Research Paper

Clozapine-treated Patients Have Marked Gastrointestinal Hypomotility, the Probable Basis of Life-threatening Gastrointestinal Complications: A Cross Sectional Study

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ABSTRACT

Background: Gastrointestinal side effects are particularly common with clozapine and occur with other antipsychotics, ranging from mild constipation to fatal bowel obstruction and/or ischemia. While this adverse-effect spectrum has been attributed to 'gastrointestinal hypomotility', gastrointestinal transit times in antipsychotic-treated patients have not previously been measured, making this mechanism speculative.

Methods: Using standardized radiopaque marker ('Metcalf') methods we established colonic transit times of antipsychotic-treated psychiatric inpatients and compared them with population normative values. We analyzed results by antipsychotic type, antipsychotic dose equivalent, anticholinergic load, duration of treatment, gender, ethnicity, and age.

Outcomes: For patients not prescribed clozapine, median colonic transit time was 23 h. For patients prescribed clozapine, median transit time was 104.5 h, over four times longer than those on other antipsychotics or normative values (p < 0.0001). Eighty percent of clozapine-treated patients had colonic hypomotility, compared with none of those prescribed other antipsychotics (olanzapine, risperidone, paliperidone aripiprazole, zuclopenthixol or haloperidol). In the clozapine group, right colon, left colon and rectosigmoid transit times were all markedly abnormal suggesting pan-colonic pathology. Hypomotility occurred irrespective of gender, age, ethnicity, or length of clozapine treatment. Transit times were positively correlated with clozapine plasma level (rho = 0.451, p = 0.045), but not with duration of treatment, total antipsychotic load or demographic factors.

Interpretation: Clozapine, unlike the other antipsychotics examined, causes marked gastrointestinal hypomotility, as previously hypothesized. Pre-emptive laxative treatment is recommended when starting clozapine.

1. Background

Gastrointestinal side effects are common with antipsychotics, particularly clozapine, ranging in severity from mild constipation to fatal bowel obstruction and/or ischemia. Constipation is reported in up to 60% of clozapine-treated patients (Hayes and Gibler, 1995) and up to 50% of those receiving other antipsychotics (Ozbilen and Adams, 2009) and is reflected in the high utilization of laxative in clozapine-treated patients (Bailey et al., 2015). The mechanism is considered to be anticholinergic inhibition of gastrointestinal smooth muscle contraction and peristalsis (Ozbilen and Adams, 2009), but serotonin receptor antagonism likely compounds the problem (Palmer et al., 2008), with

serotonin playing a crucial role in regulating gastrointestinal motility (Crowell, 2001). Symptoms of slow transit may include low stool frequency, lack of urge to defecate, abdominal distension, bloating, and abdominal discomfort (Foxx-Orenstein et al., 2008).

A systematic search of AMED, BIOSIS, CINAHL, EMBASE, MEDLINE, PsycINFO and PubMed databases with no language restrictions from inception to August 2015 revealed 61 case reports, five large case series and one cohort study on the serious or life-threatening clozapine-induced gastrointestinal effects.[1] For every 1000 patients treated with

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[1] Search terms were: anti-psychotics, keyword search anti-psychotic* or antipsychotic*, 'clozapine' (clozapine.mp OR clozapine/) together with any of the following MESH terms: constipation; intestinal obstruction; gastrointestinal motility; radiopharmaceuticals; digestive system diseases (MEDLINE); digestive system disease (EMBASE); digestive symptoms disorders (psycINFO); and related keywords (e.g. bowel; gastric; intestinal; colon*; digestive; gastrointestinal; or radiopaque and marker*).

clozapine, between 300 and 600 will develop constipation and four will develop serious gastrointestinal complications (including ileus, bowel obstruction, bowel ischemia and necrosis) from which one will die. Pharmacovigilance data shows that amongst antipsychotics, clozapine has the highest constipation-related mortality. Seventy such deaths were reported in the USA between 1997 and 2009, with a mortality rate three times that of clozapine-induced agranulocytosis (De Hert et al., 2011). A large prospective cohort study showed treatment with clozapine conferred the greatest risk of fatal ileus compared with other psychoactive medication (OR: 6.73; 95% CI 1.55–29.17) (Nielsen and Meyer, 2012).

While these complications have been described as arising from 'gastrointestinal hypomotility' (Palmer et al., 2008; Flanagan and Ball, 2011; Nguyen et al., 2014), gastrointestinal transit times in antipsychotic-treated patients have not been measured previously. There is consensus that clozapine's effect on gastrointestinal function is important, but poorly understood and under-researched.

2. Objectives

This study sought to ascertain:

- How does colonic transit time (CTT) in antipsychotic-treated inpatients, measured by radiopaque markers (ROMs), compare with standardized normative values?
- Does CTT differ significantly between people treated with clozapine and treated with other antipsychotics?
- Are other independent variables (including gender, age, ethnicity, constipation symptoms, antipsychotic load or estimated anticholinergic activity) related to CTT?

3. Research Design and Methods

Methods were pre-specified in the protocol (Every-Palmer et al., 2013 available at http://hdl.handle.net/10523/6070).

3.1. Participants

Participants were inpatients in a New Zealand general and forensic rehabilitation service. They all received similar diets (hospital meals) and had similar lifestyles. Recruitment occurred between April 2014 and April 2015.

A-priori power analysis was not conducted given the absence of earlier investigations.

Eligible participants were adults (over 18) prescribed antipsychotics for at least three months and competent to provide informed consent. Patients prescribed laxatives with a past history of significant gastrointestinal complications (such as fecal impaction) were excluded because withholding laxatives (as required for CTT testing) could expose them to risk.

This study was approved by the New Zealand Health and Disability Ethics Committee (reference 13/CEN/153).

3.2. Measuring Colonic Motility

CTT can be measured using radiopaque markers (ROMs), scintigraphy or wireless motility capsules. These methods are summarized in Table 1.

The conventional, cheapest and most practical way of measuring CTT is with ROMs. This method, used for over 40 years, is the reference standard in clinical practice (Szarka and Camilleri, 2012) and widely employed in research (Rao et al., 2011). Intra- and inter-observer reliability are high (Pomerri et al., 2007), with good correlation ($r = 0.7$, $p < 0.001$) between ROM and wireless motility capsule measurements of CTT in constipated patients (Rao et al., 2009).

