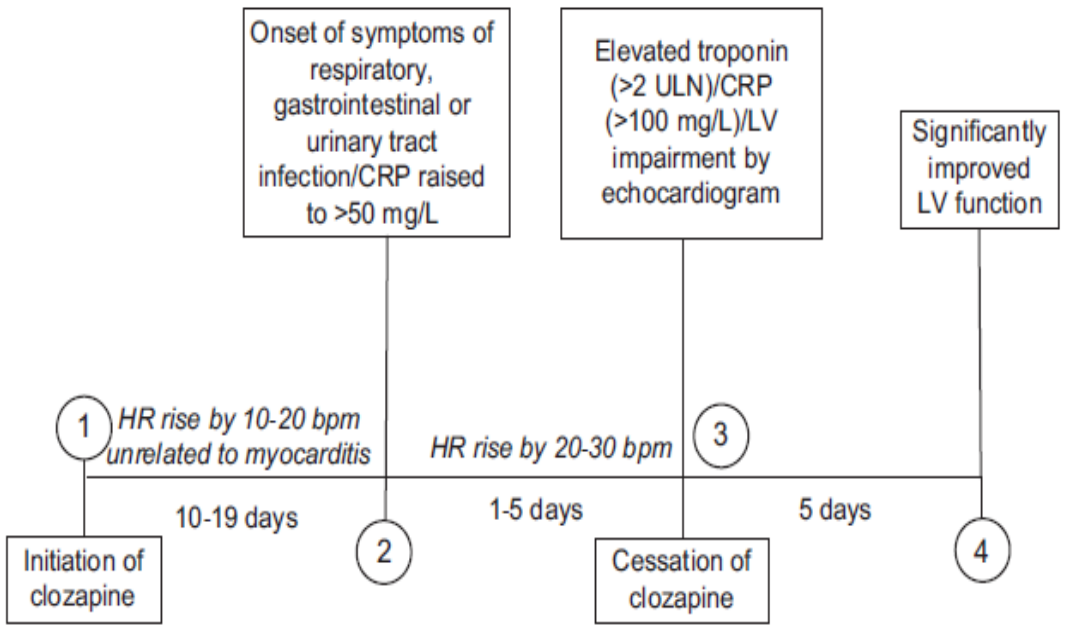

Figure 4. The typical evolution of clozapine-induced myocarditis. bpm, beats per minute; CRP, C-reactive protein; HR, heart rate; LV, left ventricular; ULN, upper limit of normal.

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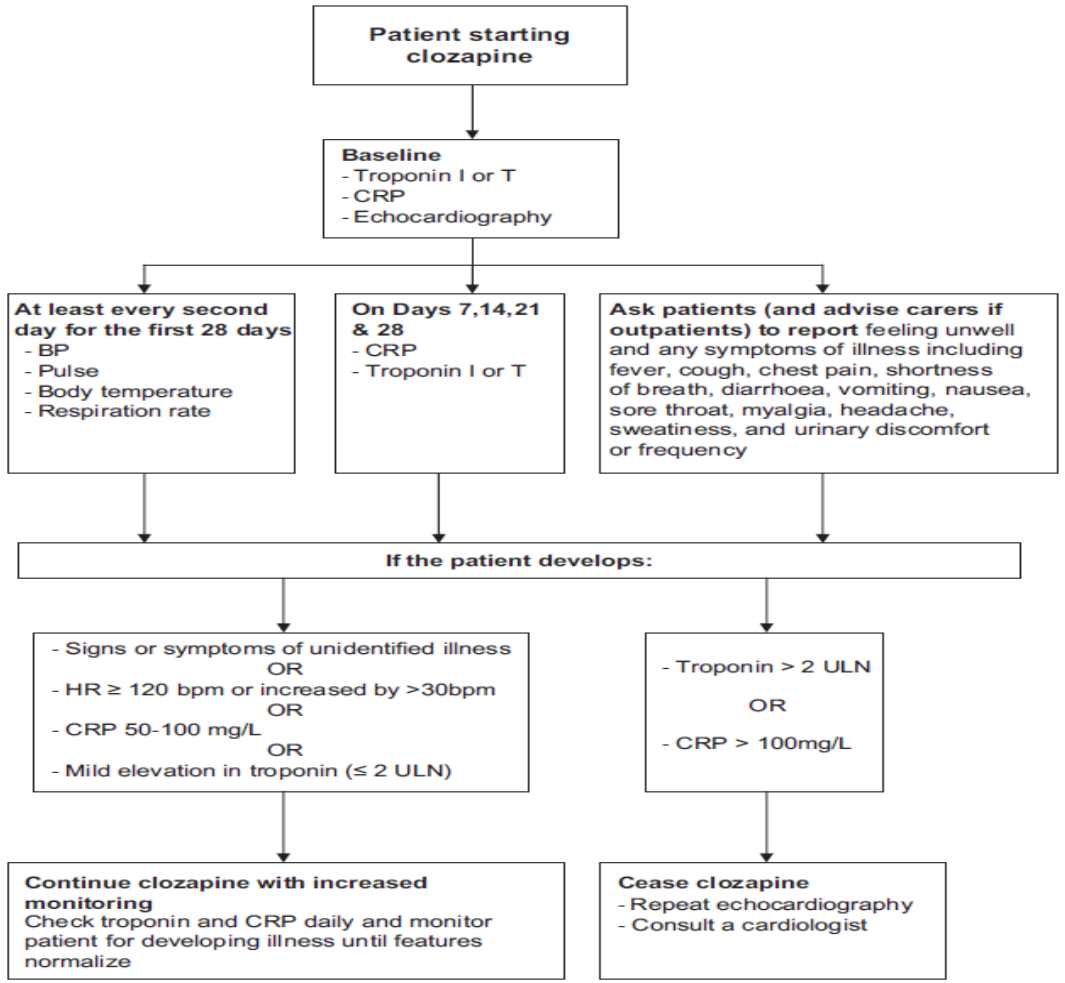


Interstitial nephritis

Cytokine induced hypersensitivity reaction

Interstitial nephritis

- First 2 months of treatment.
- Fever in 80%
- Proteinuria
- Decreased eGFR

Elias, T. J., Bannister, K. M., Clarkson, A. R., et al. (1999). Clozapine-induced acute interstitial nephritis. Lancet, 354, 1180–1181.

