Managing the Nonhematological Adverse Effects of Clozapine

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Disclosures

Jonathan Meyer, MD (Chair)
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None

George Proctor, MD
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)

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

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.


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Cardiovascular Causes

<table>
<thead>
<tr>
<th>Complication</th>
<th>Grounds for Discontinuation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc prolongation</td>
<td>QTcF &gt; 500 msec</td>
<td>Confirm QTc using Fridericia formula (not Bazett)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Troponin ≥ 2x ULN, along with other criteria</td>
<td>Rechallenge not recommended</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Echo confirmation</td>
<td>Rechallenge not recommended</td>
</tr>
<tr>
<td>Orthostasis</td>
<td>Recurrent syncope</td>
<td>May rechallenge with slower titration, and all measures</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>Never</td>
<td></td>
</tr>
<tr>
<td>Nonspecific ST/T Wave Changes</td>
<td>Never</td>
<td></td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>EKG/Holter confirmation</td>
<td></td>
</tr>
</tbody>
</table>

## Cardiometabolic Causes

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


## Other Causes

<table>
<thead>
<tr>
<th>Complication</th>
<th>Grounds for Discontinuation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign fever</td>
<td>Never</td>
<td>Assuming other causes ruled out.</td>
</tr>
<tr>
<td>NMS</td>
<td>Never</td>
<td>Assuming other causes ruled out.</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>Repeated VTE</td>
<td>Hold antipsychotics and treat. Rechallenge with slower titration.</td>
</tr>
<tr>
<td>Constipation</td>
<td>Ileus or subileus</td>
<td>Hold clozapine and treat VTE. Rechallenge if on prophylaxis.</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>AST/ALT 2-3x ULN</td>
<td>Pause clozapine and try all measures.*</td>
</tr>
<tr>
<td>Seizures</td>
<td>Never</td>
<td>Reduce dose or pause until normalized.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower or divide doses, or treat with valproate.</td>
</tr>
</tbody>
</table>

* Extensive local experience with lubiprostone in these cases.

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

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Success Rate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMS</td>
<td>100%</td>
<td>(5/5)</td>
</tr>
<tr>
<td>Myocarditis *</td>
<td>75%</td>
<td>(3/4)</td>
</tr>
</tbody>
</table>

* 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)

### Muscarinic Receptor Distribution

<table>
<thead>
<tr>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
</tr>
</thead>
<tbody>
<tr>
<td>salivary glands, GI tract, CNS (memory)</td>
<td>cardiac muscle (slows heart rate), CNS</td>
<td>smooth muscle of the bladder, bronchioles, GI tract, and endothelial cells, eye, salivary glands (bronchoconstriction, vasodilation, induces emesis, eye accommodation)</td>
<td>CNS</td>
<td>CNS</td>
</tr>
</tbody>
</table>

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.\(^2\)


### 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

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)


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.

Dose Dependent Increases in Anticholinergic Activity (AA) with Clozapine


5-HT\textsubscript{3} Antagonism and Constipation

- 5-HT\textsubscript{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\textsubscript{3} receptors) to initiate the vomiting reflex/gastric motility.
- 5-HT\textsubscript{3} receptor antagonists suppress vomiting and nausea by inhibiting serotonin binding to the 5-HT\textsubscript{3} receptors, thereby decreasing motility.

Clozapine and Constipation: 
Other Factors

Other contributing factors (aside from muscarinic and 5HT₃ antagonism):

- H₁ 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


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

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 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

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

<table>
<thead>
<tr>
<th></th>
<th>Recommendation [b]</th>
<th>Quality of Evidence [c]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bulk Agents:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psyllium, methylcellulose,</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td>calcium polycarbophil,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>wheat dextrin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nonabsorbed substances</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG 3350</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>Lactulose [d]</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Stimulants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisacodyl</td>
<td>Strong</td>
<td>Moderate NA</td>
</tr>
<tr>
<td>Senna</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Secretory drugs [d]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lubiprostone</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>Linacotide</td>
<td>Strong</td>
<td>High</td>
</tr>
</tbody>
</table>

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; NA, not assessed; PEG3350, polyethylene glycol 3350–electrolyte.