Two main ROM methods have developed: a single ROM-bolus technique; and the more sensitive multiple ROM-bolus ('Metcalf') technique used in this study (Kim and Rhee, 2012). This latter technique involves ingesting a capsule containing 24 standardized ROMs on three consecutive days with abdominal X-rays on day four and, if necessary, day seven, quantifying elimination (Metcalf et al., 1987). This method minimizes radiation exposure, is reliable, reproducible (Pomerri et al., 2007; Bouchoucha et al., 1992) and well correlated with stool form in constipated adults (Saad et al., 2010).

Normative data are available for CTT from numerous ROM studies across different countries (see Table 2). Although none are from New Zealand, ethnic differences are not marked. Meta-analysis of relevant international normative data (see Table 1) gives a population mean CTT of 28.79 h with SD of 18.07 h ($n = 304$ healthy controls). A CTT 2SD above the population mean (i.e. >64.9) was pre-specified as a positive test for colonic hypomotility, as by convention.

Any prescribed laxatives were temporarily withheld from two days prior to ROM testing and during the study. Rescue laxatives were available if participants required them (none did).

On three consecutive days ($t = 0$ h, $t = 24$ h, $t = 48$ h) participants swallowed a dissolvable gelatin capsule (SITZMARKS®, Konsyl Pharmaceuticals Inc.) containing 24 polychlorinated vinyl markers impregnated with 33% barium sulfate (4.5×1.0 mm). Each day's capsule contained different shaped markers (Fig. 1).

On day four participants were screened for constipation, firstly by being asked if they considered themselves constipated ('self-reported constipation'), which was intended to mirror normal clinical practice, and secondly by completing a researcher-assisted questionnaire incorporating all Rome III constipation symptoms (Table 3) (Longstreth et al., 2006), available on request from the authors.

At $t = 72$ h, abdominal X-rays determined ROM location and the extent of elimination. If over two-thirds (>48) of ROMs remained, X-rays were repeated at $t = 144$ h. X-rays were read independently on an InteleViewer PACS system by SEP and MN. MN was blinded to independent variables. Vertebral spinous processes demarcated right and left sides of the colon. The rectosigmoid was defined by oblique lines between the fifth lumbar vertebra spinous process and the femoral head. Images were magnified and examined regionally and black-white inversion was applied to increase marker conspicuity.

Table 1
Summary of CTT measurement techniques.

	Radiopaque markers	Scintigraphy	Wireless motility capsule
Radiation exposure	Yes (X-ray) 0.5–0.7 millisieverts (Wall and Hart, 1997)	Yes (radiolabeled meal) 2.67 millisieverts (Graff et al., 2001)	No
Assesses gastric emptying	No	Yes	Yes
Assesses small bowel transit	No	Yes	Yes
Provides segmental colonic transit times	Yes	No	No
Test location	X-ray in local radiology department	Nuclear medicine department	Ambulatory
Cost	Inexpensive (approximately $100)	Moderately expensive (approximately $800)	Expensive (over $1000)

Table 2
Colonic transit times in healthy populations).

Study	Population Mean age ± SD	Mean colon transit time +/− SD (mean + 2SD upper limit) in hours			
		Right colon	Left colon	Rectosigmoid colon	Total colon
Chaussade et al. (1986)	Healthy French adults (n = 22) No demographics given	6.9 ± 8.6 (24)	9.1 ± 10.5 (30)	18.4 ± 12.8 (44)	34.4 ± 16.3 (67)
Kim et al. (2001)	Healthy Korean adults (n = 30, males n = 15), age 43.3 ± 13.2 yrs	Not reported	Not reported	Not reported	30.3 ± 14.9 (60)
Lee (2010)	Healthy Korean adults (n = 35, males = 35), age 41.9 ± 13.7 yrs	5.4 ± 7.2 (19.8)	7.6 ± 11.0 (29.6)	7.7 ± 12.1 (31.9)	20.5 ± 20.3 (61.1)
Kim et al., (2003)	Healthy Korean adults (n = 15, males = 11), age 50.2 ± 1.5 yrs	6.9 ± 1.2 (9.3)	10.8 ± 2.6 (16)	5.0 ± 1.2 (7.4)	24.0 ± 4.1 (32.2)
Jung et al. (2003)	Healthy Korean adults (n = 42, males = 21), age 34 ± 7 yrs	5.9 ± 6.9 (12.8)	9.2 ± 9.2 (18.4)	11.5 ± 11.1 (22.6)	26.5 ± 19.4 (65.3)
Metcalf et al. (1987)	Healthy American adults (n = 73, males = 34) 21 > 40 yrs., 52 < 40 yrs	11.3 ± 10.4 (32)	11.4 ± 13.8 (39)	12.4 ± 11.8 (36)	35 ± 16.5 (68)
Chan et al. (2004)	Healthy Chinese adults (n = 51, males = 27) mean age 42 ± 12 yrs. (30–54)	5.8 ± 5.3 (16)	9.5 ± 10.3 (31)	9.2 ± 11.4 (32)	24.5 ± 18.8 (62)
Robertson et al. (1993)	Healthy American male adults (n = 16) age 25 ± 4 yrs. (19–31) CTT calculated during sedentary week and non-sedentary week	5.9 ± 6.7 (sedentary) 5.1 ± 8.2 (non-sedentary)	10.3 +/− 14.7 (sedentary) 4.2 ± 4.3 (non-sedentary)	8.3 ± 10 (sedentary) 11.0 ± 11.8 (non-sedentary)	24.5 ± 21.8 (68.1) (sedentary) 20.4 ± 16.5 (53.4) (non-sedentary)
Mahassadi et al. (2003)	Healthy African (Ivorian) adults (n = 20, males = 16) mean age 25 yrs. (21–38)	8.9 ± 5.8 (20)	12.6 ± 8.3 (29)	14.4 ± 5.45 (25)	34.9 ± 151 (65)

Numbers of ROMs in each segment were used to determine total and segmental CTT using the formula: (Metcalf et al., 1987)

$$\Delta t = \frac{T}{N} \sum_{i=1}^{j} n_i$$

where Δt = mean transit time, T = time interval between X-rays, N = number of ingested markers, j = number of X-rays taken, and n_i = total number of markers present on a given film sector.