Noturnal enuresis

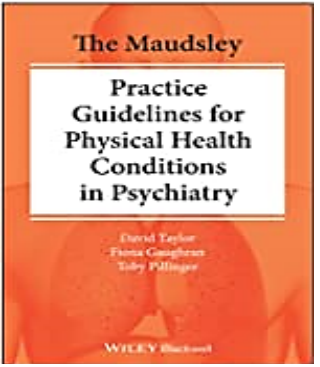
? Schizophrenia itself

Sedation

Management

- 40% during early phase & 20% in maintenance phase
- Lifestyle changes
- If during daytime rule out overactive bladder
- Urodynamic testing may be necessary

Callegari, E., Malhotra, B., Bungay, P. J., et al. (2011). A comprehensive non-clinical evaluation of the CNS penetration potential of antimuscarinic agents for the treatment of overactive bladder. British Journal of Clinical Pharmacology, 72, 235–246.



Non-pharmacological interventions

- Reduce fluid intake in the evening
- Reduce (ideally stop) caffeine and alcohol intake
- Stop smoking (if so, monitor clozapine levels)
- Weight-loss

Pharmacological interventions: step 1

- Consider stopping any co-prescribed antipsychotics
- Reduce clozapine dose or, if during a titration, slow titration rate
- If present, treat constipation

Ongoing nocturnal enuresis

Pharmacological interventions: step 2

- Desmopressin nasal spray 10–20 μg at night (monitor sodium levels)
- If desmopressin contraindicated, consider trial of anticholinergic agent e.g, oxybutynin up to 5 mg three times a day (monitor for anticholinergic symptoms) or aripiprazole augmentation (10–15 mg daily)

Venous thromboembolism

Smoking

Obesity

Sedentary lifestyle

VTE

- 1.5 times increased risk[1]
- 3 cases per every 10000 users of antipsychotics[1]
- CI of adjusted OR overlaps with other APs [Between 1-2.7][2]
- Switching may not be feasible
- Monitor for risk factors and consider anticoagulation

1 - Barbui, C., Conti, V. and Cipriani, A. (2014). Antipsychotic drug exposure and risk of venous thromboembolism: A systematic review and meta-analysis of observational studies. Drug Safety, 37, 79–90.
2 - Allenet, B., Schmidlin, S., Genty, C., et al. (2012). Antipsychotic drugs and risk of pulmonary embolism. Pharmacoepidemiology and Drug Safety, 21, 42–48.

Metabolic adverse effects

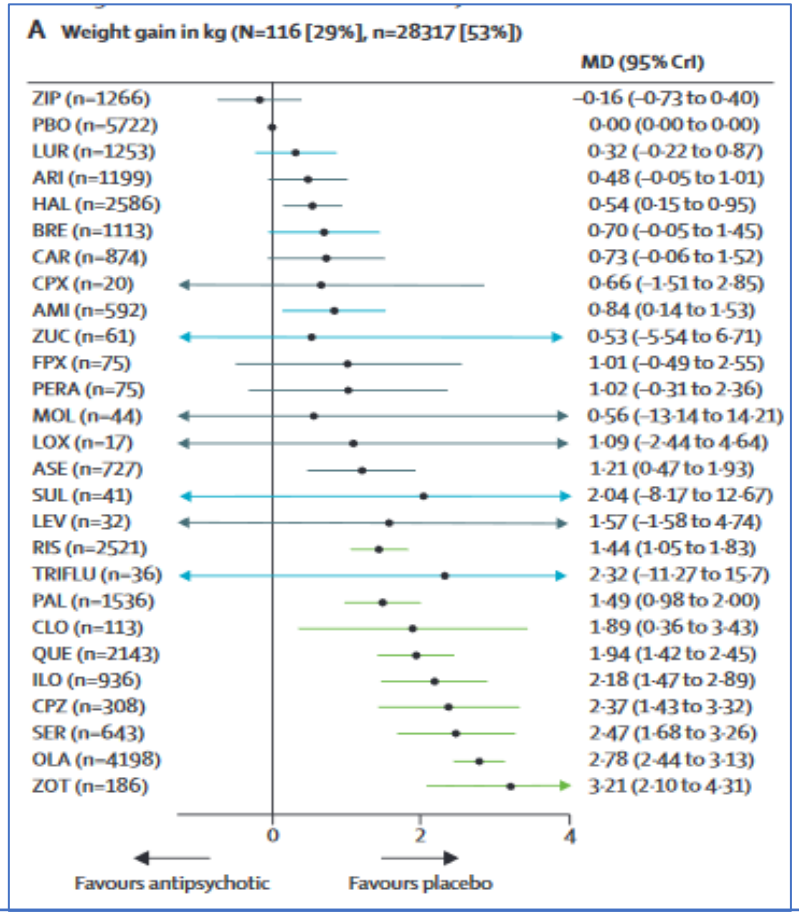
5 HT 2C antagonism– Weight gain and DM
H1 antagonism – Weight gain, DM
M3 antagonism – DM
D2, 5HT1A and Alpha 2

