Clozapine: Friend and Foe

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No Disclosures

…but off-label use of medication will be discussed
History of Clozapine

- Discovered in 1958 by an anesthetist
- Marketed heavily in late 1960s after a trial of 2200 patients
- Mid-1970s, clear choice for treatment of schizophrenia
- 27 September 1975, Lancet article - 18 Finns with agranulocytosis - active marketing stopped
- 1983 reconsidered by FDA (efficacy and safety)

Clozapine

- Used for treatment-resistant schizophrenia
  - 1988 Kane et al, Clozapine 7-8x as effective in tx psychosis
  - 1989 Meltzer et al, 2/3 of treatment-resistant patients responded to clozapine
- It is superior in its ability to reduce aggression (due to 5HT2 and 5HT1a antagonism)
- Often considered 3rd line

But wait, that’s not all…


Clozapine does even more!!!

- Approved for use in patients intolerant to other antipsychotics because of extrapyramidal symptoms
- Demonstrated reduction in psychiatric admissions frequency and duration
- Reduction in suicide rates
- Treats negative symptoms?
- Better cognitive responses compared to other medications
- CATIE showed patients were twice as likely to stay on clozapine
Act now and get:

- 37% employed on clozapine vs 14% on other meds
- 25% under compulsory treatment orders vs 46.4% on other medications (depot bias)
- In a 4-year study, patients who remained on clozapine for 3 years were 2x as likely to live independently (34% vs 18%)


Clozapine as 1st line?

- 11-year follow up of 66,881 patients
- Lowest mortality was Clozapine 0.74 (95% CI=0.60-0.91), p=0.0045
- Inverse relationship between use and mortality 0.991 (95% CI=0.985-0.997)


Relative risk of death according to cumulative use of specific antipsychotic drugs

- Risperidone
- Clozapine
- Thioridazine
- Quetiapine
- Haloperidol
- Olanzapine
- Perphenazine
Risk of death during current monotherapies

(A) Risk of death from any cause. (B) Risk of death from suicide. CIs for haloperidol and quetiapine are wide because of the low number of incidents in patients using these drugs. (C) Risk of death from ischemic heart disease.

Mortality=unadjusted absolute risk per 1000 person-years.

Clozapine issues

1. Cardiac issues – Myocarditis and Cardiomyopathy
2. Toxic Megacolon (fatal constipation) – now the leading cause of death associated with clozapine
3. Weight gain, diabetes, metabolic syndrome
4. Drooling, sedation, tremors, decreased seizure threshold, postural hypotension
5. Tachycardia at rest in ~25% of patients
6. Agranulocytosis in 1-2% of patients requiring frequent monitoring

Tachycardia

- Studies show 20%-50% of patients on clozapine will develop sinus tachycardia with no clinical significance. Patients with an elevated heart rate should be monitored for the development of additional symptoms.
Myocarditis
A medical emergency

- Inflammation of the heart muscle

Myocarditis: A rare but serious complication

- 10.3% mortality of patients with myocarditis
- Both incidence AND mortality are higher in clozapine patients (~10,000 x higher per Haas)
- Vast majority of cases occur in 1st two months of Rx (89% in our systematic review of the literature) – however cases reported up to 7 years after initiation
Myocarditis 101

- Inflammation of the heart muscle
- Initial sx: fever, tachycardia, flu-like symptoms
- Providers look for: Chest Pain, dyspnoea, palpitations, heart failure (orthopnea, paroxysmal nocturnal dyspnea, ankle edema)
- Labs: elevated troponin, CRP

Sensitivity for diagnosing myocarditis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV hypokinesis, reduced EF by echo</td>
<td>48%</td>
</tr>
<tr>
<td>ECG abnormalities</td>
<td>35%</td>
</tr>
<tr>
<td>Peripheral eosinophilia</td>
<td>35%</td>
</tr>
<tr>
<td>Elevated CK</td>
<td>22%</td>
</tr>
<tr>
<td>Troponin I</td>
<td>39%</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>17%</td>
</tr>
<tr>
<td>Cardiac MRI</td>
<td>75%</td>
</tr>
<tr>
<td>Endomyocardial biopsy</td>
<td>60-80% (Dallas criteria)</td>
</tr>
<tr>
<td>Autopsy</td>
<td>100%</td>
</tr>
</tbody>
</table>

