Managing the Nonhematological Adverse Effects of Clozapine

Faculty

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Disclosures

Jonathan Meyer, MD (Chair)

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None

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None

Agenda

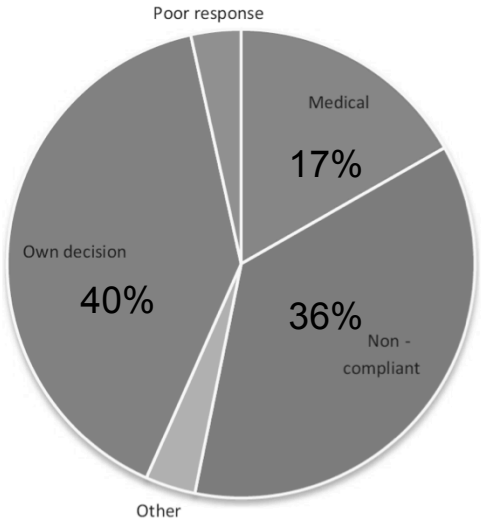
1. The Data on Clozapine Discontinuation Due to Adverse Effects: It's Not Just Neutropenia - Jonathan Meyer MD
2. The Big Three- Sialorrhea, Constipation, Orthostasis - Jennifer O'Day MD
3. Myocarditis, Fever, Tachycardia and Cardiomyopathy - George Proctor MD
4. Metabolic Effects, Sedation- George Proctor MD
5. Seizure Risk - Jonathan Meyer MD –
6. Question and Answer – Panel

Learning Objectives

1. At the conclusion of this session, the participant will be able to understand that treatable issues are common reasons for clozapine discontinuation, not severe neutropenia
2. At the conclusion of this session, the participant will be able to understand the evidence-based recommendations for management of sialorrhea, constipation, orthostasis, tachycardia, metabolic effects, sedation, and seizure risk
3. At the conclusion of this session, the participant will be able to understand the evidence-based approaches to fever, and when to appropriately consider work-up for myocarditis

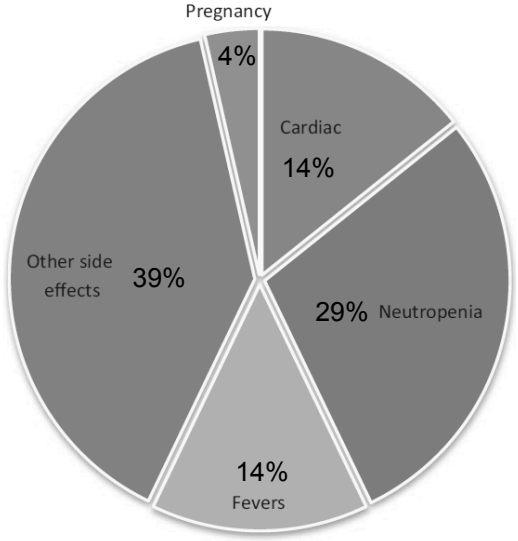
Reasons for Discontinuing Clozapine

Reasons for Clozapine Discontinuation: Data from 173 Cases in Australia (2001-10)



Pai NB and Verella SC. Acta Psychiatrica Scandinavica 2011; 125: 39-44.

Medical Reasons for Clozapine Discontinuation in Australian Outpatient Sample (n=173)



Pai NB and Verella SC. Acta Psychiatrica Scandinavica 2011; 125: 39-44.

Literature Review: Medical Reasons for Clozapine Discontinuation

Review of 81 papers through September 10, 2012. Medical reasons for discontinuation divided into 4 categories:

1. **Cardiovascular:** myocarditis & cardiomyopathy, QTc > 500 msec, tachycardia, orthostasis, nonspecific EKG changes, atrial flutter
2. **Hematological:** neutropenia, agranulocytosis, eosinophilia, thrombocytopenia, thrombocytosis, leukocytosis
3. **Cardiometabolic:** weight gain, hypertension, dyslipidemia, DM & metabolic syndrome, DKA or hyperosmolar hyperglycemic states
4. **Other:** seizures, constipation/ileus, benign fever, NMS, VTE, hepatic impairment

Comment: the list focuses on reasons why MDs interrupt therapy, but omits 2 common patient cited reasons: sedation and sialorrhea.

Nielsen J, et al. J Clin Psychiatry 2013; 74(6): 603-13

Cardiovascular Causes

Complication	Grounds for Discontinuation	Comments
QTc prolongation	QTcF > 500 msec	Confirm QTc using Fridericia formula (not Bazett)
Myocarditis	Troponin ≥ 2x ULN, along with other criteria	Rechallenge not recommended
Cardiomyopathy	Echo confirmation	Rechallenge not recommended
Orthostasis	Recurrent syncope despite measures	May rechallenge with slower titration, and all measures
Sinus tachycardia	**Never**	Exclude myocarditis/myopathy. Treatable with β-blockers
Nonspecific ST/T Wave Changes	**Never**	Exclude myocarditis/myopathy and other cardiac disease
Atrial flutter	EKG/Holter confirmation	May rechallenge if cause other than clozapine identified

Nielsen J, et al. J Clin Psychiatry 2013; 74(6): 603-13

Cardiometabolic Causes

Complication	Grounds for Discontinuation	Comments
Weight gain	**Almost never**	Try behavioral approaches, metformin
Arterial hypertension	**Almost never**	Usual management
Dyslipidemia	**Almost never**	Usual management, especially agents that lower triglycerides (e.g. niacin SR)
DM	OOC diabetes	Try usual management first and correct other diabetogenic causes. Generally manageable.
Metabolic syndrome	**Almost never**	Treat individual components
DKA or HHS	Acute episode	Hold clozapine during acute episode. Rechallenge after stabilization with tight monitoring.