3.3. Other Data Collection

Demographic and clinical information collected included age, gender, ethnicity, BMI, smoking status, medication, diagnoses, serum clozapine levels, medication commencement dates and admission date. Total antipsychotic load was the sum of all antipsychotic medications expressed in olanzapine and chlorpromazine equivalents using the International Consensus Study on Antipsychotic Drug Dosing reference tables (Gardner et al., 2010).

Anticholinergic load was estimated using the Anticholinergic Drug Scale (ADS) score; (Carnahan et al., 2006) and an anticholinergic activity (AA) model was derived from published pharmacokinetic data combined with in-vitro AA to generate AA-dose response curves (Chew et al., 2006). AA for clozapine, olanzapine, quetiapine, risperidone, aripiprazole and ziprasidone was estimated from this data, adjusted for dose, gender and age category (Chew et al., 2006). AA of all other medications was calculated adjusted for dose, but not gender or age (Chew et al., 2008). Total AA was a sum of the values ascribed to all medication.

3.4. Data Analysis

We used SPSS version-21 (SPSS Inc. Chicago, Illinois, USA). Descriptive statistics (medians with IQR, and plotted distributions of transit times) provide data summaries for transit times. For demographic and clinical covariates, continuous variables were compared between medication groups using t-tests for normally distributed variables (age, BMI) or Mann–Whitney U tests for skewed distribution variables (e.g. anticholinergic load). Categorical covariates were compared using Pearson chi-squared tests, or Fisher's exact tests when one or more expected count was less than five.

Median transit times (with 95% CI) were calculated using Kaplan–Meier survival analysis, with differences in CTT formally compared using the log-rank test. Some clozapine-treated patients (n = 8, 40%) still retained over two-thirds of ROMs at the study's end (t = 144 h). These CTT values were treated as censored at this time-point. Differences in transit times by medication group were summarized with hazard ratios calculated using Cox Proportional-Hazards regression. These regression analyses did not include adjustment for confounders (covariates were approximately balanced between groups).

We examined the relationship between CTT and other covariates such as age, gender, ethnicity, antipsychotic load, anticholinergic burden and diagnosis using Kaplan–Meier survival analysis (with log-rank tests for statistical significance). Within the clozapine group, CTT was compared with clozapine dose and clozapine serum levels (as separate analyses) using Cox proportional hazard models; differences in mean CTT were also examined using linear regression to quantify mean increase in transit time for a fixed dose/serum level difference between patients. For these linear regression analyses, CTTs for patients with incomplete transit were treated as non-censored.

Fig. 1. Sitzmarks radiopaque markers: 0-rings; D-rings; and tri-rings.

Table 3
Rome III diagnostic criteria for functional constipation.

Must include two or more of the following
a. Straining during at least 25% of defecations
b. Lumpy or hard stools in at least 25% of defecations
c. Sensation of incomplete evacuation for at least 25% of defecations.
d. Sensation of anorectal obstruction/blockage for at least 25% of defecations.
e. Manual maneuvers to facilitate at least 25% of defecations (e.g. digital evacuation, support of the pelvic floor).
f. Fewer than three defecations per week.

While CTTs displayed a skewed distribution, we also calculated means and standard deviation for comparison with population normative values.

For hypothesis tests, differences were considered statistically significant when $p < 0.05$.

3.5. Funding

Capital and Coast District Health Board provided the research grant that provided the necessary funding for the ROM studies. The District Health Board had no role in study design; collection, analysis and interpretation of the data; or in writing or submitting the report for publication.

4. Results

4.1. Participant Characteristics

Recruitment occurred between 22 April 2014 and 10 April 2015. There were 61 potentially eligible patients. Six of them (all clozapine-treated) were excluded due to known gastrointestinal motility problems. Of the remaining 55 confirmed eligible, 37 (67%) consented to participate. All 37 participants completed the study and all data were analyzed. One participant did not complete the ROME III constipation questionnaire and BMIs were missing for seven participants (three from the clozapine group and four from the non-clozapine group). Otherwise the data set was complete.

4.2. Demographic Characteristics

The mean age of participants was 39.3 ± 9.8 (SD) years (range 20–61). Twenty-nine (78.4%) were male. Twenty-three patients (62.2%) identified primarily as Māori ethnicity, eight (21.6%) as Pacific Islander (six Samoan, one Cook Island Māori, one Tokelauan) and six (16.2%) as New Zealand European (Caucasian).

Most participants (n = 33, 89.2%) had diagnoses of schizophrenia. Two others had schizoaffective disorder, one bipolar disorder and one psychosis not otherwise specified.

4.3. Medication

Antipsychotics: Twenty participants were prescribed clozapine as their primary antipsychotic (doses ranging from 100 to 750 mg, mean serum plasma level 489 ng/mL). Of these, forty percent (n = 8) received clozapine as their sole antipsychotic, while the rest also received additional antipsychotics (clozapine-related data is provided in Table 4).

Amongst the 17 participants who were not prescribed clozapine, 14 (82%) received a single antipsychotic and three received two antipsychotics. Antipsychotic regimes are summarized in Table 5 and total antipsychotic dose equivalents in Table 6.

Laxatives: Eighteen participants had no laxatives in the preceding month. Half of them had prn (as required) laxatives available, which had not been utilized. Nineteen participants had used laxatives in the preceding month, one as a prn and the other 18 regularly. Laxatives included laxsol (n = 15), polyethylene glycol (n = 6) and lactulose (n = 3).

Other medications: Participants were prescribed a number of other medications, most commonly omeprazole (n = 10), metformin (n = 10) and cholecalciferol (n = 8). The cumulative anticholinergic activity of all medication was accounted for in AA and ADS scores (shown in Table 6).

4.4. Demographic and Clinical Differences by Clozapine Status

Age, gender and ethnicity were similar in the clozapine and non-clozapine groups, as were BMI and smoking status (see Table 6). All clozapine patients had schizophrenia diagnoses (treatment-resistant schizophrenia is the sole indication for clozapine in New Zealand), while only 76.5% of non-clozapine patients had this diagnosis.