Systematic review of clozapine induced myocarditis

- 8591 articles on clozapine
- 420 cardiac issues and clozapine
- 118 of these involved myocarditis in humans
Myocarditis review results – continued

- Dose: average dose 298mg
- Outcomes: reported mortality rate of 17%

Myocarditis review results - diagnosis

- Abnormal ECGs in 19/37 case reports with T wave abnormality noted 7/25.
- Abnormal chest X-rays in 10/13 case reports
- Abnormal echocardiogram in 20/33 - most common abnormality was decreased ejection fraction in 15/33.

Myocarditis sx continued

Mild-moderate symptoms – continue clozapine and clinician (GP or psychiatrist, whomever is reviewing) orders and follows up on:

a. Troponin, CRP, FBC, ECG and CXR
b. Dose not to be increased until results reviewed.
c. If negative, GP review and close follow-up for alternative explanation as well as weekly monitoring

Severe sx: Chest pain/fever/sudden SOB- admit to Auckland Hospital, General Medicine service
Myocarditis rechallenge

- Not recommended (prohibited) by all regulatory agencies (Medsafe, FDA) and manufacturers.
- 6 cases rechallenged,
  - 1 stopped again due to re-occurrence
- 3 additional patients continued through diagnosis of myocarditis
- Clinical Experience: Cautiously positive if alternative causes thought possible
- Only should be considered in the medical hospital

ADHB Myocarditis/Clozapine monitoring

Cardiomyopathy

- Weakness of the heart muscle aka Congestive Heart Failure
- Insidious
- Symptoms can include shortness of breath on exertion, worsening fatigue, ankle edema, orthopnea, paroxysmal nocturnal dyspnoea.
- Occurs from 4+ months on clozapine
Clozapine induced cardiomyopathy systematic review

- 8591 articles on clozapine
- 420 cardiac issues and clozapine
- 46 of these involved clozapine induced cardiomyopathy in humans

The search string included: {clozapine/adverse effects [MESH] or clozapine/contraindications [MESH] or Clozapine/toxicity [MESH] or clozapine (keyword)} AND (keywords: card* or cardio* or cardiotox* or cardiac* or cardiomy* or myocard* or heart) or heart [MESH]).

Results

<table>
<thead>
<tr>
<th>Mean age</th>
<th>35 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose</td>
<td>360 mg</td>
</tr>
</tbody>
</table>

Clinical presentation:
1. Shortness of breath (63.4%)
2. Palpitations (40.9 %)
3. Cough (18.2%)
4. Fatigue (13.6 %)
5. Atypical Symptoms (13.6%)
6. Chest pain (9%)

Average time for symptoms to develop: 14.5 months

Echo findings: Dilated Cardiomyopathy (specifically mentioned in 34% of cases)

My plan for private practice


- 16/116 *apparently healthy cats* had cardiomyopathy
Cardiomyopathy symptoms

- Worsening/new fatigue
- Shortness of breath
- Pedal edema
- Orthopnea
- Paroxysmal Nocturnal Dyspnea
- Abnormal heart/lung sounds
- Cardiomegaly on CXR

No clear guidelines for monitoring

- Regulatory agencies focused on agranulocytosis
- Novartis recommends routine echo at baseline and 6 months in Australia but no evidence for this and unlikely to be cost-effective from a public health point of view.
- USA guidelines vary; at Duke a baseline CXR and ECG, and BNP; then an ECG at any admission; a repeat CXR and ECG at 6 months are recommended but no evidence for this and not rigidly enforced. Low threshold for cardiology/rx, echocardiogram.
- May be a role for BNP in symptomatic patients, but no studies and $50 each test.