Nielsen J, et al. J Clin Psychiatry 2013; 74(6): 603-13

Other Causes

Complication	Grounds for Discontinuation	Comments
Benign fever	**Never**	Assuming other causes ruled out.
NMS	If meets consensus criteria (Gurrera J Clin Psych 2011)	Hold antipsychotics and treat. Rechallenge with slower titration.
Venous thromboembolism	Repeated VTE	Hold clozapine and treat VTE. Rechallenge if on prophylaxis.
Constipation	Ileus or subileus	Pause clozapine and try all measures.*
Hepatic impairment	AST/ALT 2-3x ULN	Reduce dose or pause until normalized.
Seizures	**Never**	Lower or divide doses, or treat with valproate.

*** Extensive local experience with lubiprostone in these cases.**

Nielsen J, et al. J Clin Psychiatry 2013; 74(6): 603-13

Success Rates for Rechallenge from Serious Adverse Events

- **Review of published cases 1972-2011**
  - **138 instances where patients rechallenged with clozapine**
  - **Authors recommended rechallenge if lower bound of 95% CI > 50% for success**

Adverse Effect	Success Rate		95% CI
NMS	100%	(5/5)	56 – 100%
Myocarditis *	75%	(3/4)	30 – 95%

* Subsequent case series document 4/8 successful rechallenges after myocarditis, with one case of recurrent myocarditis. 3/8 stopped for nonspecific symptoms. (Ronaldson J Clin Psych 2012)

Manu P, et al. When can patients with potentially life-threatening adverse effects be rechallenged with clozapine? A systematic review of the published literature. Schizophrenia Res 2012; 143: 180-186.

Sialorrhea, Constipation, Orthostasis

Muscarinic Receptor Distribution

M1	M2	M3	M4	M5
salivary glands, GI tract, CNS (memory)(1)	cardiac muscle (slows heart rate), CNS	smooth muscle of the bladder, bronchioles, GI tract, and endothelial cells, eye, salivary glands (bronchocon-striction, vasodilation, induces emesis, eye accommodation) CNS	CNS	CNS

M1, M2, and M4 predominate in the CNS and are important in learning and memory. M1 and M4 play a role in motor control and pharmacotherapy of psychosis.[2]

1. Messer W, et al. Evidence for a preferential involvement of m1 muscarinic receptors in representational memory. Neurosci Lett 1990;116: 184-9.
2. Chew M, et al. A model of anticholinergic activity of atypical antipsychotic medications. Schizophrenia Research 2006;88:63-72.

Sialorrhea

- **Incidence:** 30-80%, not strongly dose dependent. Some tolerance may develop over time.
- **Concerns:** social impairment, risk for aspiration pneumonia
- **Mechanism:** likely from norclozapine's M_1 agonism
  - Evidence: Pirenzepine, an M_1 selective antagonist with limited CNS penetration previously used in Europe to decrease gastric acid secretion is effective for clozapine-induced sialorrhea.
- **Preferred Treatments:** lowering the dose if possible, or locally applied medications to avoid systemic effects of oral anticholinergics:
  - Atropine 1% ophthalmic drops: 1-2 gtts sublingually, initially at bedtime, and if needed up to tid. Recommend that patients swish and spit to spread the medication around the oral mucosa.
  - Ipratropium bromide 0.03% or 0.06% nasal spray: 1-2 puffs orally swish and spit, and if needed up to tid

Bird AM, Smith TL, Walton AE. Current treatment strategies for clozapine-induced sialorrhea. Ann Pharmacother. 2011;45:667-75
Gurrera RJ. Aspiration pneumonia an underappreciated risk of clozapine treatment. J Clin Psychopharm 2016; 36(2): 174-176

Sialorrhea

Second Line Treatments:

- Glycopyrrolate 2 to 4 mg at night
  - Evidence: A randomized trial compared glycopyrrolate with biperiden. Both associated with reduced rate of drooling, but a larger decrease seen in glycopyrrolate group.
  - Glycopyrrolate does not penetrate the blood-brain barrier, avoiding central anticholinergic effects such as impaired memory.
  - **However, it adds to clozapine's significant peripheral anticholinergic burden and increases risk for ileus.**
- Other treatment approaches, based on case reports or case series:
  - Use of sugarless chewing gum to increase the rate of swallowing
  - Anticholinergic agents (e.g. 5 to 15 mg/day of trihexyphenidyl)
  - Alpha-2 agonists (e.g. 0.1 to 0.5 mg/day of clonidine)
  - Alpha-1 antagonist (e.g. 1 to 2 mg qhs of terazosin)