Metabolic syndrome in schizophrenia

- Four fold increased risk[1]
- The overall prevalence of Metabolic Syndrome in SCZ is 32.5% [2]
- Contributes to 50% of mortality in SCZ[2]
- Minimal difference[3]
    - According to the different definitions
    - Treatment setting (inpatient vs. outpatient),
    - Country of origin
    - Gender

1 – Northern Finland Birth Cohort study 1966
2 - Interventions for the metabolic syndrome in schizophrenia: a review, Evangelos Papanastasiou 2012
3 - Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders--a systematic review and meta-analysis, Mitchell 2013

Relative antipsychotic propensity for weight gain



Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis . Huhn et al 2019

Nonpharmacologic interventions

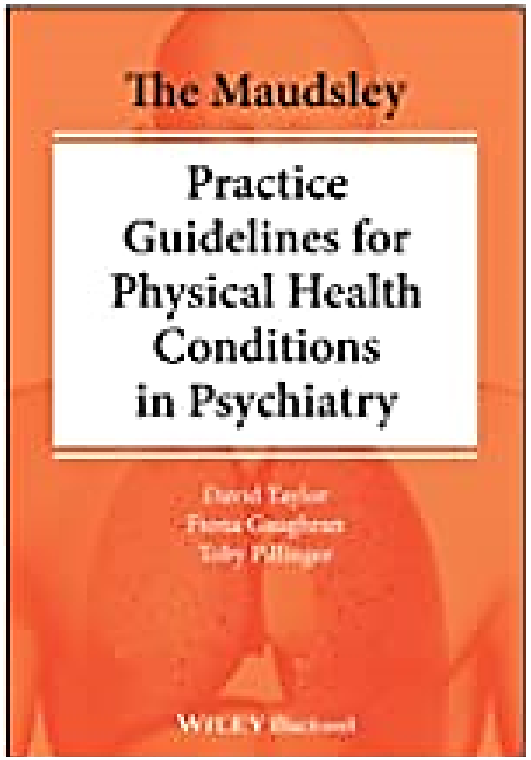
- Abdominal obesity Goal: 10% weight loss first year, thereafter continued weight loss or maintain weight

  Recommendation: caloric restriction; regular exercise; behaviour modification

- Physical inactivity Goal: regular moderate-intensity physical activity

The metabolic syndrome and schizophrenia; J. M. Meyer & S. M. Stahl

Dietary advise for weight loss



Adaptive modifications

How much physical activity?

- Physical activity vital sign

- Target
  - 150 minutes per week of moderate aerobic PA (an activity that leads to the person becoming slightly short of breath, such as cycling or brisk walking)

    Or

  - 75 minutes per week of vigorous PA (where the person struggles to talk and breathe at the same time, such as running fast).

David M Taylor et al. The Maudsley Practice Guidelines for Physical Health Conditions in Psychiatry 2020

Nonpharmacologic interventions

- Atherogenic diet Goals: reduced intakes of saturated fats, trans fats and cholesterol[1]

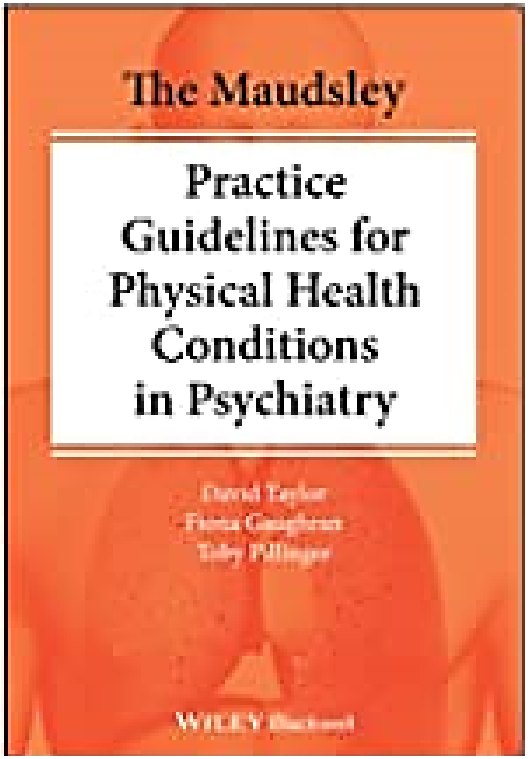
  Recommendations: saturated fat ,7% of total calories; reduce trans fat; dietary cholesterol 200 mg daily; total fat 25–35% of total calories

- Cigarette smoking Goal and recommendation: complete smoking cessation[1]

