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Metformin reduces 12-month change in body weight among people newly commenced on clozapine: a retrospective naturalistic cohort study

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Abstract

Background: People with schizophrenia have a 15–20-year reduction in life expectancy, driven in part by the metabolic effects of antipsychotics. Clozapine is associated with the highest rates of weight gain. As clozapine remains the most effective antipsychotic for treatment-resistant schizophrenia (TRS), identifying treatments to ameliorate clozapine-induced weight gain (CIWG) is urgently needed to reduce this morality gap.

Methods: We retrospectively analysed digital health records of patients with TRS aged 18–65 newly initiated on clozapine at four tertiary hospitals in south-east Queensland from 1 March 2017 to 30 June 2019. Our primary outcome was the effect of metformin on change in percentage bodyweight at 12 months after clozapine initiation, with secondary outcome being proportion with >5% or >7% bodyweight change. We also explored impact on bodyweight change of other variables including sex, tobacco smoking, type 2 diabetes (T2DM), age, clozapine level and dose and clozapine/norclozapine ratio.

Results: Among 90 patients initiated on clozapine, metformin use ($n = 48$) was associated with a smaller increase in percentage bodyweight (1.32% *versus* 5.95%, $p = 0.031$), lower rates of >7% gain in bodyweight (37.8% *versus* 63.0%, $p = 0.025$) but not >5% gain in bodyweight. Age below the median (32.0 years) was associated with greater bodyweight gain (5.55% *versus* 1.22%, $p = 0.046$). Sex, tobacco smoking, T2DM, clozapine dose and level and clozapine/norclozapine ratio were not associated with differences in change in bodyweight.

Conclusion: In this small retrospective cohort study, use of metformin within 12-months of clozapine initiation was associated with a statistically and clinically significant reduction in CIWG. Although there is increasing evidence for the role of metformin to ameliorate bodyweight gain at time of clozapine initiation, our findings need replication and testing in a randomised controlled trial before recommending metformin co-commencement with clozapine as standard clinical practice.

Keywords: clozapine, metformin, schizophrenia, weight gain

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Introduction

Schizophrenia impacts 7 in 1000 people.[1] Of this group, one in three will have treatment-resistant schizophrenia (TRS) with inadequate response to first line antipsychotics.[2] Clozapine is the most effective treatment for the positive symptoms of TRS,[3] and is associated with reductions in hospitalisations and all-cause mortality.[4,5]

Patients with schizophrenia die 15–20 years earlier than the general population,[6] and have an age- and sex-adjusted mortality rate three times

higher than the general population.[7] This mortality gap is driven largely by avertable cardiometabolic illness including bodyweight gain and metabolic syndrome.[6] Clozapine is associated with the highest rate of bodyweight gain and metabolic syndrome of all antipsychotics.[8] As such, monitoring of metabolic parameters among patients on clozapine is important.[9]

Beyond monitoring is the need to identify effective treatments to ameliorate clozapine-induced weight gain (CIWG) at time of clozapine initiation. Metformin has previously been shown to reduce bodyweight in obese patients who are stable on clozapine.[10] This is due partly to its effect on glucagon-like peptide 1 (GLP-1) – an intestinal peptide that modulates glucose regulation.[11] This is particularly relevant for clozapine as it disrupts the GLP-1 pathway in the intestinal epithelium, reducing GLP-1 levels and leading to bodyweight gain.[11]

Using retrospectively collected routine clinical data of patients with TRS, we investigated the effect of metformin on percentage change in bodyweight over the 12 months following clozapine initiation. Secondary outcomes included the difference in proportion of patients with clinically significant bodyweight change (>5% or >7%) by metformin use, as well as the impact of other potential moderators of CIWG, including age, sex, type 2 diabetes (T2DM), tobacco smoking, clozapine dose and levels, and clozapine/norclozapine ratio on percentage change in bodyweight.[11]

Methods

Ethics approval

Ethics approval was granted by the Metro South Health Human Research Ethics Committee and the University of Queensland (HREC/2020/QMS/60964).

Study design

This study used digital medical records collected retrospectively from four tertiary public hospitals in south-east Queensland (Princess Alexandra, Logan, West Moreton and Gold Coast University hospitals). We included all patients initiated on clozapine between 1 March 2017 and 30 June 2019. We excluded people under the age of 18 or over the age of 65 years, as well as those who were pregnant when initiated on clozapine or up to 12 months after initiation, and people for whom 12-month follow-up data were unavailable.

Data collection

Everyone initiated on clozapine at the four hospitals was identified through a review of pharmacy dispensing electronic records. We then extracted data from both the integrated electronic Medical Record (MR) and the Consumer Integrated Mental Health Application (CIMHA) programs on the following variables: age, sex, date of initiation, weight (at baseline and 12 months), clozapine dose, clozapine levels, presence of tobacco smoking, use of metformin and presence of T2DM, where available. However, data on antipsychotics prior to clozapine and metformin dose, time of metformin initiation or discontinuation were not available. The distribution of percentage change in body-weight was non-normally distributed with a rightward skew. To normalise distribution, we excluded patients with extreme body-weight change (greater than 22% change in bodyweight over 12-months) from the dataset.