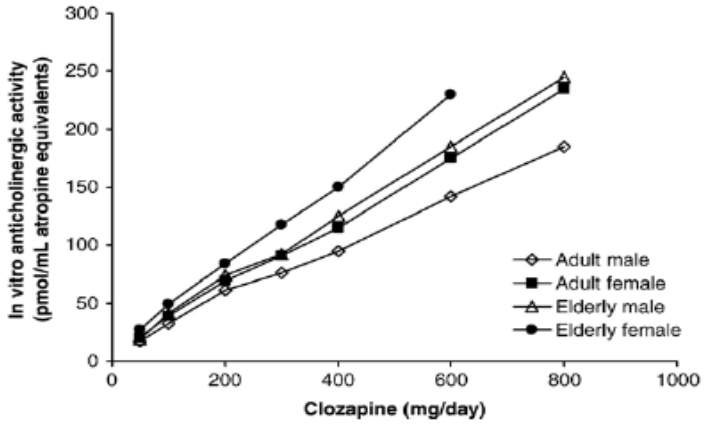
Liang CS, et al. Comparison of the efficacy and impact on cognition of glycopyrrolate and biperiden for clozapine-induced sialorrhea in schizophrenic patients: a randomized, double-blind, crossover study. Schizophr Res. 2010;119(1-3):138.

Constipation

- Due to potent **M_1** (1.4 M) and moderate **$5HT_3$** (50 nM) antagonism
  - 100 mg clozapine ~ 2 mg benztropine
- **Incidence:** up to 60%, and 1.3% develop ileus
  - Management is a critical part of clozapine treatment
  - Multiple fatalities due to obstruction
- Danish study of ileus incidence in 26,720 schizophrenia patients from records 1996-2007
  - Treatment with **clozapine** (OR: 6.73 CI: 1.55–29.17) **or anticholinergics** (OR: 5.88 CI: 1.47–23.58) were **associated with increased risk of fatal ileus.**

Nielsen J and Meyer JM. Risk factors for ileus in patients with schizophrenia. Schiz Bull 2012; 38(3):592-8

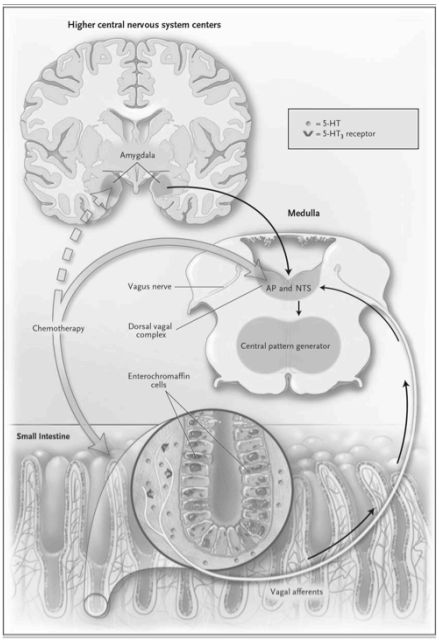
Dose Dependent Increases in Anticholinergic Activity (**AA**) with Clozapine



Chew M, et al. A model of anticholinergic activity of atypical antipsychotic medications. Schizophrenia Research 2006;88:63-72.

5-HT_3 Antagonism and Constipation

- 5-HT_3 receptor distribution
  - Vagal afferents
  - Solitary tract nucleus (STN)
  - Area postrema
- Serotonin is released by the enterochromaffin cells of the small intestine and may stimulate vagal afferents (via 5-HT_3 receptors) to initiate the vomiting reflex/gastric motility.
- 5-HT_3 receptor antagonists suppress vomiting and nausea by inhibiting serotonin binding to the 5-HT_3 receptors, thereby decreasing motility.



Hesketh PJ. N Engl J Med 2008 358: 2482-2494.

Clozapine and Constipation: Other Factors

Other contributing factors (aside from muscarinic and $5HT_3$ antagonism):

- H_1 antagonism- sedation resulting in inactivity, clozapine has a higher affinity than other sedating antipsychotics
- Clozapine patients are usually an extremely ill cohort
- Patients with schizophrenia may have decreased pain sensitivity
- Patients with schizophrenia often have a sedentary lifestyle due to negative symptoms

Nielsen J and Meyer JM. Risk factors for ileus in patients with schizophrenia. Schizophrenia Bulletin 2010, 1-7.

Constipation Management - 1

- **KUB often considered prior to treatment to document baseline**
  - emphasize to patient (and staff) need to report if no BM > 48 hours
  - encourage adequate fluid intake
- **Minimize other anticholinergics!!**
  - At start of treatment routine docusate, especially if clinical or KUB evidence of constipation. Dose: 250 mg PO qD or bid
- **Additional agents can be added including:**
  - **Osmotic laxatives (pick only one):**
    - Polyethylene glycol 3350: 17 grams in 4-8 oz. water qD (Preferred based on superior evidence for efficacy)
    - Lactulose: start 15 mL qhs, max 30 mL bid
  - **Stimulating laxatives (pick only one):**
    - Senna glycosides (8.6 mg tabs) : start 17.2 mg qhs, max 34.4 mg bid OR
    - Bisacodyl 5 – 15 mg qD, max 30 mg/d

Nielsen J and Meyer JM. Risk factors for ileus in patients with schizophrenia. Schiz Bull 2012; 38(3):592-8

Constipation Management - 2

If the combination of docusate + PEG-3350 + a stimulant is not effective there is one evidence-based option:

– **Lubiprostone 8-24 mcg PO bid**: very effective, often obviates the need for other agents, but expensive. Typically reserved for those who have failed the above or who have had a history of ileus with clozapine.[2]

Comments:

– **DO NOT add bulk forming laxatives (e.g. psyllium) to patients who are currently constipated! It can exacerbate the problem.** Can be added once patient has regular BMs ***and*** *if they maintain adequate water intake.*

– **Vomiting, especially feculent vomitus, or abdominal pain should prompt immediate examination and probable referral to ER for evaluation of ileus or obstruction. [1]**

1. Nielsen J and Meyer JM. Risk factors for ileus in patients with schizophrenia. Schiz Bull 2012; 38(3):592-8.
2. Meyer JM, Cummings MA. Lubiprostone for treatment-resistant constipation associated with clozapine use. Acta Psych Scand 2014; 130(1): 71-72.