The metabolic syndrome and schizophrenia; J. M. Meyer & S. M. Stahl

Pharmacological strategies for metabolic syndrome

Diabetes



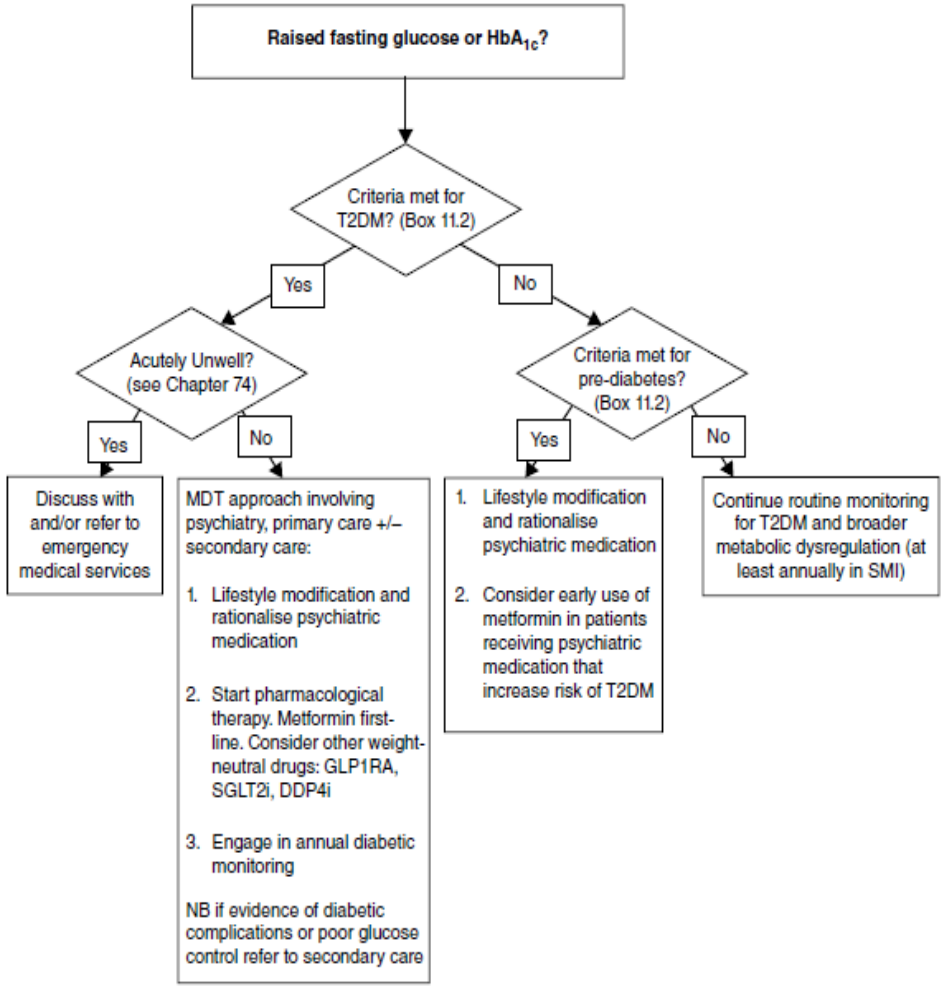


Figure 11.1 Approach to management of type 2 diabetes mellitus (T2DM) in patients with serious mental illness. DPP4i, dipeptidyl peptidase-4 inhibitor; GLP1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Aripiprazole

- 3 RCTs Meta-analysis ; Mean Weight loss of 2.13 Kg[1]
- Switching to Aripiprazole decreases odds of MeS (OR -1.748) and improves Framingham risk score[2]
- FRS - twenty-four weeks of switch to aripiprazole resulted in calculated risk reduction in predicted CHD events over 10 years from 7.0% to 5.2% (reduction of 25.7%) [2]
- Cochrane review – Switch to Aripiprazole from Olanzapine leads to decreased weight, improved BMI, improved fasting glucose[3]
- Contrario – No differences between Aripiprazole when compared with Olanzapine in terms of rate of discontinuation and rates of MeS[3]

1 - Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis , Mizuno et al. 2014.
2 - Antipsychotic switching for people with schizophrenia who have neuroleptic-induced weight or metabolic problems , Mukundan et al 2010
3 - Metabolic syndrome and drug discontinuation in schizophrenia: a randomized trial comparing aripiprazole olanzapine and haloperidol , Parabiaghi 2016

Metformin

- 1000 – 1500 mg/day[1]
- Significant weight loss (Mean 3.17 kg) and reduction in BMI[1]
- Significant reduction in Waist Circumference (SMD 0.35) but not the waist hip ratio[1]
- Improves fasting glucose significantly (SMD 0.65) [1]
- Improves serum cholesterol (SMD 0.51), HDL (SMD 0.45) and Triglycerides (SMD 0.56) but not LDL (SMD 0.03)[2]
- No significant effects on the Blood Pressure[1]
- Significant adverse effects included – Diarrhea (NNH 6) and Nausea/ Vomiting (NNH 16) [1]

1 - Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis , Mizuno et al. 2014.
2 - Adjunctive metformin for antipsychotic-induced dyslipidemia: a meta-analysis of randomized, double-blind, placebo-controlled trials, Jiang et al. 2020

Topiramate

- 100 – 400 mg
- May have additional role in improvement of psychopathology (SMD 0.57)
- Mean weight reduction of 3.14 kg
- Side effects - Paresthesia

Efficacy for Psychopathology and Body Weight and Safety of Topiramate-Antipsychotic Cotreatment in Patients With Schizophrenia Spectrum Disorders: Results From a Meta-Analysis of Randomized Controlled Trials, Correll et al 2016

Betahistine

- 3 RCTs
- Maximum evidence in counteracting the H1 antagonism related obesity and therefore – Clozapine, Olanzapine.
- High dose upto 144 mg; 37% reduction in mean weight gain (Upto 0.7 kg) barack 2016. Improves daytime alertness[1]
- 48 mg/ day – attenuates weight gain upto 1.95 kg[2]
- Does not decrease weight but aids in decreasing clozapine's propensity for weight gain (3 kg). Does not work as well with other antipsychotics[3]

1 - Betahistine decreases olanzapine-induced weight gain and somnolence in humans, Barak et al. 2016
2- A Randomized, Double-Blind, Placebo-Controlled Pilot Study of Betahistine to Counteract Olanzapine-Associated Weight Gain, Barak et al. 2016
3 - Betahistine effects on weight-related measures in patients treated with antipsychotic medications: a double-blind placebo-controlled study. Smith et al. 2018

RCT evidence

- D- Fenfluramine[1]
- Reboxetine – Betahistine combination[2]
- Zonisamide[3]
- Phentermine + Topiramate (Qysmia)[4]