Clozapine-treated patients received higher antipsychotic doses than the comparison group (olanzapine clinical daily dose equivalents of 35.8 mg compared with 20.0 mg, SMD 15.8, $p = 0.003$). Clozapine participants also had significantly higher estimated total anticholinergic activity (median AA = 147.1 compared with 2.0, $p < 0.0001$), but their *additional* anticholinergic burden (i.e. due to medications other than clozapine) was lower than non-clozapine participants (see Table 6).

Significantly more clozapine-treated participants had been prescribed laxatives (pre-emptive laxative treatment is a clinical recommendation for patients starting clozapine within the service). All laxatives were stopped prior to ROM testing. There was no significant difference between groups in reporting of constipation symptoms, either subjective experience of constipation, or ROME III criteria (Table 6).

4.5. Patients Treated on Clozapine had Pronounced Hypomotility

Almost all clozapine users exhibited colonic hypomotility (80%, defined as CTT > 65 h, 2 SD above the population mean) compared to no patients (0%) in the non-clozapine group (χ^2(1 df) = 20.8, $p < 0.0001$). Summary transit time statistics by antipsychotic are shown in Table 7. Typical day four X-rays from non-clozapine and clozapine-treated patients appear in Fig. 2.

The non-clozapine group had a median CTT of 23.0 h (95% CI 9.6–36.5 h). All non-clozapine treated patients had normal CTT (i.e within 2SD of the reference population mean), irrespective of their total antipsychotic load (CPZ/OLA equivalents), anticholinergic load or whether they received monotherapy or polypharmacy.

Colonic transit was over four times longer in the clozapine group compared with the non-clozapine group (Fig. 3, Table 8; $p < 0.0001$). Clozapine patients had a median CTT of 104.5 h (95% CI 73.3–134.7). Kaplan–Meier survival curves plotting time to elimination by clozapine status are shown in Fig. 4. The hazard ratio for the difference between medication groups also indicated a substantially slower rate of elimination in the clozapine group (HR = 0.04, 95% CI 0.01, 0.17; $p < 0.0001$).

Table 4
Summarized clozapine data for clozapine-treated participants.

	Median	Mean	SEM	SD	Range
Clozapine dose	550 mg	528 mg	36 mg	161 mg	100-750 mg
Clozapine serum level	1457.5 nmol/L (476 ng/mL)	1495 nmol/L (489 ng/mL)	94 nmol/L (31 ng/mL)	419 nmol/L (137 ng/mL)	870–2707 nmol/L (284–885 ng/mL)
Length of time prescribed clozapine	3 years, 3 months	3 years, 4 months	11.5 months	4 years, 3 months	4 months-14.5 years

Table 5
Antipsychotic medication participants were receiving.

	Antipsychotic/s prescribed	Number
Clozapine group (n = 20)	Clozapine monotherapy	8
	Clozapine + risperidone	2
	Clozapine + aripiprazole	1
	Clozapine + aripiprazole + quetiapine	1
	Clozapine + haloperidol	1
	Clozapine + amisulpride	7
Non-clozapine group (n = 17)		
	Olanzapine monotherapy	5
	Olanzapine + aripiprazole	1
	Olanzapine + zuclopenthixol	1
	Risperidone monotherapy	6
	Risperidone + aripiprazole	1
	Aripiprazole monotherapy	2
	Haloperidol monotherapy	1

Table 6
Comparison between clozapine and non-clozapine-treated groups.

Variable	Clozapine (n = 20)	Non-clozapine (n = 17)	
Categorical variables	Number (%)	Number (%)	Significance[a]
Gender			
Male	14 (70.0%)	15 (88.2%)	$p = 0.25$
Female ratio	6 (30.0%)	2 (11.8%)	
Ethnicity			
Māori	12 (60%)	11 (64.7%)	$p = 0.29$
Pacific islander	6 (30%)	2 (11.8%)	
Pakeha (NZ European)	2 (10%)	4 (23.5%)	
Diagnosis			
Schizophrenia	20 (100%)	13 (76.5%)	$p = 0.04$
Other diagnosis	0 (0%)	4 (23.5%)	
Status			
Forensic	10 (50%)	10 (58.8%)	$p = 0.84$
Non-forensic	10 (50%)	7 (41.2%)	
Smoking status			
Smoker	13 (65%)	9 (52.9%)	$p = 0.68$
Non-smoker	7 (35%)	8 (47.1%)	
Constipation			
Reports constipation	4 (20.0%)	3 (17.6%)	$p = 1.00$
Denies constipation	16 (80.0%)	14 (82.4%)	
Rome III	[NB n = 19]		
Rome III positive	11 (57.9%)	4 (23.5%)	$p = 0.08$
Rome III negative	8 (42.1%)	13 (76.5%)	
Laxatives taken			
Regular laxatives	16 (84.2%)	3 (17.6%)	$p = 0.001$
No regular laxatives	4 (22.2%)	14 (82.4%)	
Laxatives prescribed (regular or prn)			
Laxatives prescribed	19 (95.0%)	8 (47.1%)	$p = 0.005$
None prescribed	1 (5.0%)	9 (52.9%)	
Continuous variables (parametric)	Mean ± SD	Mean ± SD	Significance[b]
BMI (kg/m^2)	36.8 ± 9.2	35.9 ± 8.6	$p = 0.78$
Age (in years)	37.0 ± 8.2	42.0 ± 10.90	$p = 0.12$
Continuous variables (non-parametric)	Median (IQR)	Mean ± IQR	Significance[c]
Chlorpromazine clinical equivalent dose estimates	1072 (627–1371)	600 (400–650)	$p = 0.004$
Olanzapine clinical equivalent dose estimates	35.8 (20.9–45.8)	20.0 (13.3–21.7)	$p = 0.003$
Total atropine activity	147.1 (104.0–163.9)	2.0 (0.4–8.4)	$p < 0.0001$
Atropine equivalents with effect of clozapine removed	0.0 (0.0–1.4)	2.0 (0.4–8.4)	$p = 0.01$
Cholinergic load (ADS) with effect of clozapine removed	0.0 (0.0–1.8)	1.0 (0.0–2.0)	$p = 0.44$

[a] Hypothesis tests for categorical variables: chi-squared or Fisher's exact test.
[b] Hypothesis tests for continuous variables (normally distributed): t-test.
[c] Hypothesis tests for continuous variables (non-normally distributed): Mann–Whitney test.