Available Laxatives and Strength of Recommendations to Treat Chronic idiopathic Constipation According to GRADE Criteria [a]

	Recommendation [b]	Quality of Evidence [c]
Bulk Agents:		
Psyllium, methylcelluose, calcium polycarbophil, wheat dextrin	**Strong**	**Low**
Nonabsorbed substances		
PEG 3350	**Strong**	**High**
Lactulose [d]	**Strong**	**Low**
Stimulants		
Bisacodyl	**Strong**	**Moderate**
Senna	**NA**	**NA**
Secretory drugs [d]		
Lubiprostone	**Strong**	**High**
Linaclotide	**Strong**	**High**

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; NA, not assessed; PEG3350, polyethylene glycol 3350–electrolyte.
a.From American College of Gastroenterology Monograph on the Management of Irritable Bowel Syndrome and Chronic Constipation. American Journal of Gastroenterology 2014; 109: S2-S26.
b.Strong recommendation indicates the committee felt that most individuals should receive the treatment and recommendation would apply to most clinical situations.
c.Low quality of evidence suggests that future research is very likely to affect future assessments and recommendations.
d.Prescription only.

Cost Comparison of Treatments

Cost Comparison of Constipation Treatments [a]

Treatments	Cost per Month 2015 $US
Nonabsorbed substances	
PEG 3350 (17 g daily) [b]	18.25
Lactulose (20 g daily)	144.00
Stimulants	
Senna (2 tabs daily)	0.34
Bisacodyl (2 tabs daily)	0.75
Secretory drugs	
Lubiprostone (24 µg twice daily)	293.02
Linaclotide (145 µg daily)	283.70

Abbreviation: PEG 3350, polyethylene glycol 3350–electrolyte.
[a] Data from the University of Wisconsin. Retail costs are higher.
[b] Data from Super Target, Madison, Wisconsin, December 2015

Wald A. Constipation: Advances in diagnosis and treatment. JAMA 2016; 315(2):185-191

Orthostasis

- **Due to α_1-adrenergic antagonism**
- **Incidence:** up to 20%, especially early in treatment. Some tolerance may develop.
- **Management strategies:**
  - Use standard or slower dose titration, and lowest effective dose based on clinical response and plasma levels
  - Encourage adequate fluid intake, may add NaCl if possible
  - Minimize use of concurrent α_1-adrenergic antagonists and benzodiazepines
  - **If patient remains symptomatic:**
    - Volume expansion with 9α-fludrocortisone 0.1 mg PO qD. May increase every 1-2 weeks by 0.1 mg increments. Max 0.3 - 0.4 mg/d as higher doses rarely more effective.
    - 9α-fludrocortisone is a potent mineralocorticoid that increases Na+ reabsorption -> water retention and increased intravascular volume. Cannot be used in pts with CHF.

Testani M. Clozapine-induced orthostatic hypotension treated with fludrocortisone. J Clin Psychiatry 1994;55(11):497-8.

Myocarditis, Fever, Tachycardia and Cardiomyopathy

Case

- Clozapine is initiated
- After 2 weeks, patient has:
  - Tachycardia
  - Low grade fever
  - Chest discomfort
  - Dyspnea
  - Fatigue

What should you do?

Fever

- Benign fever and flu-like symptoms in 55% of patients during first month of clozapine
  - Consider additional CBC to r/o infection, neutropenia
- Fever work-up should consider:
  - routine sources of infection, myocarditis (if other symptoms present), inflammatory conditions (including DRESS, acute interstitial nephritis [rare])
- Fever workup:
  - WBC/ANC, EKG, Troponin I/T, chem panel (for LFTs, renal function)

Benign fevers are NOT a reason to discontinue clozapine treatment, though it may be temporarily held during work-up

Nielsen, J., et. al. (2013). Termination of clozapine treatment due to medical reasons: when is it warranted and how can it Be avoided?. *The Journal of clinical psychiatry*, *74*(6), 603-613.

Fever

Incidence

- In a sample of 93 consecutive new clozapine starts 20.4% had at least one oral temp ≥ 38.0° C [100.4° F]
- Mean time to fever onset: 13.8 ± 5.1 days (range 3-26)
- Mean fever duration: 3.8 ± 2.6 days (range 1-9)
- At 1 year, there was no difference in discontinuation rates between those who developed fever (21.0%) and those with no fever (24.3%), or in the incidence of severe adverse effects

Benign fevers are NOT a reason to discontinue clozapine treatment, though it may be temporarily held during work-up

Tham JC & Dickson RA. Clozapine-induced fevers and 1-year clozapine discontinuation rate. J Clin Psych 2002