1 - Goodall et al. A clinical trial of the efficacy and acceptability of D-fenfluramine in the treatment of neuroleptic-induced obesity. Br J Psychiatry. 1988
2- Poyurovsky et al.. Reducing antipsychotic-induced weight gain in schizophrenia: a double-blind placebo-controlled study of reboxetine-betahistine combination. Psychopharmacology (Berl). 2013
3 – Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP) , Allison et al. 2012

Other agents

- Reboxitine: Weight loss – 1.9 kg (9 RCTs for efficacy, 3 for weight loss)[1,2]
- Sibutramine: Weight loss – 2.86 kg (3 RCTs)[3]
- Melatonin and Ramelteon[4]
- Orlistat – OTC Medicine[3]

1 - Goodall et al. A clinical trial of the efficacy and acceptability of D-fenfluramine in the treatment of neuroleptic-induced obesity. Br J Psychiatry. 1988
2 – Zheng et al. Adjunctive Reboxetine for Schizophrenia: Meta-analysis of Randomized Double-blind, Placebo-controlled Trials
3 – Poyurovsky et al.. Reducing antipsychotic-induced weight gain in schizophrenia: a double-blind placebo-controlled study of reboxetine-betahistine combination. Psychopharmacology (Berl). 2013
4 - Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP) , Allison et al. 2012

Emerging evidence

- Naltrexone-Bupropion
- Liraglutide
- Tesofensine - NA, DA, and 5HT reuptake inhibitor
- Bupropion and zonisamide combination
- Pramlintide (Leptin analogue) and metreleptin (amylin analogue) combination

GLP 1 analogues

Acta Psychiatrica Scandinavica

SYSTEMATIC REVIEW | Open Access

Glucagon-like peptide agonists for weight management in antipsychotic-induced weight gain: A systematic review and meta-analysis

Maarten Bak, Bea Campforts, Patrick Domen, Therese van Amelsvoort, Marjan Drukker

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FindIT

Maarten Bak and Bea Campforts are shared first authors.

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GLP 1 analogues

Effectiveness: Exenatide and liraglutide, effectively reduce weight and BMI in patients with antipsychotic-induced weight gain, with liraglutide showing more consistent and significant results.

Safety: GLP-1 agonists do not worsen psychiatric symptoms, and while nausea, vomiting, and diarrhea were common side effects, they were generally tolerable; further research is still necessary to confirm long-term efficacy and safety.

Bariatric surgery

- Body mass index loss at 5 years post-surgery was 12 to 17
- The complication rate was 17%
- Reoperation rate was 7%
- Gastric bypass was more effective in weight loss but associated with more complications
- Adjustable gastric banding had lower mortality and complication rates; yet, the reoperation rate was higher and weight loss was less substantial
- Mortality rate within 30 days was 0.31%

Chang et al. 2014. Bariatric surgery: an updated systematic review and meta-analysis, 2003–2012. JAMA Surgery

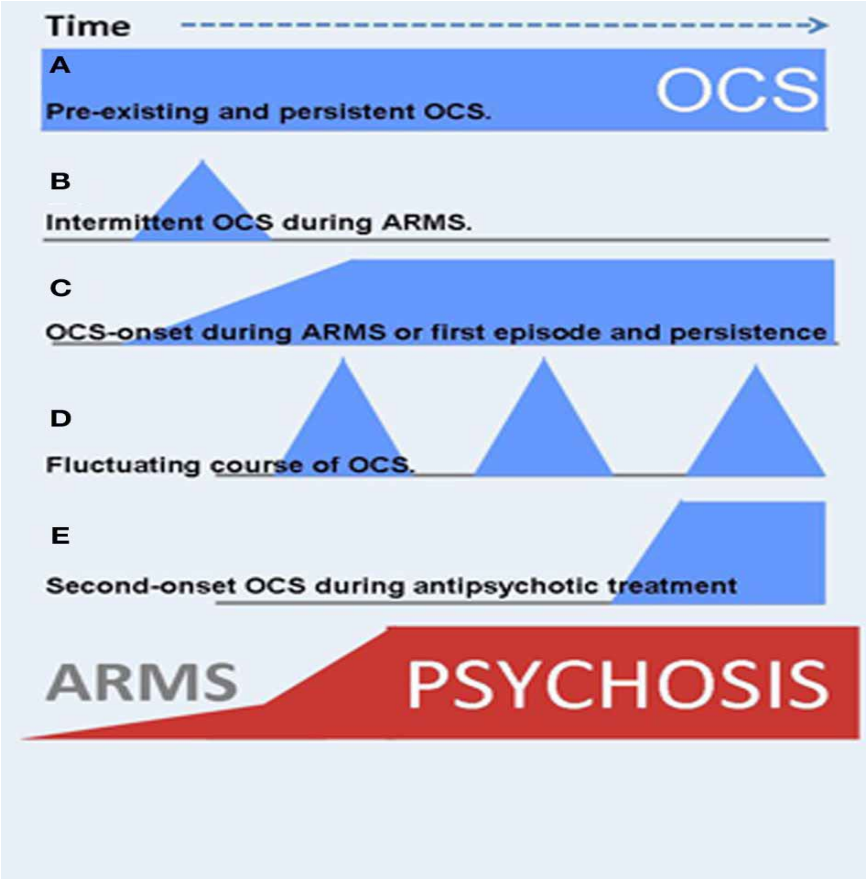
Clozapine and OC symptoms

Different studies suggest an effect of AAPs on serotoninergic receptors in the basal ganglia as a crucial mechanism.