The mean CTT for clozapine-treated participants (M = 100.6 h, SD = 42.0) was markedly longer than normal values (SMD = 71.8 h, $p < 0.0001$). Right colon, left colon and rectosigmoid transit were all significantly delayed in clozapine-treated patients (Table 8). There was no significant difference ($p = 0.72$) between CTTs of participants who received clozapine monotherapy and those who received clozapine + another antipsychotic (Table 7).

Comparison of CTT by age, gender, smoking status, ethnicity, complaints of constipation or positive ROME III criteria for constipation showed no significant differences in median CTTs (Table 9). Across the sample, estimated anticholinergic activity and total antipsychotic load were not significant predictors of CTT after controlling for serum clozapine level. Duration of clozapine treatment was not correlated with CTT (Fig. 5).

Fig. 6 shows CTT plotted against clozapine dose and serum level. There was a positive correlation between CTT and clozapine dose (Spearman's $rho = 0.31$), which was not statistically significant ($p = 0.165$). However, simple correlation does not account for censoring, and, in this case, will underestimate the magnitude of this relationship. Using proportional hazard survival analysis (Cox regression model), the ROM clearance rate decreases by a factor of 0.69 for each 100 mg increase in clozapine dose (HR = 0.685, 95% CI: 0.470–0.999, $p = 0.049$).

Clozapine serum level had a stronger association with CTT than clozapine dose (Spearman's $rho = 0.45$, $p = 0.045$). Using Cox regression analysis, the ROM clearance rate was shown to decrease by a factor of 0.54 for each 250 nmol/L (80 ng/ml) incremental increase in serum level (HR = 0.539, 95% CI: 0.304–0.953, $p = 0.034$).

Interestingly, self-reported constipation was a poor predictor of hypomotility, with a sensitivity of only 25%. Using Rome III criteria improved sensitivity, but only to 53.3%. Both those clozapine-treated participants who endorsed and those who denied constipation symptoms had hypomotility.

5. Discussion

5.1. Key Results

1. CTTs of clozapine-treated participants were four times longer than population norms and those on other antipsychotics, with 80% of clozapine-treated patients exhibiting clear hypomotility.
2. Right colon, left colon and rectosigmoid transit were all abnormal suggesting pan-colonic hypomotility.
3. Clozapine-treated participants displayed this pattern of hypomotility independent of age, ethnicity, gender and duration of clozapine treatment.
4. Higher clozapine serum levels were associated with longer transit times.
5. In 40% of clozapine-treated patients at least two-thirds of markers remained in the colon at the study's end ($t = 144$ h).
6. Subjective reporting of constipation symptoms had low sensitivity in predicting hypomotility.
7. All non-clozapine-treated participants had transit times within the normal range.

5.2. Limitations

This study had a number of limitations, enumerated below:

a) We were unable to determine the upper bound of CTTs in clozapine-treated patients. We had not expected such significant delays in transit. We terminated the study at the start of day seven (144 h) as specified a-priori, as it was considered against participants' interests to extend the study and continue withholding laxatives, leading to censored data for 40% of clozapine treated patients.
b) The ROM technique used does not provide information about gastric emptying or small bowel transit.

Table 7
Colonic transit times shown by primary antipsychotic.

Antipsychotic	Abnormal CTT test (%)	Mean CTT (95% CI) in hours Median (95% CI) (IQR) in hours	Median CTT (days)	Standard mean difference (SMD) with 95% CI compared with population norms)
Clozapine-treated participants				
All clozapine n = 20	16 (80%)	M = 100.6 (82.1–119.0) Median = 104.5 (73.3–134.7) IQR: 66.5–>126.0[a] Range: 8·0–>144.0[a]	4.4	SMD = 71.8 h, 95% CI: 62.6 to 81.0 (p < 0.0001)
Clozapine only antipsychotic n = 8 Mean clozapine dose = 75 mg (±116)	7 (87.5%)	M = 94.1 (62.8–125.5) Median = 88.0 (56.1–119.9) IQR: 66.5–>135.0[a] Range: 8.0–>144.0[a]	3.7	SMD = 65.3 h 95% CI: 51.9 to 78.7 (p < 0.0001)
Clozapine augmented n = 12 Mean clozapine dose = 564 mg (±180)	9 (75%)	M = 100.7 (80.7–120.6) Median = 105.0 (94.8–115.2) IQR: 55.0–>124.5[a] Range: 35.0–>134.0[a]	4.4	SMD = 71.9, 95% CI: 60.9 to 82.9 (p < 0.0001)
Non-clozapine-treated participants				
Aripiprazole n = 4	0 (0%)	M = 28.5 (12.7–4.3) Median = 24.5 (11.2–34.0) IQR: 10.0–30.0 Range 14.0–51.0	1.0	SMD = −0.3 h 95% CI: −18.2 to 17.6 (p = 0.97)
Zuclopenthixol n = 1	0 (0%)	42	1.75	NA
Haloperidol n = 1	0 (0%)	23	1.0	NA
Olanzapine n = 7	0 (0%)	M = 22.3 (10.7–33.8) Median = 24.0, (95% CI 0–-62.0) IQR: 8.0–41.0 Range: 6.0–41.0	1.0	SMD = −6.2 h 95% CI: −20.1 to 7.1 (p = 0.35)
Risperidone (includes LAI risperidone and paliperidone) n = 8	0 (0%)	M = 20.5, SEM = 5.5, SD = 15.6 Median = 11.0, (5.5–16.5) IQR: 9.0–30.0 Range: 8.0–52.0	0.5	SMD = −8.3 95% CI: −21.0 to 4.4 (p = 0.20)

