

Prophylactic laxatives in clozapine-treated patients: a long road ahead

RAÚL ALBERTO ESTEVEZ-CORDERO¹

<https://orcid.org/0000-0002-1791-3880>

TERESA MORERA-HERRERAS^{1,2}

<https://orcid.org/0000-0002-7601-4914>

RAFAEL HERNANDEZ³

<https://orcid.org/0000-0003-4408-7411>

JUAN MEDRANO⁴

<https://orcid.org/0000-0001-9141-6236>

SUSANNA EVERY-PALMER⁵

<https://orcid.org/0000-0001-6455-9741>

UNAX LERTXUNDI⁶

<https://orcid.org/0000-0002-9575-1602>

¹Department of Pharmacology, Faculty of Medicine and Nursing, University of the Basque Country (UPV/EHU), Leioa, Spain

²Neurodegenerative Diseases Group, BioCruces Bizkaia Health Research Institute, Barakaldo, Bizkaia, Spain

³Internal Medicine Service, Araba Psychiatric Hospital, Araba Mental Health Network, C/alava 43, 01006 Vitoria-Gasteiz, Alava, Spain

⁴Biocruces Bizkaia Health Research Institute, Mental Health Network Research Group, Osakidetza, Bizkaia, Spain

⁵Head of Department, Department of Psychological Medicine, University of Otago, Wellington, New Zealand

⁶Bioaraba Health Research Institute; Osakidetza Basque Health Service, Araba Mental Health Network, Araba Psychiatric Hospital, Pharmacy Service, Vitoria-Gasteiz, Spain

Received: 20-05-2020 – Accepted: 28-06-2020

DOI: 10.15761/0101-60830000000280

ABSTRACT

Introduction: In recent years, higher rates of mortality have been recorded from clozapine-induced gastrointestinal hypomotility than from agranulocytosis. Still, this adverse reaction does not receive enough attention. Some authors recommend prophylactic laxatives for every clozapine-treated patient but little information exists about laxative use in this patient cohort.

Methods: To conduct this study we identified all patients treated with clozapine of Araba, Northern Spain. To identify eligible patients we used PRESBIDE which contains all outpatient prescription medications funded or not by the drug benefit plan. We measured the medication possession ratio (MPR) as an indirect measure of adherence both for clozapine and other medications including laxatives.

Results: A total of 217 clozapine-treated outpatients were included. Mean age was almost 47 years, and about three-quarters were male. The most frequent reason for clozapine use was schizophrenia, and mean duration of clozapine treatment was 4.5 years. Six of the 217 patients (2.7 %) had a laxative prescription, with a mean MPR of 8.4% in this therapeutic class.

Conclusions: Laxatives were under-utilized and adherence was poor. We recommend healthcare professionals educate clozapine-treated patients and their families as to the risks of gastrointestinal hypomotility, offer prophylactic laxatives and advise patients to take them as prescribed.

Estevez-Cordero RA / Arch Clin Psychiatry. 2021;48(1):66-68

Keywords: Laxatives, constipation, clozapine, adherence, gastrointestinal hypomotility

Introduction

In recent years, higher rates of mortality have been recorded from clozapine-induced gastrointestinal hypomotility (CIGH) than from agranulocytosis¹. This has driven the Food and Drug Administration to warn that untreated constipation caused by clozapine result in serious bowel problems². Still, this dangerous adverse reaction, affecting up to 80% of patients treated with this antipsychotic³, does not receive enough attention from healthcare professionals.

Based on the frequency^{3,4}, potential deadly consequences^{5,6} and challenges in the diagnosis of clozapine-induced gastrointestinal hypomotility (CIGH)³, some authors^{7,8} advocate for prophylactic laxative use, because waiting for the patient to report constipation symptoms will fail to detect most cases of CIGH (as most people with CIGH do not complain of constipation)³. An example of such

a regime is the Porirua Protocol developed in New Zealand, which recommends a stimulant like docusate and senna tablets for all people starting clozapine and adding macrogol as necessary⁸.

However, there is little information about how often laxatives are co-prescribed with clozapine, even for patients on clozapine exposed to additional drugs that could worsen constipation, such as anticholinergics⁹.

Adherence to prescribed drugs is a key issue in schizophrenia¹⁰. A lot of research has been conducted on antipsychotic adherence for obvious reasons, but information about other therapeutic drug classes, such as laxatives, is scarce or non-existent¹¹. Not taking laxatives as prescribed could have harmful consequences.

So, in this study, we aimed to measure the rates of laxative utilisation and for the first time, adherence to these drugs in clozapine-treated outpatients.



Method

To conduct this cross-sectional prevalence study we identified all patients treated with clozapine data in the Araba Mental Health Network, the public health service providing care for the 327,967 inhabitants of the province of Araba, Northern Spain. To identify eligible patients we used PRESBIDE, an administrative healthcare database which contains all outpatient prescription medications funded or not by the drug benefit plan.