Both 5-HT2A and 5-HT2C receptor antagonism

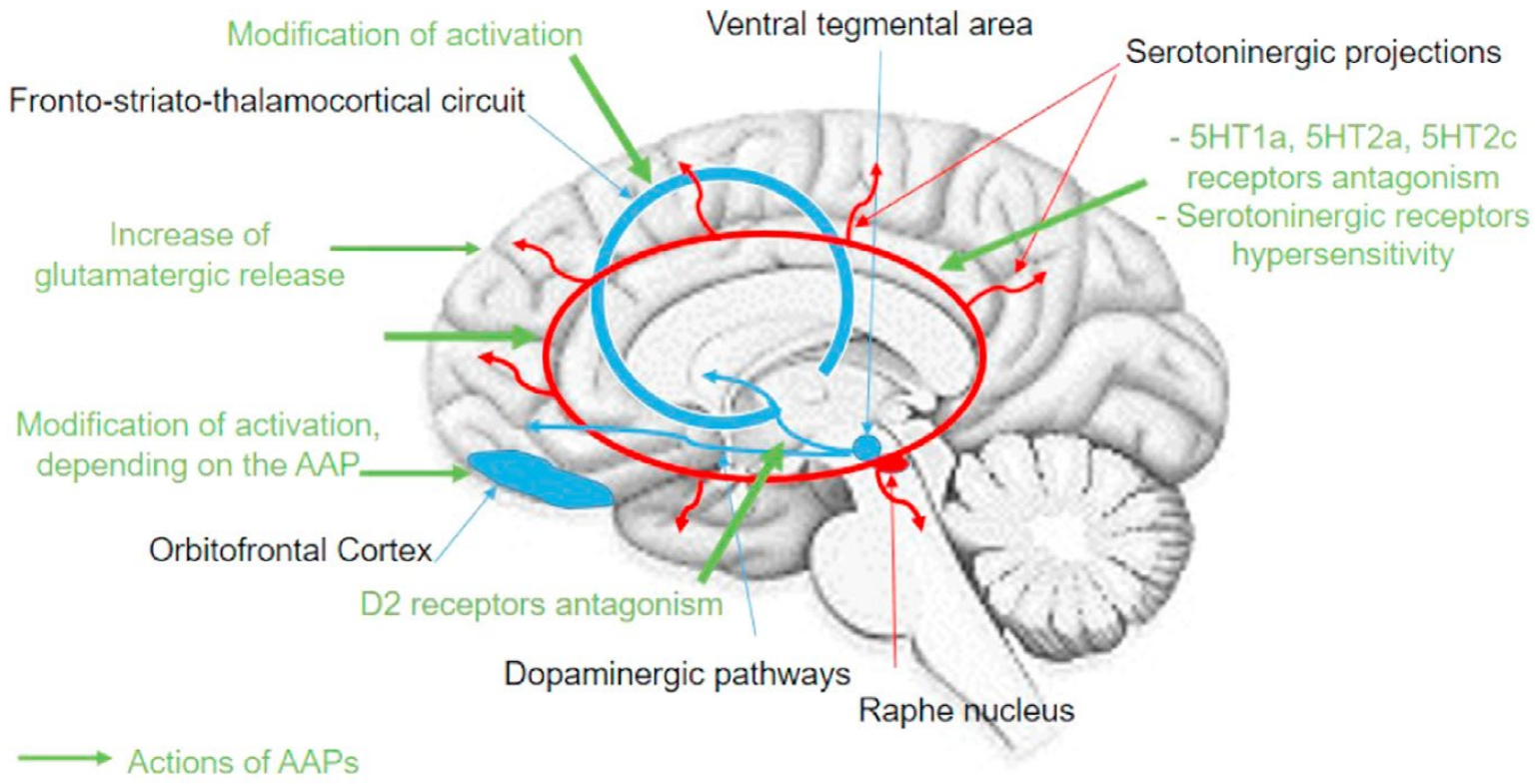
For clozapine this effect, combined with low anti-dopaminergic potency, could explain induced OCS

Clozapine and OC symptoms – A complex relationship



Clozapine-Induced Obsessive-Compulsive Symptoms in Schizophrenia: A Critical Review. Frederike Schirmbeck and Mathias Zink 2012

Antipsychotic induced OC Symptoms



Serotonin-dopamine interaction and its relevance to schizophrenia S Kapur, G Remington

Arguments for Antipsychotic induced OC Sx

- The prevalence rates of OCS in schizophrenia increased after market approval of clozapine
- The comorbidity rates in later disease stages are higher than at first manifestation of schizophrenia
- Schizophrenia patients with comorbid OCS are most frequently found to be treated with clozapine
- The severity of OCS is positively correlated with duration, dosage and serum levels of clozapine treatment
- Dose response relationship

Clozapine-Induced Obsessive-Compulsive Symptoms in Schizophrenia: A Critical Review. Frederike Schirmbeck and Mathias Zink 2012

Comparison of clinical characteristics and comorbidity in schizophrenia patients with and without obsessive-compulsive disorder: schizophrenic and OC symptoms in schizophrenia, Poyurovsky et al. 2003

Statistics – In persons at risk for SCZ

1. OC Sx can occur in between 5 % to 30 % [1]
2. Males at more risk[3]
3. In those with insidious onset, negative symptoms and long period of attenuated psychosis[4]
4. May be a/w depression and suicidality [3]
5. Are NOT predictors for transition from prodrome into psychosis[5]
6. Sx profile – aggressive, checking, hoarding[1,2]

1. Marine et al. 2015;
2. Soyata et al. 2018;
3. Hur et al. 2012;
4. Iida et al. 1995;
5. McAusland 2017

Antipsychotic induced OC Sx

1. Clozapine, risperidone, and olanzapine implicated
2. Causes de novo OC Sx in about 25 %
3. Worsens pre-existing OC Sx in 15 %

1. Foneska et al. 2014
2. Schirmbeck 2011
3. Schirmbeck 2014

When do OC Sx emerge after antipsychotics?