[a] In these cells, more than 25% of the data points were censored, so IQRs and ranges are reported as the time the true 25th centile and upper bound of CTT range respectively must lie above.
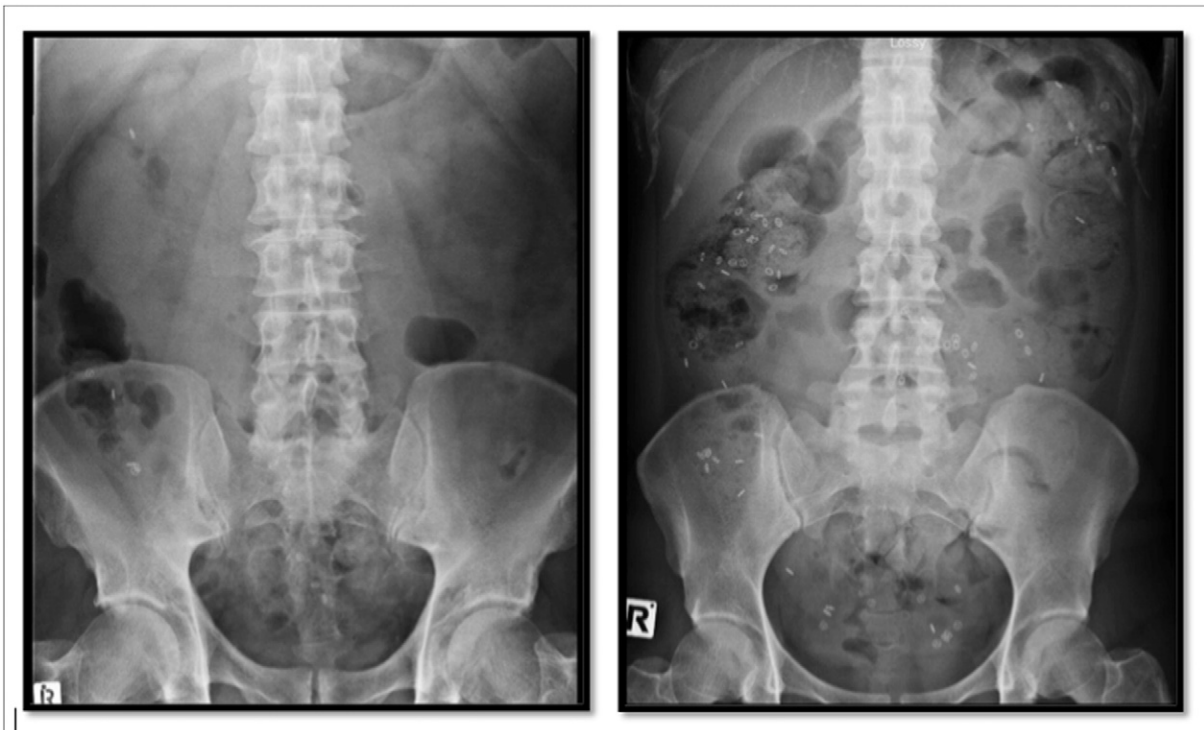

Fig. 2. ROM studies of a non-clozapine and clozapine-treated participant. Typical day four abdominal X-rays from a non-clozapine patient (left) and clozapine (right). The ROMs have almost all been excreted on the left, whereas on the right in the clozapine-treated patient all 72 ROMs are retained and scattered throughout the bowel in a pattern indicating global hypomotility.
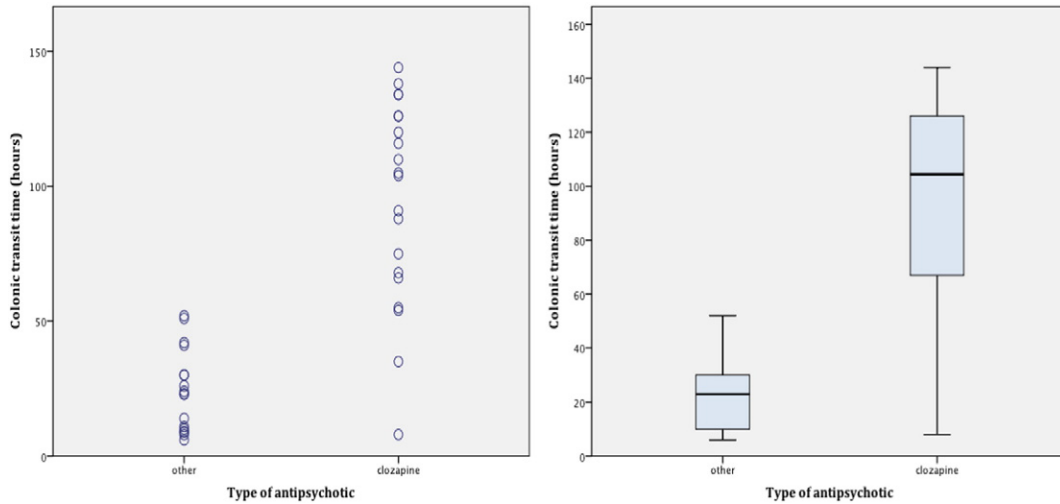
Fig. 3. Colonic transit time (in hours) for non-clozapine and clozapine-treated participants.

c) We used a summary statistic of normal colonic transit time collated from other studies for population normative values. New Zealand reference standards do not exist.

d) Determining patterning of CTT by some variables (e.g gender, ethnicity) is hindered by a small sample size and therefore estimates of differences are imprecise.

e) We could not test CTT of the same patients before and after clozapine initiation. This would have yielded information about clozapine's effect on the individuals' gastrointestinal motility.

f) Anticholinergic activity was calculated from standardized dose–response tables, not individual receptor assays, giving estimates that did not account for individual pharmacokinetic variability.

5.3. Generalizability

Our participants were physically healthy and psychiatrically stable forensic and rehabilitation inpatients. They all had similar diets and lifestyles, reducing confounding, but possibly limiting the potential for generalization to patients treated in other settings. Patients with established significant hypomotility were excluded (10% of the local study population), resulting in spectrum bias toward individuals with serious, but adequately treated mental illness who had not overtly manifested gastrointestinal hypomotility.

5.4. Interpretation

While it has previously been speculated that clozapine's spectrum of serious and life-threatening gastrointestinal effects is due to gastrointestinal hypomotility (Palmer et al., 2008; Flanagan and Ball, 2011; Taylor et al., 2015), this study now confirms that such hypomotility occurs.

Table 8
Comparison of segmental transit times for clozapine and non clozapine-treated participants.