Tachycardia

- Incidence: 25%, especially early in treatment. Some tolerance may develop.
- Due to combined effects of α_1-adrenergic and M_1 antagonism
  - Leads to sympathetic hyperactivity
- Usually benign, but if left untreated, a risk factor for dilated cardiomyopathy
- May be related to rate of titration and dose
- In the literature may be a cause for clozapine discontinuation in 4% of patients
  - Generally one of the more easily managed problems

Meyer JM, et al. Clozapine and dilated cardiomyopathy. *Clinical Schizophrenia & Related Psychoses* 2007; 1(2): 175-180.
Lally J, et al. Pharmacological interventions for clozapine-induced sinus tachycardia. *Cochrane Database Syst Rev* 2016 Jun 9; (6):CD011566
Stryjer, R. et al. (2009). β-Adrenergic antagonists for the treatment of clozapine-induced sinus tachycardia: a retrospective study. Clin Neuropharmacol 2009; 32(5):290-2

Tachycardia and QT_c

- Prolonged QT_c (> 500 msec) is associated with arrhythmias such as Torsades de Pointes
- Bazett rate correction formula significantly overcorrects the QTc for faster heart rates
- Fridericia formula handles tachycardia better

Bazett Formula: **QTcB =** $QTcB = QT / \sqrt{R-R}$

Fridericia Formula: **QTcF =** $QTcF = QT / \sqrt[3]{R-R}$

Meyer, J., Rao, S., & Nielsen, J. (2007). Clozapine and dilated cardiomyopathy. *Clinical Schizophrenia & Related Psychoses*, *1*(2), 175-180.
Nielsen, J., et. al. (2011). Assessing QT interval prolongation and its associated risks with antipsychotics. CNS drugs, 25(6), 473-490.

Tachycardia

Table 1: R-R Intervals For Various Heart Rates With Square Root and Cube Root Calculations

Heart Rate (BPM)	R-R Interval (sec)	$\sqrt{R-R}$	$\sqrt[3]{R-R}$
60	1.00	1.00	1.00
72	0.83	0.91	0.94
80	0.75	0.87	0.91
90	0.67	0.82	0.87
100	0.60	0.77	0.84
110	0.55	0.74	0.82
120	0.50	0.71	0.79

Table 2: Example: Uncorrected QT = 400 msec

Heart Rate (BPM)	QTcB (Bazett) (msec)	QTcF (Fridericia) (msec)
60	400	400
72	438	425
80	462	440
90	490	458
100	516	474
110	542	490
120	566	504

Nielsen, J., et. al. (2011). Assessing QT interval prolongation and its associated risks with antipsychotics. CNS drugs, 25(6), 473-490.

Tachycardia

- **Management strategies:**
  - Use standard titration, and lowest effective dose
  - Minimize use of concurrent α_1-adrenergic and M_1 antagonists
- **Symptomatic tachycardia, and persistent tachycardia with rates ≥ 110 BPM must be treated**
  - Long-standing tachycardia is well recognized for its potential to induce dilated cardiomyopathy.
  - Beta blockers are agents of choice, **usually atenolol** as it is much less lipophilic than propranolol and unlikely to cause CNS effects
  - Low doses (e.g. atenolol 12.5 mg qam) used initially until tolerance for beta blockade is established to minimize risk of hypotension

Meyer JM, et al. Clozapine and dilated cardiomyopathy. *Clinical Schizophrenia & Related Psychoses* 2007; 1(2): 175-180.
Lally J, et al. Pharmacological interventions for clozapine-induced sinus tachycardia. *Cochrane Database Syst Rev* 2016 Jun 9;(6):CD011566

Myocarditis – Early Reviews

- 1993-9 Killian Australian review
  - 15 cases of myocarditis within 3 weeks of clozapine start, 5 of which were fatal
  - Eosinophilic infiltrate noted
  - Type I IgE mediated hypersensitivity reaction
  - Novartis Australia circulates cardiac monitoring guidelines 1999
- 2001 WHO review of reported antipsychotic drugs association with myocarditis and cardiomyopathy:
  - 231 cases reported with clozapine
  - 89 cases reported for all other antipsychotics
- 2007 Australian review of 116 cases of suspected myocarditis:
  - 116 cases reported to the ADR registry 1993-2003
  - Danger period during first 4 weeks
  - "Wide diversity of nonspecific symptoms that occur in afflicted patients"

Kilian, J. G., et. al. (1999). Myocarditis and cardiomyopathy associated with clozapine. *The Lancet*, *354*(9193), 1841-1845.
Coulter, D. M., et. al. (2001). Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study. *BMJ*, *322*(7296), 1207-1209.
Haas, S. J., et. al. (2007). Clozapine-associated myocarditis. *Drug Safety*, *30*(1), 47-57.

Myocarditis - Associated Features

- 2010 analysis of 38 cases and 47 clozapine-treated controls from Australia
- Mean clozapine exposure: **17.6** ± **2.3 days** (range 14 - 22 days)

	Present	Absent	Unknown
Persistent HR > 100 BPM (x 24hrs)	**34**	**4**	**0**
Tachycardia ≥ 120 BPM	**30**	**8**	**0**
Fever (> 37° C)	**33**	**5**	**0**
Chest Pain	22	16	0
T-Wave Abnormalities	27	9	2
ST elevation/depression	14	22	2
Eosinophil Count > ULN	23	12	3
Eosinophil Count ≤ 100/µL	6	29	3
Troponin I/T Level ≥ 2x ULN	**31**	**5**	**2**

Ronaldson, K. J., Taylor, A. J., et. al. (2010). Diagnostic characteristics of clozapine-induced myocarditis identified by an analysis of 38 cases and 47 controls. *Journal of Clinical Psychiatry*, *71*(8), 976.