Guidelines for Cardiomyopathy sx monitoring at ADHB

- At Initiation
  - Echo around (usually within 4 weeks) of initiation
  - ECG at baseline and 3 months
  - CXR at baseline if none within 5 years
- After Initiation:
  - Regular screening for sx of heart failure
  - Low threshold for repeat echo
Cardiomyopathy pathway

- Severe symptoms – severe shortness of breath, edema – refer to ACH urgently (GenMed)
- Mild-moderate symptoms – GP review and/or low threshold for consideration of echocardiogram
- Abnormal echocardiogram should trigger Gen Med admission with psychiatry review

Recovery

- Literature on recovery from clozapine induced cardiomyopathy is controversial. Mortality is higher than the general population, but several case reports note a rebound in ejection fraction after cessation of clozapine.
- Anecdotally, patients with low ejection fraction at diagnosis (<25%) seem to do proportionally much worse

Rechallenge after cardiomyopathy – not for the faint of heart

- All regulatory agencies (Medsafe, FDA) and manufacturers recommend against this
- Paucity of data
- 1 successful case in the literature, 1 failed attempt
- Clinical experience generally negative
- Does not need to be a medical inpatient; but a clear plan with cardiology support is required before considering.
Interlude

- This guy went to see a highly recommend psychiatrist. The doctor showed the man an inkblot and asked, “What does this remind you of?”
- The guy replied, “A naked woman.”
- Then the shrink showed the man another inkblot and asked the guy the same question. The guy responded, “A naked woman on a bed.”
- This went on and on, inkblot after inkblot. The psychiatrist finally said to the guy, “You are a sick pervert.”
- The guy replied, “I’m not the pervert here. You’re the one who keeps showing me all of those naughty pictures.”

Managing Clozapine at ADHB
Policies and Guidelines Library:
Clozapine – Managing Toxicity

Common Pathway
- All patients with clozapine related problems come to General Medicine
- Other specialties consulted as necessary (cardiology, GI, surgery)
- Liaison Psychiatry referred ALL patients who are admitted to ACH on clozapine (even if not toxic or related to the reason for admission)
- ADHB Clozapine specialist role
Contact me with questions
Chris Kenedi
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Happy to share our evidence-based guideline.

The Case
- SN, 46 year-old male
- Extensive and violent criminal history over 20 years. Multiple incarcerations.
- History of abuse, gang involvement, methamphetamine use, alcohol abuse.
- Med Hx: TBI from motor vehicle accident -> Left sided hemiparesis, diabetes, smoker.
- Mason Clinic after assault; After several trials placed on clozapine in 1999

SN’s Case 2
- Over next 9 years, does well psychiatrically; engages with staff, drug free, outpatient transition, employed for some periods.
- Numerous A&E visits for chest pain with normal ECG, CXR and troponin each time.
- Several visits and Gastro r/v for constipation; they recommend reducing the dose and it gradually goes from 725mg/d to 425mg/d.
SN’s Case 3
- July 2009 during routine psychiatric r/v, noted to have increased dyspnoea on exertion. GP noted only “tachycardia.”
- Due to partial paralysis, no gross functional impairment
- Plan was to ask GP to refer to cardiology.
- However his vision began to deteriorate.

SN’s Case 4
- SN developed blurry vision and then gradually became blind in his left eye and began losing vision in his right eye.
- Imaging revealed 10 meningiomas, the largest of which pressed on/near his optic chiasm.
- Neurosurgery plans a procedure to remove 3, including the one affecting his vision.
- In preparation for surgery, SN stops smoking and psychiatry monitors clozapine levels to avoid increases.

SN’s Case 5
- Pre-op evaluation notes orthopnea, PND and an echo is ordered.
- Echocardiogram shows an ejection fraction of ~14%.
- Surgery cancelled and patient transferred to Hospital to come off of clozapine in an inpatient setting.
SN’s case

• SN had no recent symptoms of heart failure but due to hemiplegia was exerting himself very little
• No gross evidence of ischemia (many negative ECGs and troponins), but a history of smoking, diabetes
• A remote history (>10 years ago) of stimulant abuse and alcohol abuse
• Plan was to see if his EF improves; if this occurred before blindness, to reconsider surgery (8+hours)

Clozapine-Induced Gastrointestinal Hypomotility: More Than Just Constipation

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Disclosures

• No relevant financial relationships
• Off-label use of medication will be discussed
Case

- 60 y.o. male with longstanding paranoid schizophrenia
- Admitted from group home with abdominal pain and distention of several days in duration and vomiting for the previous 24 hours
- Patient seen in both family practice clinic and ED on day prior to admission; sent home after 3 soap suds enemas with only minimal results
- CT scan on admission: profound pneumatosis and portal venous gas with moderate grade partial small bowel obstruction