Segment	Clozapine group Median CTT (95% CI)	Non-clozapine group Median CTT (95% CI)	Difference in medians	Significance (log-rank test)
Right colon	31.0 (14.4–47.6)	8.0 (6.1–9.9)	23.0	$p < 0.0001$
Left colon	48.0 (15.0–81.0)	6.0 (4.7–7.3)	42.0	$p < 0.0001$
Rectosigmoid	33.0 (17.9–48.1)	3.0 (1.0–5.0)	30.0	$p < 0.0001$
Total	104 (73.3–134.7)	23.0 (9.6–36.4)	81.0	$p < 0.0001$

The results of another recent study support our findings. Baptista et al (Baptista et al., 2015) gave 137 Venezuelan antipsychotic-treated outpatients a single oral bolus of 25 silver rings (they could not access standardized ROMs). They considered studies indicative of gastrointestinal hypomotility if six or more rings remained visible on abdominal X-rays five days later, which occurred in 51% of their clozapine group, compared with 31.3% of those receiving other antipsychotics. No significant relationship existed between abnormal tests and clozapine treatment duration or dose (serum level was not measured). Similar to our study, self-reported symptoms were not sensitive in predicting abnormal transit.

Our study found a higher prevalence of clozapine-related hypomotility (80%), which may relate to methodology, differences in participant characteristics or to random error. Clozapine serum levels in our study (mean = 489 ng/mL, SD = 137 ng/mL) were consistent with recommended levels in the treatment of schizophrenia (Remington et al., 2013). In the Venezuelan study, clozapine was also used for indications other than schizophrenia with half the participants receiving less than 160 mg of clozapine. The likely relationship between
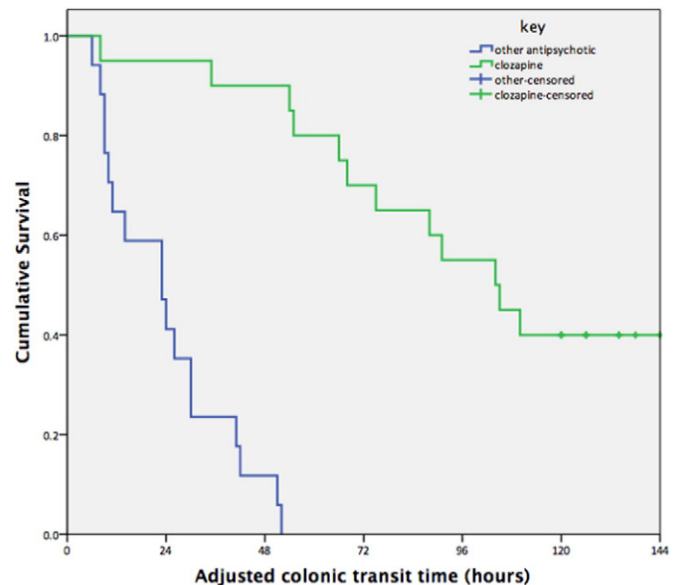

Fig. 4. Survival analysis of colonic transit time (in hours) for clozapine and nonclozapine-treated participants.

Table 9
Relationship between different categorical variables and CTT within clozapine-treated patients.

Predictor variable	Median CTT (95% CI)	Difference in medians	Significance (log-rank test)
Smoking status			
Non-smoker ($n = 7$)	126[a]	35	$p = 0.06$
Smoker ($n = 13$)	91 (46.4–135.6)		
Gender			
Male ($n = 14$)	105 (94–116)	37	$p = 0.45$
Female ($n = 6$)	68 (44–92)		
Ethnicity			
Caucasian ($n = 2$)	108.5[a]	4.5, 14.5	$p = 0.90$
Māori ($n = 12$)	104 (75–132)		
Pacific Islander ($n = 6$)	94.0[a]		
Constipation?			
Yes ($n = 4$)	104 (60.9–147.1)	13	$p = 0.84$
No ($n = 16$)	91 (57.7–124.3		
Rome III			
Positive ($n = 11$)	104 (84.6–123.4)	16	$p = 0.68$
Negative ($n = 8$)	88 (40.5–135.6)		

[a] In these cases, more than 50% of the data points were censored, so medians are reported as the figure the true median must lie above and confidence intervals cannot be accurately calculated.

clozapine dose/serum level and CTT may explain the more severe pathology in our cohort.

The mechanism of clozapine-induced colonic hypomotility remains to be established, as does clozapine's effects on esophageal, gastric and small bowel motility. Pre- and post-clozapine comparison of CTTs would be useful, as would replication of findings in different populations. It was surprising that all non-clozapine participants had normal CTTs. For example, given olanzapine's similar pharmacology and propensity to cause constipation (Kennedy et al., 2003; Frenchman, 2005; Kelly et al., 2006), we expected some olanzapine-treated patients to experience delayed transit.

We also had not anticipated that constipation symptoms, with a sensitivity of 25%, would have such poor predictive validity for colonic hypomotility. Indeed, half the censored patients, whose CTT extended beyond the seven-day study period, denied constipation and scored negatively on the Rome III. This included the most extreme case where none of the 144 ROMs had even reached the rectosigmoid by day seven, let alone been excreted. However this participant categorically denied any constipation symptoms and claimed to be passing
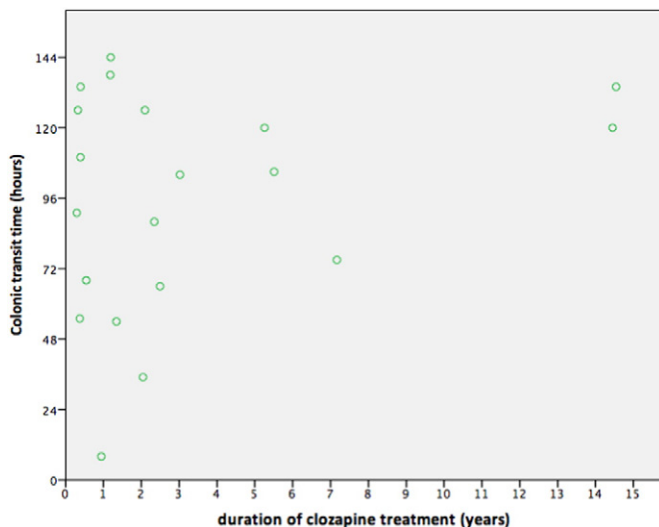

Fig. 5. Colonic transit time plotted by duration of clozapine treatment.

regular normal bowel motions. Similarly, in a series of 102 patients classified as suffering severe or life-threatening clozapine-induced gastrointestinal hypomotility (Palmer et al., 2008), many had not complained of constipation or other symptoms, but were discovered to have massive fecal impaction in the operating theater or on autopsy.