Data analysis

We extracted data until 30 June 2020 to ensure all patients had the opportunity for 12 months of follow up. Data was analysed using IBM SPSS for Windows (version 27) using *t* tests and chi-square tests, as appropriate. The primary analysis was the difference in 12-month percentage bodyweight change by use of metformin. Our secondary outcome was proportion of patients with >5% or >7% bodyweight gain by metformin. The numbers of patients with a body mass index (BMI) < 25 or BMI ⩾ 25 (overweight/obese) were counted at baseline and 12 months. Patients changing between BMI categories were compared by metformin use. Additional secondary analyses were difference in 12-month percentage bodyweight change by tobacco smoking, sex, presence of T2DM diagnosis, age, clozapine dose and level and clozapine/norclozapine ratio (dichotomised at median).

We undertook one-way analysis of variance (ANOVA) by tobacco smoking, age, sex, T2DM diagnosis, clozapine dose and clozapine level and clozapine/norclozapine ratio to explore the impact of covariates on the primary analysis of difference in 12-month percentage bodyweight change by use of metformin.

Table 1. Patient demographics.

Demographics	All patients	Metformin	No metformin
	Number (%)		
Total number of included patients	90 (100)	48 (53.3)	42 (46.7)
Male sex	64/90 (71.1)	32/48 (66.7)	32/42 (76.2)
T2DM diagnosis[a]	12/60 (20.0)	10/38 (26.3)	2/22 (9.1)
Tobacco smoker	56/90 (62.2)	27/48 (56.3)	29/42 (69.0)
Baseline BMI ⩾25	74/90 (82.2)	43/48 (89.6)	31/42 (73.8)
Weight	Mean (and SD)		
Baseline weight (kg)	93.5 (±25.0)	99.2 (±27.2)	87.1 (±20.6)
Change in weight over 12 months (kg)	2.93 (±9.63)	1.27 (±10.6)	4.82 (±8.09)
Percentage change in weight over 12 months	3.5% (±10.3%)	1.3% (±10.6%)	6.0% (±9.4%)
Age	Median and IQR		
Age (years)	32.0 (24.0–44.3)	35.5 (26.3–45.8)	30.0 (23.0–42.0)
Clozapine			
Dose (mg)	300 (200–450)	363 (200–488)	300 (200–400)
Level (ng/ml)[b]	425 (230–595)	445 (293–648)	405 (104–580)
Clozapine/norclozapine ratio[c]	1.86 (1.57–2.38)	1.71 (1.56–2.26)	1.91 (1.56–2.83)
Metformin			
Daily dose (mg)[d]	–	1000 (1000–2000)	–

[a]Data on T2DM diagnosis was only available for 60/90 patients.
[b]Data on clozapine levels available for 70/90 patients.
[c]Data on clozapine/norclozapine ratio available for 53/90 patients.
[d]Data on metformin dose available for 30/48 patients.
BMI body mass index; IQR, interquartile range; SD, standard deviation; T2DM, type 2 diabetes mellitus.

Results

A total of 105 people were commenced on clozapine during the study period, of whom 90 had data that could be included in the analysis. The median age of included patients was 32.0 years [interquartile range (IQR) 24.00–44.25] and 71.1% were male (Table 1). The median clozapine dose at 12 months was 300 mg (IQR 200 mg–450 mg), with levels of 425 ng/ml (IQR 230 ng/ml–595 ng/ml) and clozapine/norclozapine ratio of 1.86 (IQR 1.57–2.38). Mean baseline weight was 93.5 kg (SD 25.0 kg), with 74/90 (82.2%) having a BMI of 25 or greater, placing them in the overweight or obese range. The mean percentage increase in weight after 12 months was 3.5% (SD 10.3%), equating to 2.93 kg (SD 9.63 kg).

Unadjusted analyses

Of the 90 patients initiated on clozapine, 48 (53.3%) were prescribed metformin. Metformin dose was available for 30 of 48 patients, with a mean daily dose of 1000mg (IQR 1000 mg–2000 mg) (Table 1). Use of metformin was associated with a statistically significantly lower increase in bodyweight (1.32% *versus* 5.95%, $p = 0.031$) (Table 2).

In terms of other moderators of CIWG, younger participants (i.e. those below the median of 32.0 years) gained significantly more bodyweight than those with an age below the median (Table 2). By contrast, sex, T2DM status tobacco smoking, clozapine dose and levels and clozapine/

Table 2. Percentage weight gain at 12 months by predictors and moderators of CIWG.