Case

- Medications: clozapine 100 mg AM and 300 mg HS, chlorpromazine 200 mg daily, polyethylene glycol (PEG) 3350 17 g daily, psyllium 3.4 g daily
- Recommended to hold clozapine and to consider holding chlorpromazine
- Developed delirium after one dose of clozapine 300 mg PO HS and five doses of chlorpromazine 25 mg IV QID
- Clozapine & chlorpromazine discontinued, psychotic symptoms managed with IV haloperidol for next 5 days until the ileus resolved

Case

- Disorganized thoughts and word salad speech upon ileus resolution
- Documented history of treatment-refractory psychotic symptoms
- Clozapine retitrated very slowly with an initial bowel regimen of PEG 3350 17 g daily and close monitoring of bowel movements
- Patient’s psychiatric condition slowly stabilized over the nearly 4 month admission
- Discharged to state mental health institute on clozapine 150 mg AM and 300 mg HS with docusate 200 mg BID, calcium polycarbophil 625 mg daily, PEG 3350 17 g BID
### Clozapine and Constipation

- Constipation may affect as many as 50% of those treated with clozapine.

- Proposed mechanisms: significant anticholinergic effects, possible contribution of 5-HT₂ and H₂ antagonism.

- Clozapine 300-600 mg/d has greater serum antimuscarinic activity than anticholinergic agents used to treat antipsychotic-induced parkinsonism.

- Higher serum antimuscarinic activity has been linked to clinical presentation of constipation.


### More Than Just Constipation

- Numerous case reports of significant gastrointestinal (GI) hypomotility with clozapine, including multiple fatalities.

- Mortality rate of 28% in one large case series.

- Mortality rate greater than agranulocytosis.

- Severe fecal impaction leading to feculent vomiting or bowel necrosis is a commonly reported cause of death in these cases.

- Almost 40% of reported cases of serious clozapine-induced GI hypomotility occurred within the first 4 months of initiating treatment.

- Several case of GI-related death occurred years after initiation of clozapine.

DeHert M et al. Eur Psychiatry 2011;26:34-44.

### Risk for Ileus in Schizophrenia

- Demographic risk factors
  - Increasing age (OR: 1.03)
  - Female sex (OR: 1.60)

- Drug Treatment risk factors
  - Tricyclic antidepressants (OR 2.29)
  - Opioids (OR: 2.14)
  - Clozapine (OR: 1.99)
  - High potency FGAs (OR: 1.81)
  - Anticholinergics (OR: 1.48)

- Risk factors for ileus-related death
  - Treatment with clozapine (OR: 6.73) or anticholinergics (OR: 5.88)

Risk for GI ADEs with Clozapine

- Proposed risk factors
  - Higher clozapine doses
    - Mean dose 428 mg/d in large case series of pts severe GI hypomotility, 535 mg/d in fatal cases
  - Concomitant use of other anticholinergic medications (e.g. benztropine, chlorpromazine)
  - Concomitant illness with fever
  - Concomitant CYP1A2 inhibitors

Management of Serious GI ADEs

- Recognize the problem
  - Patients who present with symptoms indicating a potentially life-threatening GI complication (e.g. abdominal pain with nausea in the context of constipation) require urgent treatment
  - Hold clozapine in the case of serious GI adverse events

Prevention of Serious GI ADEs

- Improve recognition
- Patient education
  - Clozapine-treated patients should be educated to seek immediate medical attention if abdominal pain/distension and vomiting occur
  - Avoid concomitant medications that may slow GI transit time (e.g. anticholinergic agents, opiates)
- Good bowel regimen
**Constipation Management**

- No established guidelines and no clear consensus on which is the best laxative
- Suggested strategies include PEG 3350, lactulose, or senna combined with docusate
- Combination of agents is often required
- Bulk-forming laxatives may be less preferable
- Close monitoring to ensure success of the chosen bowel regimen is necessary
- May consider minimizing the clozapine dose if possible, particularly if serum levels are 500-700 ng/mL

**Other Reported Treatments**

- **Lubiprostone**
  - Chloride channel activator
  - Case report, 24 mcg daily then BID with bowel regimen
- **Bethanechol**
  - Muscarinic agonist
  - Case report, 10 mg TID with bowel regimen
- **Orlistat**
  - Lipase inhibitor
  - Small RCT, 120 mg TID