The reasons for the disparity between subjective symptoms and objective pathology are unclear, but are speculated to arise from a combination of reduced pain sensitivity in patients with schizophrenia (Fishbain, 1982; Rosenthal et al., 1990; Dworkin, 1994; Singh et al., 2006), difficulty in communicating discomfort (Bickerstaff et al., 1988) and clozapine's sedative and anti-serotonergic properties, which may reduce intestinal nociception (Palmer et al., 2008). If bowel function is chronically deranged, the affected individual may also lack a sense of what is normal. The clinical implications are concerning; the commonly accepted practice of enquiring whether clozapine treated patients are constipated has little utility, and may even be misleading. Colonic hypomotility should be suspected regardless of whether gastrointestinal symptoms are endorsed. Laxatives should be started pre-emptively in clozapine-treated patients.

Unfortunately there is little evidence on which laxatives are most effective. There are no high-quality trials on the management of clozapine-induced gastrointestinal hypomotility, and current recommendations are pragmatic rather than evidence-based (e.g. the Maudsley Guidelines) (Taylor et al., 2015). A Cochrane review underway (Every-Palmer et al., 2014) has not yet identified any adequate clinical trials on the pharmacological treatment of clozapine or other antipsychotic-related constipation (unpublished data: Every-Palmer et al.). This identifies a significant evidence gap.

In other pharmacologically-related hypomotility disorders such as opiate-induced constipation, experts and guidelines often advocate for the first-line use of stimulant laxatives (Twycross et al., 2012; Sykes et al., 2005; Goodheart and Leavitt, 2006). In the general population there is good evidence for macrogols such as polyethylene glycol (PEG) in the treatment of constipation (Lee-Robichaud et al., 2010; Bharucha et al., 2013). Our experience suggests that both senna and PEG are effective in improving bowel motility in clozapine-treated patients. To test this hypothesis we are currently conducting a follow up study re-measuring CTTs once participants are established on laxative regimes involving these agents.

Other recommended strategies involve using the lowest effective clozapine dose, with our results showing a positive association between clozapine plasma level and CTT. Co-prescription of other medications with known effects on bowel motility (e.g. opiates and anticholinergic medication) should be avoided wherever possible. A high degree of vigilance for the emergence of serious gastrointestinal pathology such as bowel obstruction is mandated. The commonest reported symptoms heralding such evolution were moderate to severe abdominal pain and abdominal distension (Palmer et al., 2008). Emergence of these symptoms in clozapine-treated patients warrants urgent medical referral and treatment.

Overall clozapine remains an important treatment in psychiatry, necessitating careful risk–benefit analysis. While gastrointestinal hypomotility is but one of the drug's considerable adverse effects, clozapine is still the most effective pharmacological agent for otherwise treatment-resistant schizophrenia, significantly improving outcomes for many patients (Kane et al., 1988) and decreasing overall mortality due to reduced suicide-rates (Hennen and Baldessarini, 2005; Meltzer and Okayli, 1995; Walker et al., 1997; Munro et al., 1999).

6. Conclusions

The effect of clozapine on colonic motility is highly significant, and appears to occur regardless of gender, ethnicity, clozapine dose and duration of treatment.

Our results suggest, counter-intuitively, that when screening for hypomotility, little is gained by asking clozapine-treated patients
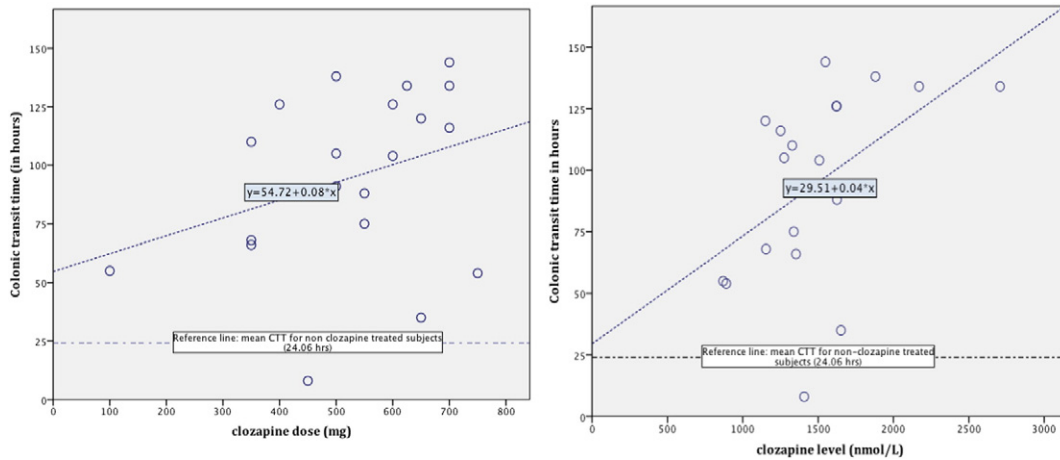
Fig. 6. Colonic transit time plotted by clozapine dose and serum level.

about constipation. While important in assessing subjective distress, constipation symptoms were not sensitive in predicting hypomotility. This is consistent with many earlier reports where subjects had no prior complaints until serious pathology emerged.

The results suggest that all clozapine-treated patients are at risk of gastrointestinal hypomotility, which needs to become part of the consent process. We recommend starting prophylactic laxative treatment when commencing clozapine in the same way as is recommended for long-term opioids (Caraceni et al., 2012). Given our observation that patients prescribed prn (as required) laxatives did not use them, we suggest prescribing regular laxatives.

Declaration of Interests

We declare no competing interests.

Authorship

SEP conceived of the study, designed and coordinated it and had overall responsibility for all aspects of the research including drafting the study protocol and report. MN was the radiologist who analyzed and reported all the ROM studies. JS participated in statistical analysis. PE was involved in the conception and design of the study and in drafting the manuscript. EG was involved in recruiting participants and in data collection. MH was involved in study design. HD participated in pharmacological data collection. All authors critically appraised and revised the draft manuscript and approved the final version.

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