



# BC Mental Health & Addiction Services Psychopharmacology Newsletter

December 2009

## Serious Gastrointestinal Adverse Effects of Clozapine

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### Introduction

Clozapine is an atypical antipsychotic medication used for treatment refractory schizophrenia. It is most well known for its serious hematological adverse effects that resulted in its removal from the European market in the 1970's. Clozapine was however subsequently remarketed with stringent hematological monitoring owing to its efficacy for patients failing other agents. [Palmer et al]

Other potential side effects include lowering of the seizure threshold, myocarditis and cardiomyopathy, orthostatic hypotension, urinary incontinence, metabolic syndrome, and anticholinergic effects. Of the anticholinergic side effects, constipation is quite common, occurring in 14-60% of patients. [Pelizza et al] Of concern are the ongoing reports of associated bowel obstruction and fatalities associated with clozapine therapy published throughout the medical literature. The fact that case reports are continuing to be published may imply that life-threatening bowel complications are not widely appreciated or the potential to develop them is not fully monitored for in patients receiving clozapine.

As such the objective of this review is to increase awareness of this uncommon, but serious adverse effect of therapy.

### Pathophysiology

Clozapine is considered one of the most strongly anticholinergic (anti-muscarinic) psychotropic medications available. [Pelizza et al] Additionally, due to its unique receptor profile, including strong antagonism of serotonin receptors compared to other anti-psychotics, clozapine has the potential to induce a greater degree of gastrointestinal (GI) dysmotility.

As is well known, the parasympathetic (cholinergic) innervation of the gut is essential to maintain forward function. That clozapine has such a strong anticholinergic effect, quoted in overdose to rival the effects of atropine [Palmer et al], it is not unexpected to see significant decreases in GI motility. Where clozapine may be different from other antipsychotic medications is its ability to block the serotonin receptors within the gut. Clozapine antagonizes a wide array of serotonin receptors, including the 5-HT<sub>2</sub>, 5-HT<sub>3</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub>. The 5-HT<sub>3</sub> receptor is appreciated within the gut to be involved in motility. It is a key target for antagonism to prevent chemotherapy induced nausea and vomiting with medications such as ondansetron. The use of 5-HT<sub>3</sub> antagonists

is often complicated by constipation, which demonstrates the negative effect of blocking 5-HT<sub>3</sub> on gut motility. [Micromedex]

As such, it has been postulated that it is the combined balance of anticholinergic and anti-serotonergic effects of clozapine that contribute to its more significant GI effects over other similar agents; despite these other agents, such as olanzapine, also possessing anticholinergic and antiserotonergic effects. [Potvin et al]

### Literature Search

Starting with a previously published systematic review of 102 cases of clozapine related gastrointestinal hypomotility published in 2007, an updated search was conducted to identify more recent publications. PubMed was searched using the MeSH terms “intestinal obstruction” and “clozapine” and limited to references published since 2007.

### Published Reviews

Palmer et al. [Palmer et al] in 2008 published a systematic review of published cases and Australian/New Zealand adverse event registry data of occurrences of clozapine-induced gastrointestinal hypomotility (CIGH) up to 2007. They identified 29 published cases and 74 events in the registries, with the earliest dating back to 1992. Of the patients experiencing CIGH, 67% were male, with an average age of 42 years, on a mean dose of clozapine of 428mg/d (range 12-1000mg/d), for a range of 3 days to 15 years. Fifty percent of episodes occurred during the first year of therapy and the reported mortality rate was 27%. Of note, though, is the occurrence of events years into therapy. Only one third of patients were on concurrent anticholinergic medications, and surprisingly only 10% were prescribed laxatives.

Based on an estimated exposure rate in Australia and New Zealand, Palmer et al. calculated the prevalence of CIGH to be 3 per 1000 patients exposed to clozapine.

Since the 2008 publication by Palmer et al, there continues to be reports of clozapine-induced bowel obstruction leading to significant morbidity and mortality in patients receiving clozapine (see Table 2). While many of these cases were complicated by confounding concurrent medications or comorbidities, the ongoing occurrence of these events is concerning.

### Discussion

Clozapine induced bowel obstruction is an uncommon, but appears to be a widely underappreciated adverse effect that has the potential to cause significant morbidity and mortality. Under-recognition is likely multifactorial. Patients with schizophrenia and schizoaffective disorders often have dietary habits and lifestyles that increase their risk of constipation i.e. low fiber intake and sedentary lifestyle. These patients may be less likely to report symptoms to their health care team due to negative symptoms, paranoia, etc, and may not be able to verbalize discomfort or concerns easily due to thought process disorders. [Levin et al] Additionally, members of the psychiatric care team may minimize the potential importance of episodes of constipation in their patients due to its commonness.

The mechanism behind clozapine’s effect on GI motility is not fully understood, but its ability to block both cholinergic and serotonergic receptors likely plays a role.

That case reports have repeatedly shown the potential for rapid and serious consequences of unrecognized constipation in clozapine treated patients demonstrates the need for an increased awareness. Patient education on healthy bowel habits and lifestyle may help, but for more disorganized and ill patients, monitoring for this adverse effect is essential.