1. Few weeks to 12 months [Clozapine induced OC Sx]
2. For Risperidone induced OC Sx paradox – there is a dose relationship
3. Mechanism - 5-HT2A and 5-HT2C receptor antagonism

1. Sa et al. 2009
2. Dold et al. 2015
3. Schirmbeck et al. 2015

Management principle

Adequate treatment of psychosis may treat OC Sx as well

Management

1. Low dose Aripiprazole, Risperidone, Memantine and Neuromodulation
2. Evidence for Ziprasidone in pre-existing overlap
3. Additionally consider antipsychotics with negligible serotonergic properties
4. APA guidelines: concurrent use of SSRI [Escitalopram/Sertraline]
5. Level C evidence for worsening of psychosis with Fluvoxamine and Clomipramine although it improves OC Sx significantly.
6. Reduction of dose and changing over to HPL/ ARP/ AMI in cases of SGA induced OC Sx. If it fails add SSRI> CBT

1. Poyurvovsky et al. 2000
2. Juven Wetzler et al. 2014
3. Stryger et al. 2013
4. Koran et al. 2010
5. Shamra et al. 2019

Management

- Augmentation with antidepressants: Clomipramine, fluvoxamine and other SSRIs. [Level of evidence: RCTs, CS, CR]
- Augmentation with mood stabilizers (lamotrigine, valproic acid) aiming at a reduction of SGA-dosage to minimally sufficient levels [Level of evidence: CS, CR]
- Combination of pro-obsessive SGAs with neutral or anti-obsessive SGAs (amisulpride, aripiprazole) in order to reduce the clozapine-dosage to minimally sufficient levels [Level of evidence: RCT, CS, CR].

Schirmbeck and Zink 2013

Psychotherapy

- CBT – ERP [Level of evidence: CS, CR]
- Improvement was seen in up to 70% of cases

Schirmbeck and Zink, 2012; Tundo et al., 2012

Clozapine induced OC symptoms

- Consider 5% reduction in dose per month till OC symptoms reduce
- If you use SSRI, avoid CYP interactions
- Sertraline [Minimal CYP interaction, No QT prolongation as compared to Escitalopram] may be preferred
- ? Role of Aripiprazole
- Psychotherapeutic interventions

Clozapine-Induced Obsessive-Compulsive Symptoms in Schizophrenia: A Critical Review; Frederike Schirmbeck and Mathias Zink

Agranulocytosis, neutropenia

Antibodies against myeloperoxidase

Clozapine oxidized to Nitrenium ion (dehydrogenation of the piperazine ring of CLO/NC/CNO) inside neutrophils

Hapten based – Immune response against haptenized neutrophils

Direct toxicity of BM Stromal cells

Histamine 4 receptors mediated immune dysfunction

Agranulocytosis, neutropenia

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Direct toxicity of BM Stromal cells

Histamine 4 receptors mediated immune dysfunction

Acta Psychiatrica Scandinavica

Agranulocytosis in patients treated with clozapine. A study of the Finnish epidemic

H A Amsler, L Teerenhovi, E Barth, K Harjula, P Vuopio

PMID: 920225 DOI: 10.1111/j.1600-0447.1977.tb00224.x

Fundamental concepts

- Clozapine is associated with neutropenia and not leucopenia
- Be aware of Benign ethnic neutropenia
- Risk may be increased with co-prescribed medications. E.g. Valproate.
- The risk of clozapine induced agranulocytosis is same as any other antipsychotic after 1 year of treatment[3,4]

1- Alvir et al., 1993; 2 - Myles 2008; 3 -Taylor et al., The Maudsley Prescribing Guidelines in Psychiatry 13th edition; 4 – Flanagan et al., 2008

Risk

- Incidence - 0.8% at 1 year (Incidence of Neutropenia is higher at 2-3%)[1,2]
- Death due to neutropenia – 1 per 7700 people exposed to clozapine (0.0013%)[2]
- Increasing age at more risk[2]
- Although idiosyncratic, majority of the agranulocytosis occurred in first 3 months[1-4] [80 % in first 18 weeks]
- The risk of clozapine induced agranulocytosis is same as any other antipsychotic after 1 year of treatment[3,4]

1- Alvir et al., 1993; 2 - Myles 2008; 3 -Taylor et al., The Maudsley Prescribing Guidelines in Psychiatry 13th edition; 4 – Flanagan et al., 2008

Lithium – a double edged sword

- Increases WBC acutely and chronically
- Mean raise of 2000 per mm^3
- Minimum of 0.4 mmol/l may be needed. However, subsequently may not produce a dose related response
- GM- CSF and demargination
- Probably has a role in non-clozapine related neutropenia
- Neurological toxicity with lower doses

Taylor et al., The Maudsley Prescribing Guidelines in Psychiatry 13th edition

G-CSF

- ? Masking impending neutropenia or agranulocytosis
- A/E – Bone pain and neutrophil dysplasia
- A test dose of 300 µg subcutaneously
- Thrice weekly doses of 300 µg might be necessary