**Orlistat for Clozapine-Induced Constipation**

- 16-week study of orlistat 120 mg TID vs placebo in clozapine-treated patients, N=54
  - Secondary completer analysis of study focused on weight loss
  - Clozapine doses 250-900 mg/d, mean 481 mg/d
  - Conventional laxatives used in 87% of patients
  - At week 4, constipation shifted to nonconstipation in 35% of patients in the orlistat group (P=0.035); remained significant at week 16
  - 20% of orlistat group continued to have self-reported constipation at endpoint
  - Overall, no strong data to support
Summary

- Constipation is common with clozapine
- In some cases, severe constipation can progress to small bowel obstruction and even death
- Patients receiving clozapine therapy should be regularly monitored for constipation and treated aggressively when constipation occurs
- No particular pharmacotherapy is preferred and multiple agents are often needed
- Continued evaluation of the success of the chosen bowel regimen is imperative

Reappraising the Role of Clozapine Therapeutic Drug Monitoring

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Conflict of Interest Disclosure

Honorarium - None
Stock or Patents - None
Consulting - None
Publishing/Royalties - None
Organization - None
Government - None

- Off-label use of medication will not be described
Objectives

- Describe the rationale for obtaining serum clozapine levels
- Assess the clinical implication of clozapine and norclozapine serum concentrations
- Formulate a therapeutic drug monitoring plan for patients prescribed clozapine

Select Clozapine Adverse Reactions

- Dose Dependent
  - Seizure
  - Constipation, ileus, obstruction
  - Pneumonia
  - Hypotension
  - Weight gain
  - Tachycardia
  - Sedation
  - (Sialorrhea)

- Idiosyncratic
  - Agranulocytosis
  - Myocarditis
  - Fever

Clozapine: Therapeutic Drug Monitoring

- Can play an important role for the safe and effective utilization of clozapine
- Laboratory values are reported as [clozapine] and [norclozapine] levels
- Reference levels and “toxicity” may vary between institutions
  - At Mayo Clinic
    - Clozapine: > 350 ng/mL
    - Norclozapine: [ n/a ]
    - Clozapine + Norclozapine: > 450 ng/mL
    - Elevated levels not “flagged”
**Why Therapeutic Drug Monitoring?**

1. When the drug of interest has a therapeutic range
   - Ineffective when too low
   - Toxic when significantly elevated

2. When alterations in drug levels may occur
   - Drug interactions
   - Impact of concurrent illness

3. Significant interpatient variability

4. When nonadherence or overadherence is suspected

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**Clozapine: Therapeutic Drug Monitoring**

- Numerous studies have evaluated the utility of clozapine levels in clinical practice
  - The majority concluded levels >350 ng/mL are more likely to produce a clinical response

- No correlations between norclozapine levels and response
  - Norclozapine levels can be useful to evaluate the clozapine to norclozapine ratio
### Clozapine: Therapeutic Drug Monitoring

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>N =</th>
<th>“Therapeutic Level”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ackenheil, et al. (1976)</td>
<td>26</td>
<td>No correlation</td>
</tr>
<tr>
<td>Thorup and Fog (1977)</td>
<td>11</td>
<td>No correlation</td>
</tr>
<tr>
<td>Perry, et al. (1991)</td>
<td>29</td>
<td>&gt;350 ng/mL</td>
</tr>
<tr>
<td>Haegawa, et al. (1993)</td>
<td>59</td>
<td>&gt;370 ng/mL</td>
</tr>
<tr>
<td>Potkin, et al. (1994)</td>
<td>58</td>
<td>&gt;420 ng/mL</td>
</tr>
<tr>
<td>Kronig, et al. (1995)</td>
<td>45</td>
<td>&gt;350 ng/mL</td>
</tr>
<tr>
<td>VanderZwaag, et al. (1996)</td>
<td>56</td>
<td>&gt;250 ng/mL</td>
</tr>
<tr>
<td>Spina, et al. (2000)</td>
<td>45</td>
<td>&gt;350 ng/mL</td>
</tr>
</tbody>
</table>