We extracted data on age, gender, total dose, diagnosis and time since clozapine initiation, and any laxative prescription (A06)¹². In addition, global anticholinergic burden was measured using three different scales: The Anticholinergic Risk Scale (ARS)¹³ the Anticholinergic Cognitive Burden Scale (ACB)¹⁴ and Duran's list¹⁵.

The medication possession ratio (MPR) was used as an indirect measure of adherence both for clozapine and other medications including laxatives. MPR expresses the proportion of days of drug supply received by a given patient, divided by a certain period of time¹¹. In our case, we chose an 8-month study period, from August 2019 to March 2020. Patients admitted to a hospital were excluded. Only long-term medications were included, that is, those which could be dispensed to the outpatient in the pharmacy during the whole study period. Suboptimal adherence was considered when mean MPR for all drugs was < 80%, as taking medication as prescribed 75–80% of the time has been generally considered an acceptable level of adherence¹⁶.

The Clinical Research Ethics Committee of the Basque Country approved this study and it was in accordance with the Declaration of Helsinki.

Descriptive statistics were used to summarize the results of the survey. The t-test and the X² test were applied to compare continuous and categorical variables, respectively between those who received laxatives and those who did not. Analyses were performed using SPSS software (SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

Results

A total of 217 clozapine-treated outpatients were identified. Mean age was almost 47 years, and about three-quarters were male. The most frequent reason for clozapine use was schizophrenia, and mean duration of clozapine treatment was 4.5 years.

Six of the 217 patients (2.7 %) had a laxative prescription, with a mean MPR of 8.4% in these therapeutic class drugs. For patients showed a MPR of 0%.

No differences in clozapine dose, duration of treatment or anticholinergic burden were observed between patients with or without laxatives. The proportion of patients with suboptimal mean adherence to all prescribed drugs was higher in patients on laxatives (66.7% versus 17.5%). Macrogol was the most frequently used laxative (3) drug followed by lactulose (2) and bisacodyl (1). No differences in anticholinergic burden were found between groups. The main results are summarized in Table 1

Table 1. Clinical and demographical characteristics of outpatients on long-term clozapine

	ALL PATIENTS	LAXATIVE USE		Significance
		YES n = 6	NO n = 211	
Age (years, Mean ± SD)	46.9 ± 10.9	58.5 ± 7.9	46.5 ± 10.8	p = 0.008
Gender (% male)	73.7%	50%	74.4%	p = 0.18
Clozapine daily dose (mg, Mean ± SD)	296.9 ± 150.5	300 ± 221.3	296.8 ± 148.7	p = 0.96
Duration of clozapine treatment (days, Mean ± SD)	1529.10 ± 2993.7	1605.6 ± 963.3	1526.9 ± 3032.5	p = 0.95
Total number of drugs	3.3 ± 1.8	6.8 ± 3.5	3.2 ± 1.7	p = 0.002
Anticholinergic burden ± SD				
ARS	3.8 ± 1.0	3.5 ± 0.54	3.8 ± 0.9	p = 0.44
ACB	3.6 ± 1.2	3.3 ± 0.51	3.6 ± 1.2	p = 0.56
Duran	3.6 ± 0.96	3.5 ± 0.83	3.6 ± 0.9	p = 0.75
Suboptimal adherence (Proportion of patients with MPR <80%)†	18.8%	66.7%	17.5%	p = 0.002
Diagnosis (n)*				
F20-29 (Schizophrenia, schizotypal and delusional disorders)	204			
F30-39 (Mood [affective] disorders)	14			
G20 Parkinson's Disease	2			
Prescribed laxative		Macrogol = 3 Lactulose = 2 Bisacodyl = 1	-	

*One patient can have more than one diagnosis

† Mean MPR <80% considering all drugs.

DISCUSSION

In the present study, the results show that only a small minority of clozapine treated outpatients (2.7%) had a laxative prescription. Furthermore, those patients on laxatives did not seem to be taking them as prescribed, as shown by poor adherence rates (MPR = 8.4%). Patients with prescribed laxative drugs were 12 years older and were on around three more drugs on average than patients without laxatives. No difference between groups were found in clozapine dose, duration of clozapine treatment or anticholinergic burden. Anyway, the small number of patients on laxatives makes drawing solid conclusions difficult.

Our findings highlight that awareness of this prevalent and dangerous adverse reaction is not widespread across prescribers in Araba, Northern Spain, and that recommendations about starting prophylactic laxative use in every patient on clozapine are not followed. Interestingly, adherence was very poor in the six patients receiving laxatives, with four patients not refilling any laxatives at all. The proportion of patients with suboptimal adherence to any drug was also higher in this group. Although MPR is an indirect method to measure adherence, true adherence will likely be even lower, since pharmacy refills do not guarantee that the medication collected was actually swallowed.