Medications that may contribute to decreased GI motility such as anticholinergics (see Table 1) and opiates should be minimized as much as possible. Bulk laxatives such as psyllium fiber are contraindicated with GI obstruction, megacolon or megarectum and thus should be used cautiously in patients receiving clozapine. If bulking agents are used in patients, they should be instructed and monitored to maintain sufficient oral hydration. Additionally, in controlled inpatient environments, especially where clozapine dose titrations occur, bowel monitoring should be implemented to facilitate the early recognition of problems. In outpatient settings, it should be best practice to inquire about bowel habits for clozapine treated patients at each visit or health care contact. The utilization of standardized, escalating bowel regimens that progress from stool softeners, to stimulant laxatives, to enemas and suppositories for patients on clozapine may be effective at managing constipation and preventing progression to impaction. At least one center [Hayes et al.] recommends a standard management algorithm that includes comprehensive screening of patients with abdominal x-rays, rectal and abdominal exam prior to initiating clozapine; incorporates gradual titrations which increase dosage by no more than 25mg per day and 100mg per week; and utilizes standardized documentation of bowel and dietary habits to preemptively identify problems. As there have been numerous reports of patients rapidly decompensating after first reporting abdominal symptoms, the team should have a low threshold for initiating a diagnostic work up to exclude obstruction.

Summary

Patients receiving clozapine are at risk for serious GI complications related to their psychiatric treatment. Under-recognition may contribute to the morbidity and mortality associated with this uncommon but serious adverse effect. Efforts should be made to modify risk factors, facilitate early recognition and treatment of constipation, and initiate timely diagnostic work-up in patients with abdominal symptoms.

**Table 1 – Commonly prescribed medications with anticholinergic properties [Bruns]**

<b>Category</b>	<b>Medications</b>
Anticholinergics	Atropine, benztropine, glycopyrolate, scopolamine
Antihistamines	Chlorpheniramine, cyproheptadine, doxylamine, hydroxyzine, dimenhydrinate, diphenhydramine, meclizine
Antispasmodics	Dicyclomine, hyoscyamine, oxybutynin
Antidepressants	Amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, paroxetine
Miscellaneous	Carbamazepine, cyclobenzaprine

**Table 2 – Case reports of clozapine induced gastrointestinal hypomotility**

Report	Case	Relevant Concurrent Medications and Comorbidities	Complications and Outcome
Pelizza (2007)	45yo ♂ with schizophrenia on clozapine 400mg/d x 5 months.	Sertraline 100mg/d.	3 week history of constipation with abdominal distension. After 2 episodes of biliary vomiting, patient was transferred to acute care. Diagnosed with bowel obstruction, resolved with 1 week of conservative treatment (IV fluids, enemas, etc).
Dahmen (2008)	44yo ♀ with schizoaffective disorder on clozapine 725mg/d x 41 months.	Hydroxyzine 50mg BID, clonidine 0.1mg BID; chronic constipation and COPD.	48 hour history of abdominal distension, lethargy, vomiting and altered level of consciousness; partially responded to laxatives and enemas initially. Thereafter, continued to decline and therefore transferred to acute care. CT scan showed bowel obstruction, patient required total colectomy, and fully recovered.
Rege (2008)	53yo ♂ with schizoaffective disorder on clozapine 700mg/d x 1 year.	Olanzapine 10mg BID, Lithium Carbonate 250mg BID, Oral iron supplements.	Taken to ER with severe abdominal pain and bilious vomiting. CT scan showed colon loaded with feces until the rectum and dilated small bowel, without obstruction. Due to sepsis, patient required laparotomy to <u>disimpact</u> . Patient fully recovered, but on re-challenge with clozapine, constipation reoccurred requiring discontinuation of clozapine.
Leung (2008)	38yo ♂ with schizophrenia on clozapine 900mg/d x 5 years.	Ziprasidone 160mg/d.	During bathing, episode of feculent vomiting occurred. Patient soon developed decreased level of consciousness and died one hour later. Post mortem indicated fecal impaction and aspiration pneumonia as cause of death.
Leung (2008)	62yo ♀ with schizophrenia on clozapine 550mg/d x 6 weeks.	Nil.	Sudden onset vomiting and urinary incontinence with abdominal distension. Patient rapidly deteriorated and expired 3 hours later. Post mortem indicated pulmonary edema and intestinal obstruction as cause of death.
Hibbard (2009)	61yo ♂ with schizophrenia on clozapine 600mg/d x 7 years.	Procyclidine 5mg BID, oxybutynin 5mg BID. Chronic constipation x 12 years on high fiber diet and stool softeners.	3 day history of no bowel movements, increasing abdominal distension, transferred to acute care. CT scan showed severe fecal impaction. Episode of feculent vomiting during NG tube insertion. Patient developed pneumonia, sepsis, and expired.
Hibbard (2009)	63yo ♂ with schizophrenia on clozapine 400mg/d x 2 weeks.	Levothyroxine for Hypothyroid.	Several day history of no bowel movements, found down with distended abdomen, transferred to ICU, CT scan showed near-complete collapse of inferior vena cava due to bowel distension and high intra-abdominal pressure. Patient rapidly deteriorated, was taken to OR for surgical decompression, peri-operatively developed multisystem organ failure and expired.
Lavi (2009)	62yo ♂ with schizophrenia on clozapine for 16 years. 6 months prior had dose increased to 400mg/d.	Prior inguinal hernia repair.	24 hour history of severe abdominal pain, transferred to acute care. CT scan showed fecal impaction of entire rectum and colon. Emergency laparotomy with transverse colostomy for decompression was required. 5 days post op, developed increased intra-abdominal pressure and required re-laparotomy. Patient had complicated course in the ICU and is recovering.

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