Myocarditis – Proposed Dx Criteria

New signs of cardiac dysfunction (e.g. persistent HR > 100 BPM for ≥ 24 hours, 3rd heart sound, basilar rales, peripheral edema)

PLUS at least one of the following:

a. Elevated cardiac enzymes: troponin

b. EKG changes consistent with myocarditis without other cause (≥ 1 mm ST depression or T wave inversion in 2 or more contiguous leads excluding aVR)

c. CXR evidence of heart failure

d. Other diagnostic evidence of L or R ventricular systolic dysfunction (e.g. echo, gated pool scan)

e. MRI scan consistent with myocarditis

ABSENCE of alternative plausible etiologies:

- Confirmed viral infection
- Exposure to other possible causative agents
- Other likely causes (e.g. acute MI, NMS, pneumonia, pulmonary embolism, sepsis, etc.)

Ronaldson KJ, et al. Diagnostic characteristics of clozapine-induced myocarditis identified by an analysis of 38 cases and 47 controls. J Clin Psychiatry 2010; 71(8): 976-81

Myocarditis – Later Reviews

- 2011 Australian analysis of 75 potential clozapine-myocarditis cases compared 94 controls:
  - Time to onset 10-33 days
  - Troponin I/T level ≥ 2x ULN in 90% of cases
  - **5 cases** with CRP > 100 mg/L and LV impaired on echocardiography **without increased troponin**
- 2015 Australian review of 250 cases of suspected myocarditis with clozapine:
  - Review of published cases up to 2014
    - **Incidence may be ~3%** (1.1%-5.0%)
    - Previous incidence estimated < 0.1%
  - **Highest risk** period is **first month**: 82% occurring 14-21 days
  - Increased risk with fast clozapine titration, concurrent VPA

Ronaldson, K. J., et. al. (2011). A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. *Australian and New Zealand Journal of Psychiatry*, *45*(6), 458-465.
Ronaldson, K. J., Fitzgerald, P. B., & McNeil, J. J. (2015). Clozapine‐induced myocarditis, a widely overlooked adverse reaction. *Acta Psychiatrica Scandinavica*, *132*(4), 231-240.

Myocarditis – Monitoring, Tx

Ronaldson's protocol (2011): **sensitivity high, specificity unknown**

- Suggested baseline of troponin I/T, CRP, echo
- Weekly troponin I/T and CRP, Can increase to daily if suggestive features
- Stop clozapine if troponin I/T ≥ 2x ULN (troponin I/T >2.0 ng/ml)

Reasonable protocol:

- Clinical suspicion: tachycardia, fever, dyspnea, flu-like illness
- Troponin I/T or CRP to confirm: troponin I/T > 2.0 ng/ml; CRP > 10.0 mg/l

If the above are positive: **stop clozapine**, **send to hospital**

- To prevent **cholinergic rebound**: 50-75 mg clozapine = 1 mg benztropine

?Rechallenge: If benefits outweigh risks, well after myocarditis is resolved (mos)

- Collaborate with cardiologist; slow titration, frequent monitoring
- **7/12 rechallenge cases reported in literature were successful**

Ronaldson, K. J., et. al. (2011). A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. *Australian and New Zealand Journal of Psychiatry*, *45*(6), 458-465. de Leon, et. al. (2003). Serum antimuscarinic activity during clozapine treatment. *Journal of clinical psychopharmacology*, *23*(4), 336-341. Manu P, et al. When can patients with potentially life-threatening adverse effects be rechallenged with clozapine? A systematic review of the published literature. Schizophrenia Res 2012; 143: 180-186.

Cardiomyopathy

Largest series: 41 cases from FDA records (1989-99)

- Male: 78%
- Median age: 34 years (range 20-59)
- Median duration of clozapine: 9 mos (range 14 d-7 yrs)
- Deaths: 24%

¼ the risk of myocarditis (< 0.1%). Features:

- Dilated and non-specific cardiomyopathy
- Ventricular dilatation, contractile dysfunction, CHF
- Most emerge at 6-9 months
- suspect with: increased fatigue without recent change in dose or addition of other sedating medications, or obvious signs/Sx: S3, peripheral edema, basilar rales or other signs of heart failure

Dx: Echocardiography or other imaging for definitive diagnosis

La Grenade L, et al. Myocarditis and Cardiomyopathy Associated with Clozapine Use in the United States. NEJM 2001; 345(3): 224-5.
Merrill, D. B., Dec, G. W., & Goff, D. C. (2005). Adverse cardiac effects associated with clozapine. *Journal of clinical psychopharmacology*, *25*(1), 32-41.
Ronaldson, K. J., et. al. (2011). A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. *Australian and New Zealand Journal of Psychiatry*, *45*(6), 458-465.
Meyer, J., Rao, S., & Nielsen, J. (2007). Clozapine and dilated cardiomyopathy. *Clinical Schizophrenia & Related Psychoses*, *1*(2), 175-180.