Some laxatives are available as over the counter medications in Spain. Both prescription and over the counter drugs can be recorded by doctors in PRESBIDE, but over the counter drugs are not always prescribed. So the proportion of patients taking laxatives in our study may be underestimated.

Laxatives are excluded from reimbursement in Spain, as occurs in many countries (other drugs, such as antipsychotics are almost totally funded by the government, patients paying a maximum of around €5 per prescription). Although we did not study the reasons for this non-adherence, we believe having to pay laxatives in full might have deleterious consequences in clozapine-treated patients.

In conclusion, laxatives appeared to be under-utilized in clozapine-treated patients in Northern Spain. We recommend psychiatrists, general practitioners and healthcare professionals consider offering laxative drugs to all clozapine-treated patients, explaining the risks of CIGH and reinforcing the importance of taking laxatives as prescribed. Moreover, we urge healthcare authorities to consider reimbursement of laxatives in this patient population.

Key Points

- Laxatives are under-utilized in clozapine treated outpatients in our setting.
- Patients on laxatives showed poor adherence rates.
- We urge healthcare authorities to consider reimbursement of laxatives in this patient population.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Palmer SE, McLean RM, Ellis PM, Harrison-Woolrych M. Life-threatening clozapine-induced gastrointestinal hypomotility: an analysis of 102 cases. *J Clin Psychiatry*. 2008;69:759-68.
2. Food and Drug Administration. Safety Communication. Warning that untreated constipation caused by schizophrenia medicine clozapine (Clozaril) can lead to serious bowel problems. Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-strengthens-warning-untreated-constipation-caused-schizophrenia-medicine-clozapine-clozaril-can>. Accessed [May 4th, 2020].
3. Every-Palmer S, Inns SJ, Ellis PM. Constipation screening in people taking clozapine: A diagnostic accuracy study. *Schizophr Res*. 2020;220:179-186.
4. Every-Palmer S, Inns SJ, Grant E, Ellis PM. Effects of Clozapine on the Gut: Cross-Sectional Study of Delayed Gastric Emptying and Small and Large Intestinal Dysmotility. *CNS Drugs*. 2019;33(1):81-91.
5. Every-Palmer S, Nowitz M, Stanley J, et al. Clozapine-treated Patients Have Marked Gastrointestinal Hypomotility, the Probable Basis of Life-threatening Gastrointestinal Complications: A Cross Sectional Study. *EBioMedicine*. 2016;5:125-34.
6. Every-Palmer S, Ellis PM. Clozapine-Induced Gastrointestinal Hypomotility: A 22-Year Bi-National Pharmacovigilance Study of Serious or Fatal 'Slow Gut' Reactions, and Comparison with International Drug Safety Advice. *CNS Drugs*. 2017;31(8):699-709.
7. Attard A, Iles A, Attard S, Atkinson N. Clozapine: why wait to start a laxative? *BJPsych Advances*. 2019;25(6):1-10
8. Every-Palmer S, Ellis PM, Nowitz M, et al. The Porirua Protocol in the Treatment of Clozapine-Induced Gastrointestinal hypomotility and Constipation: A Pre- and Post-Treatment Study. *CNS Drugs*. 2017;31(1):75-85.
9. Lertxundi U, Hernandez R, San Miguel S, et al. The burden of constipation in psychiatric hospitals. *Int J Psychiatry Clin Pract*. 2018;22(2):143-150
10. Yaegashi H, Kirino S, Remington G, Misawa F, Takeuchi H. Adherence to Oral Antipsychotics Measured by Electronic Adherence Monitoring in Schizophrenia: A Systematic Review and Meta-analysis. *CNS Drugs*. 2020;34(6):579-598.
11. Lertxundi U, Hernandez R, Corcostegui B, Ibarra O, Mentxaka G, Medrano J. Influence of an inconsistent appearance of antipsychotics on drug adherence in patients with schizophrenia. *Medicine (Baltimore)*. 2018;97(44):e12990.
12. WHO ATC Classification. Available at: https://www.whocc.no/atc_ddd_index/. Accessed [April 20th, 2020].
13. Rudolph J, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. *Arch Intern Med*. 2008;165:508-513.
14. Boustani MA, Campbell NL, Munger S, Maidment I, Fox GC. Impact of anticholinergics on the aging brain: a review and practical application. *Aging Health*. 2008;4:311-320.
15. Durán CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. *Eur J Clin Pharmacol*. 2013;69(7):1485-96.
16. Velligan DI, Wang M, Diamond P, et al. Relationships among subjective and objective measures of adherence to oral antipsychotic medications. *Psychiatric Services*. 2007;58:1187-1192.