### Clozapine: Therapeutic Drug Monitoring

- Controversy exists regarding an upper limit
  - **Upper limit:**
    - Significant concern for side effects: > 900-1300 ng/mL.
    - >700 ng/mL results in a lack of incremental benefit and increase risk of side effects:
      - Seizure
      - Constipation, obstruction, perforation
      - Pneumonia
  - However: Treat the patient, not the number

### Clozapine: Therapeutic Drug Monitoring

- Clozapine:norclozapine ratio should be examined
  - 1.5:1 to 2:1 = “normal metabolizers”
  - Maximizes efficacy while reducing side effects
  - Inverted ratios (e.g. 1:2) may have a poor response and increased side effects
    - 1A2 rapid metabolizers or presence of inducer
  - Non-trough levels may artificially produce a ratio >2:1

- Norclozapine: 70%
  - 1A2: 3A4, 2C19
  - Clozapine-N-oxide: 3A4

Legare, Med Hypothesis. 2013
Kuo CJ. Schizophren Bull. 2013
Why Therapeutic Drug Monitoring?

1. When the drug of interest has a therapeutic range
   - Ineffective when too low
   - Toxic when significantly elevated

2. When alterations in drug levels may occur
   - Drug interactions
   - Impact of concurrent illness

3. Significant interpatient variability

4. When nonadherence or overadherence is suspected

Alteration of Clozapine Serum Concentrations

- 1A2 contributes up to 70% of clozapine’s metabolism
- 3A4 also contribute to a lesser extent
- 2D6 and 2C19 play minor roles

Select interactions:
- Inhibitors:
  - Fluvoxamine, ciprofloxacin, erythromycin
  - Fluoxetine, paroxetine, caffeine
- Inducers
  - Smoking
  - Phenytoin, carbamazepine, omeprazole, rifampin

Alteration of Clozapine Serum Concentrations

- Impact of infectious or inflammatory processes
  - Mild to severe clozapine toxicity
  - Increased production of cytokines may inhibit CYP 1A2 by up to 90%
  - Numerous reports describing this phenomenon
    - UTIs, URIs, sepsis
    - Surgical procedures
    - COPD exacerbations

- An underrecognized phenomenon
- Increased monitoring in patients who develop an acute medical illness

Darling P. Clin Schizophr Relat Psychoses. 2011
Why Therapeutic Drug Monitoring?

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   - Ineffective when too low
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   - Drug interactions
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Interpatient variability

- Numerous fixed dose studies have demonstrated the high interpatient variability of clozapine levels
  - 8-45-fold differences between subjects
- Age
- Sex
- Interactions
- Genetic polymorphisms (i.e. CYP 1A2)

Oleson O. Psychopharmacology. 1995
Haring C. Am J Psychiatry. 1990
Gibbons O. Psychopharmacology. 1995

Why Therapeutic Drug Monitoring?

1. When the drug of interest has a therapeutic range
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   - Drug interactions
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Practical Considerations

- 100 mg will yield a clozapine level of ~ 100 ng/mL
  - Higher in females by ~20-30%
- Titrate to 250-300 mg
  - Check level as a trough steady-state; 3-5 days
- "Send out" level
  - Decisions should still be made on clinical presentation
- ng/mL vs. nmol/L
  - ng/mL X 3.06 = nmol/L

Clozapine Levels: Place in Practice

- Obtaining clozapine levels should be considered:
  - To establish an initial baseline
  - When there is a suboptimal response or rule out nonadherence
  - To confirm toxicity or in the setting of significant side effects
  - With suspected drug interactions or changes in smoking pattern
  - Routine clozapine level monitoring is likely not warranted

Clozapine Therapeutic Drug Monitoring: Summary

- Serum levels > 350 ng/mL are associated with greater response
- Lack of incremental benefit > 700 ng/mL
- Significant concern for side effects > 900-1300 ng/mL
- Monitoring serum clozapine levels can be useful to maximize patient safety and optimize response
Assessment Question

Which is most accurate regarding clozapine serum levels?
A. There is no association between clozapine levels and response
B. There is no association between the clozapine levels and the risk of seizure.
C. There is a greater likelihood of response when clozapine levels reach a certain threshold
D. As clozapine levels increase there is a clear linear response effect

Questions?