Cardiomyopathy - Management

- **Management approach:**
  - Remove clozapine (possibly reversible)
  - Provide anticholinergic coverage is stopped abruptly
  - Manage as with CHF from other causes
    - Diuretics, beta blockers, ACE inhibitors
- **Prognosis:**
  - Mortality 12-24%
  - May improve after removal of clozapine
  - Clozapine **rechallenge not recommended**
- Question is whether there are any viable options for patient
  - Obvious ethical dilemmas, especially in patients with low ejection fractions
  - Patients with decision making capacity may choose to remain on clozapine rather than suffer from unremitting psychosis

Merrill, D. B., Dec, G. W., & Goff, D. C. (2005). Adverse cardiac effects associated with clozapine. *Journal of clinical psychopharmacology*, *25*(1), 32-41.
Meyer JM, et al. Clozapine and Dilated Cardiomyopathy. Clin Schiz & Rel Psychoses 2007; 1(2): 175-80.
Curto, M., teal. (2016). Systematic review of clozapine cardiotoxicity. *Current psychiatry reports*, *18*(7), 1-18.

Metabolic Effects, Sedation

Metabolic Changes

- **Weight gain: due to appetite increase from H_1 antagonism**
  - Associations with polymorphisms in the promoter regions of the leptin gene and the 5HT2C receptor
  - Management: diet, exercise and possibly **metformin**
- **Lipids:** mechanism unknown, but greatest impact on triglycerides, to a lesser extent on cholesterol parameters
  - Management: statins/fibrates as indicated
    - Triglycerides > 500 mg/dL presents a risk for pancreatitis and should be aggressively treated
- **Glucose:** multiple mechanisms including weight gain, personal risk factors (ethnicity, race, family Hx, h/o gestational DM), direct impact on glycemic control independent of weight gain
  - Management: diet, exercise and possibly **metformin**

Meyer JM. Antipsychotics and metabolics in the post-CATIE era. Current Topics in Behavioral Neurosciences 2010; 4: 23-42

Is Clozapine Much Worse than Other APs?

Retrospective analysis of pts on clozapine (n=96) vs. other AP (n=211). Mean duration of cloz use: 7.6 yrs [1]

- **Results:** no statistically significant differences between clozapine and other antipsychotic groups on the basis of mean BMI (31 vs. 32 kg/m^2); or prevalence of type 2 DM (17% vs. 18%); dyslipidemia (35% vs. 39%); htn (32% vs. 39%); or obesity (48% vs. 54%).
- **Conclusion:** "We found no evidence of increased risk in any individual measure for those receiving clozapine."

What about the rare but serious diabetic ketoacidosis (DKA)?

Of the 11 cases examined at Massachusetts General Hospital 1995-2001, mean A1C on admission was 13.3 ± 1.9%, suggesting a significant period of poorly controlled DM prior to the DKA episode. [2]

1. Kelly, A. C., et. al. (2014). A naturalistic comparison of the long-term metabolic adverse effects of clozapine versus other antipsychotics for patients with psychotic illnesses. *J Clin Psychopharm*, *34*(4), 441-445.
2. Henderson DC, et al. Henderson Elevated Hemoglobin A1c as a Possible Indicator of Diabetes Mellitus and Diabetic Ketoacidosis in Schizophrenia Patients Receiving Atypical Antipsychotics. J Clin Psych 2007; 68(4): 533-541.

Pharmacological Management of Clozapine Induced Obesity and Metabolic Syndrome

- 2016 Review of 15 RCTs
  - 60-75% have wt gain of ≥ 10%
- Effective agents:
  - Metformin (3 RCTs)
    - Robust effect on body mass index and waist circumference and small beneficial effect on blood lipids and insulin levels
    - Benefits stop when metformin is stopped
  - Aripiprazole (2 RCTs)
    - Beneficial effect on clozapine-induced obesity and metabolic syndrome
  - Orlistat (1 RCT)
    - Beneficial body weight effect only and only in men

Zimbron, J., et. al. (2016). A systematic review and meta-analysis of randomised controlled trials of treatments for clozapine-induced obesity and metabolic syndrome. *Eur. Neuropsychopharm.*, *26*(9), 1353-1365.

Metformin for Metabolic Prophylaxis

- Multiple studies for AP associated weight gain and metabolic changes
  - Increases insulin sensitivity, reduces hepatic glucose production, improves peripheral glucose uptake and regulation
  - Reduces glucose absorption in a dose-dependent manner by effects on mucosal and serosal glucose transfer, **but does not increase insulin secretion**
  - Impact seen in new users of olanzapine and clozapine started on metformin concurrently, with positive data on minimization of ongoing weight gain and glycemic parameters in established users of olanzapine and clozapine
- One double-blind 14-wk study of 61 patients (94.4% schizophrenia) on clozapine (196.8 ± 132 mg/d) for >86.5 ± 40.6 months, assigned to metformin 500-1000 mg/d (n=31) or placebo (n=30)

  Completer analysis: 24/31 metformin subjects completed the study
  - Wt changes: MET: −1.87 ± 2.9 kg vs. PBO +0.16 ± 2.9 kg; p=0.01 (effect size: 0.70).
  - Other: insulin and TG-HDL ratio significantly decreased ($p<0.05$, effect size 0.59 & 1.99 respectively), HDL-C significantly increased (p=0.001, effect size 0.95).