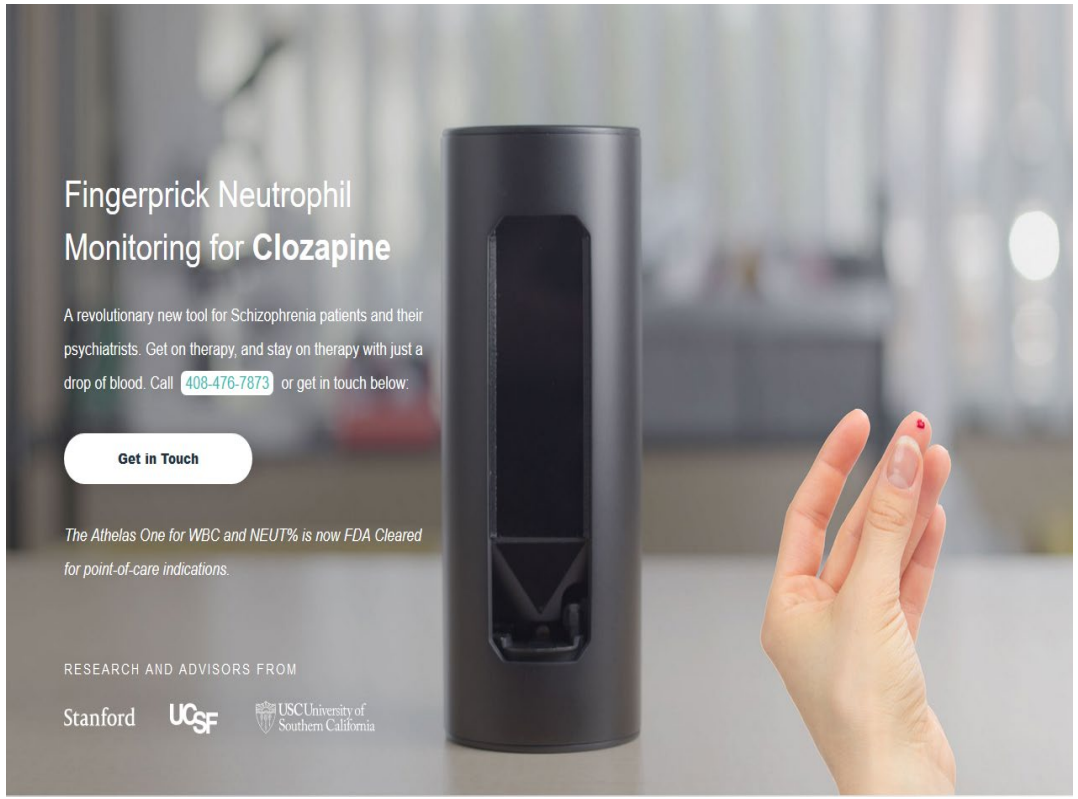
Myles, N., Myles, H., Clark, S. R., et al. (2017). Use of granulocyte-colony stimulating factor to prevent recurrent clozapine-induced neutropenia on drug rechallenge: A systematic review of the literature and clinical recommendations. Australian & New Zealand Journal of Psychiatry, 51, 980–989

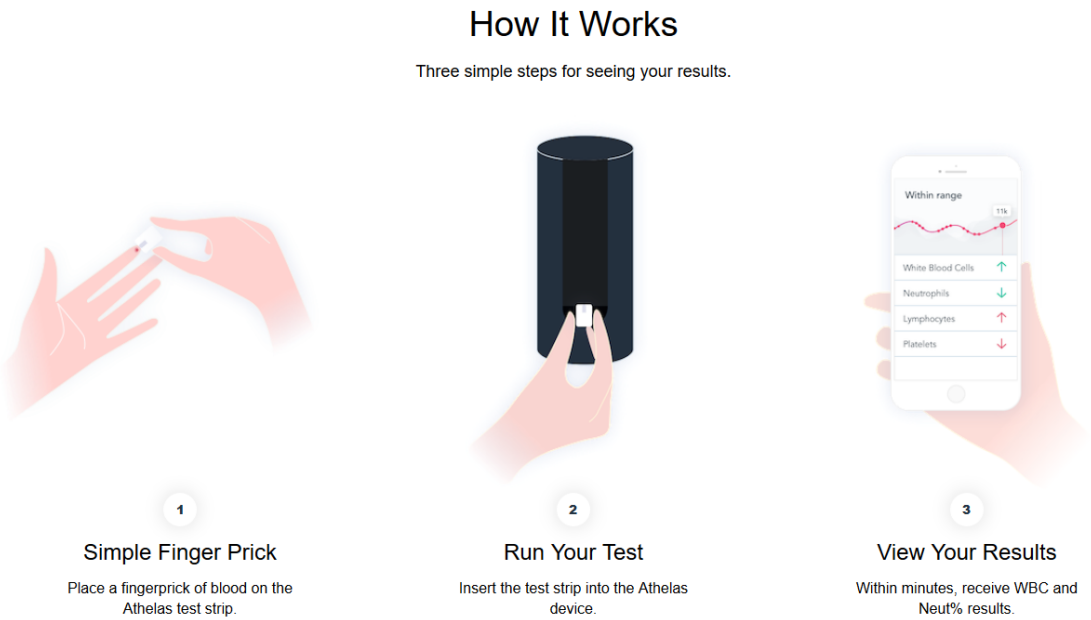
What if there is severe neutropenia?

- < 500/ mm^3
- Case fatality rate of 2.1 %
- How long will it last ? 12 to 21 days
- Stop clozapine
- Admit in a sterile ward
- Filgrastim

Myles, N., Myles, H., Xia, S., et al. (2018). Meta-analysis examining the epidemiology of clozapine-associated neutropenia. Acta Psychiatrica Scandinavica, 138, 101–109.

Point-of-Care (POC) blood monitoring devices





Contraindications to clozapine rechallenge

- If the total WBC count falls below 2000/mm^3 or the ANC falls below 1000 /mm^3, bone marrow aspiration should be considered to ascertain granulopoietic status and patients should not be rechallenged with clozapine [FDA].
- Drastic low WBC count
- Severe neutropenia [Neutrophils < 500/mm^3]
- Prolonged neutropenia

1- Alvir et al., 1993; 2 - Myles 2008; 3 -Taylor et al., The Maudsley Prescribing Guidelines in Psychiatry 13th edition; 4 – Flanagan et al., 2008

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