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]

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

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

Orthostasis

- **Due to α1-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 α1-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.

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.

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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**

Tachycardia

- Incidence: 25%, especially early in treatment. Some tolerance may develop.
- Due to combined effects of $\alpha_1$-adrenergic and M1 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


Tachycardia and QTc

- Prolonged QTc (> 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

\[
\text{Bazett Formula: } \quad QTc_B = \frac{QT}{\sqrt{R-R}} \\
\text{Fridericia Formula: } \quad QTc_F = \frac{QT}{\sqrt{R-R}}
\]

Tachycardia

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

<table>
<thead>
<tr>
<th>Heart Rate (BPM)</th>
<th>R-R Interval (sec)</th>
<th>√(R−R)</th>
<th>(R−R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>70</td>
<td>0.83</td>
<td>0.91</td>
<td>0.94</td>
</tr>
<tr>
<td>80</td>
<td>0.75</td>
<td>0.87</td>
<td>0.91</td>
</tr>
<tr>
<td>90</td>
<td>0.67</td>
<td>0.82</td>
<td>0.87</td>
</tr>
<tr>
<td>100</td>
<td>0.60</td>
<td>0.77</td>
<td>0.84</td>
</tr>
<tr>
<td>110</td>
<td>0.55</td>
<td>0.74</td>
<td>0.82</td>
</tr>
<tr>
<td>120</td>
<td>0.50</td>
<td>0.71</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Table 2: Example: Uncorrected QT = 400 msec

<table>
<thead>
<tr>
<th>Heart Rate (BPM)</th>
<th>QTcB (Baselt) (msec)</th>
<th>QTcF (Fridericia) (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>70</td>
<td>438</td>
<td>425</td>
</tr>
<tr>
<td>80</td>
<td>462</td>
<td>440</td>
</tr>
<tr>
<td>90</td>
<td>490</td>
<td>458</td>
</tr>
<tr>
<td>100</td>
<td>518</td>
<td>474</td>
</tr>
<tr>
<td>110</td>
<td>542</td>
<td>490</td>
</tr>
<tr>
<td>120</td>
<td>566</td>
<td>504</td>
</tr>
</tbody>
</table>


Tachycardia

- **Management strategies:**
  - Use standard titration, and lowest effective dose
  - Minimize use of concurrent α₁-adrenergic and M₁ 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

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”


Myocarditis - Associated Features

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

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

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.)


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

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

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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

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Cardiomyopathy - Management

- **Management approach:**
  - Remove clozapine (possibly reversible)
  - Provide anticholinergic coverage if 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


Metabolic Effects, Sedation
Metabolic Changes

- **Weight gain**: due to appetite increase from H1 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**

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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**

- **Results**: no statistically significant differences between clozapine and other antipsychotic groups on the basis of mean BMI (31 vs. 32 kg/m²); 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.

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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


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).

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 $\geq$ 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 H1 and muscarinic M1 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.

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

**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%


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**Seizure Type and Frequency**

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>n</th>
<th>%</th>
<th>Mean dosage of clozapine, mg daily (n = available sample)</th>
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<tbody>
<tr>
<td>Generalized</td>
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<td></td>
<td></td>
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<tr>
<td>Tonic-clonic</td>
<td>55</td>
<td>54</td>
<td>461 (n = 49)</td>
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<tr>
<td>Myoclonic</td>
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<td>23</td>
<td>535 (n = 15)</td>
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<tr>
<td>Atonic</td>
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<td>1</td>
<td>600 (n = 1)</td>
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<td>4</td>
<td>488 (n = 4)</td>
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<tr>
<td>Tonic-clonic with other seizure types</td>
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<td>12</td>
<td>419 (n = 12)</td>
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<tr>
<td>Partial</td>
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<td>275 (n = 1)</td>
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<tr>
<td>Total</td>
<td>101</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

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<sub>max</sub> 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


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