Carrizo E, et al. Extended release metformin for metabolic control assistance during prolonged clozapine administration: A 14 week, double-blind, parallel group, placebo-controlled study. Schiz Research 2009; 113: 19-26

Managing Metformin

Risks:

- Lactic acidosis: 8.1 per 100,000 person-years, but increased in context of renal dysfunction or CHF
  - Original package insert states contraindicated with serum Cr ≥ 1.4 and 1.5 mg/dL levels in women and men, respectively
  - In UK, eGFR threshold used: **reevaluate metformin if eGFR < 45, and stop if < 30**
- Diarrhea: up to 50%, associated with higher initial doses and rapid titration
  - Keep starting doses to 500 mg qam first week, then 500 mg BID 2nd week. Titrate slowly to higher doses.

Lipska KJ, Use of Metformin in the Setting of Mild-to-Moderate Renal Insufficiency. Diabetes Care 2011; 34: 1431-37

Sedation

- Due to combined effects of histamine H_1 and muscarinic M_1 antagonism
- Incidence at least 40% (may resolve within 6-12 weeks)
- **Management strategies:**
  - Use standard titration, and lowest effective dose based on clinical response and plasma levels
  - Maintain bulk of daily dose at night. Single evening doses up to 500 mg are well tolerated.
  - Minimize use of concurrent sedating medications especially agents with central muscarinic properties (e.g. oxybutynin)
- Does modafinil work?
  - 4 double-blind, randomized, placebo controlled studies at doses from 200-300 mg/d
  - Only one study proved positive. No apparent risk of symptomatic worsening.

Saavedra-Velez C, et al. Modafinil as an adjunctive treatment of sedation, negative symptoms, and cognition in schizophrenia: a critical review. J Clin Psychiatry. 2009 Jan;70(1):104-12.

Seizures

Clozapine and Seizures

- Antipsychotics have been demonstrated to reduce seizure threshold
- EEG studies indicate high prevalence of EEG abnormalities in clozapine-treated patients
  - 59%-67% of patients without clinical evidence of seizure activity demonstrate EEG abnormalities
  - Given high prevalence of EEG abnormalities in clozapine-exposed patients without seizures, **routine EEG surveillance is not recommended as it has limited predictive value**
  - Anticonvulsants should not be added based on EEG findings in the absence of clinical seizure activity
- Overall seizure risk appears dose dependent with clozapine, but cases exist for seizures with very low dose exposure

Spatz R. The incidence of abnormal EEG patterns with clozapine therapy. Arzneimittelforschung 1978; 28(9):1499-500
Pacia SV, Devinsky O. Clozapine-related seizures: experience with 5,629 patients. Neurology 1994; 44:2247
Wong J, Delva N. Clozapine-induced seizures: recognition and treatment. Can J Psychiatry 2007 ; 52(7):457

Clozapine Seizure-Incidence

- In a review of 1418 patients treated with clozapine, the cumulative seizure risk was estimated to be 10% after 3.8 years of treatment.
- Higher doses of clozapine were associated with a greater rate of seizures:
  - 600 mg/day or more: 4.4%
  - 300 to 600 mg/day: 2.7%
  - 300 mg/day or less: 1.0%

Pacia SV, Devinsky O. Clozapine-related seizures: experience with 5,629 patients. Neurology 1994; 44:2247
Wong J, Delva N. Clozapine-induced seizures: recognition and treatment. Can J Psychiatry 2007 ; 52(7):457.

Seizure Type and Frequency

Seizure type	*n*	%	Mean dosage of clozapine, mg daily (*n* = available sample)
Generalized			
Tonic-clonic	55	54	461 (*n* = 49)
Myoclonic	23	23	535 (*n* = 15)
Atonic	1	1	600 (*n* = 1)
Myoclonic and atonic	4	4	488 (*n* = 4)
Tonic-clonic with other seizure types	12	12	419 (*n* = 12)
Partial			
Simple	3	3	400 (*n* = 2)
Complex	3	3	275 (*n* = 1)
Total	101	100	

Wong J, Delva N. Clozapine-induced seizures: recognition and treatment. Can J Psychiatry 2007 ; 52(7):457.

Clozapine Related Seizure Management

Seizures are NOT a reason to stop clozapine treatment

Management Strategies

- Temporary reduction back to prior tolerable dose
  - Greatest reduction of seizure threshold occurs at maximal plasma (and brain levels). Reducing C_{max} by dividing large single doses is also helpful
  - If above strategies are not successful (i.e. a 2nd sz occurs), or pt requires a dose at or above their seizure threshold -> anticonvulsant treatment
- Depakote is agent of choice: best covers the full spectrum of seizures (tonic-clonic, myoclonic) and has limited kinetic interactions with clozapine
  - Phenytoin is less effective for myoclonic seizures and lowers plasma clozapine levels 50%
  - Carbamazepine is contraindicated due to possible leukopenia

Wong J, Delva N. Clozapine-induced seizures: recognition and treatment. Can J Psychiatry 2007 ; 52(7):457.

Conclusions

- Many patients are deprived of adequate clozapine trials due to inadequate management of common nonhematologic adverse effects
- Most common adverse effects from clozapine are manageable
  - Seizures, sialorrhea, constipation, orthostasis, and metabolic issues should not be reasons to terminate clozapine
  - Lubiprostone for refractory constipation, even with h/o ileus
- Clozapine treated patients are often tachycardic
  - Use the Fridericia QT correction formula if HR > 72 to avoid mistaken assumptions about QTc