	Weight gain (%)	Number	Mean difference (%)	95% CI (%)	*p* value
Metformin use					
Yes	1.32	48	4.63	3.90–8.87	0.031
No	5.95	42			
Age					
⩽Median (32.0 years)	5.55	47	4.33	0.08–8.57	0.046
>Median (32.0 years)	1.22	43			
Gender					
Male	4.37	64	–3.05	–7.80 to 1.69	0.204
Female	1.31	26			
Any T2DM status[a]					
Yes	1.98	12	0.46	–7.01 to 7.92	0.903
No	2.44	48			
Any tobacco smoking					
Yes	4.05	56	–1.51	–5.97 to 2.96	0.504
No	2.55	34			
Clozapine dose					
⩽Median (300 mg)	2.77	47	1.49	–2.85 to 5.82	0.497
>Median (300 mg)	4.26	43			
Clozapine levels[b]					
⩽Median (425 ng/ml)	1.71	33	2.65	–2.31 to 7.61	0.216
>Median (425 ng/ml)	4.36	37			
Clozapine/norclozapine ratio[c]					
⩽Median (1.86)	1.25%	26	0.91%	–5.12% to 6.99%	0.764
>Median (1.86)	2.16%	27			

[a]T2DM status available for 60/90 patients.
[b]Clozapine levels available for 70/90 patients.
[c]Clozapine/norclozapine ratio available for 53/90 patients.
CI, confidence interval; CIWG, clozapine-induced weight gain; SD, standard deviation; T2DM, type 2 diabetes mellitus.

norclozapine ratio were not associated with significant differences in weight change (Table 2).

Participants on metformin were statistically significantly less likely to gain >7% of their bodyweight ($p = 0.025$), but there was no statistically significant difference between the groups for >5% body weight gain ($p = 0.096$) (Table 3). There was no statistically significant difference in the number of patients who changed BMI category by metformin use (Supplemental Table S1).

Table 3. Increase in bodyweight >5% and >7% by metformin use.

	Metformin use number (%)		*p* value
	No (*n* = 42)	**Yes (*n* = 48)**	
>5% increase in bodyweight			
No (*n* = 47)	18 (42.9%)	29 (60.4%)	0.096
Yes (*n* = 43)	24 (57.1%)	19 (39.6%)	
>7% increase in bodyweight			
No (*n* = 54)	20 (47.6%)	34 (70.8%)	0.025
Yes (*n* = 36)	22 (52.4%)	14 (29.2%)	

Adjusted analyses

Metformin remained associated with statistically significantly less percentage weight gain when adjusted for sex, age, tobacco smoking status and clozapine dose and levels. It was no longer statistically significantly different when adjusted for T2DM diagnosis or clozapine/norclozapine ratio (Supplemental Tables S2–S7).

Discussion

To the best of our knowledge, this is the first study exploring the impact of metformin on amelioration of CIWG when commenced in the early stages of clozapine treatment. Amelioration of bodyweight gain after clozapine initiation is particularly important, as previous research has indicated that bodyweight gain with clozapine is greatest in the first 12 months after initiation.[12] Our study uses real-world data and, as such, may be more applicable to clinical practice.

We found that use of metformin within 12-months of clozapine initiation is associated with both a statistically and clinically significant reduction in CIWG. Patients on metformin had smaller increases in percentage bodyweight, and were less likely to gain >7% of their bodyweight. Of note, younger age was associated with greater bodyweight gain following clozapine initiation.

These findings are in keeping with previous studies of bodyweight loss with metformin use in obese people already on a stable dose of clozapine.[10] To date, there have been no published randomised controlled trials (RCTs) of metformin co-commenced with clozapine for amelioration of bodyweight gain. Of two RCTs of metformin co-commenced with olanzapine, one showed significant reduction in bodyweight gain,[13] while the other was equivocal.[14] Metformin has been shown to be effective in leading to bodyweight loss among already obese people on antipsychotics other than clozapine.[15,16]

In contrast with previous studies, we did not find an association between female sex and greater bodyweight gain,[17,18] nor did we find that non-smokers gained greater bodyweight.[17] One study with these findings speculated that female sex and smoking modulated bodyweight gain through changes to the clozapine/norclozapine ratio.[18] Support for this theory comes from the observation that alteration of the clozapine/norclozapine ratio by CYP-450 1A2 inhibitors such as fluvoxamine has been associated with weight loss.[19] Although we did not replicate the findings related to sex and tobacco smoking, we did find that the effect of metformin was no longer significant when adjusted for the clozapine/norclozapine ratio even though this did not independently influence weight change in our study. However, this result should be treated with caution, as we had data on clozapine/norclozapine ratio for only 53/90 patients.

Similarly, adjustment of the analysis by T2DM diagnosis also led to a non-significant result for metformin but, again, this finding should be treated with caution, as all but two of the patients with T2DM were on metformin.

Limitations

We used routine data collected retrospectively and so did not have information on several important

variables that may influence weight, such as antipsychotics used prior to clozapine. This is relevant, as switching from an antipsychotic with a low propensity of bodyweight gain to one with a high propensity for bodyweight gain (such as clozapine) may lead to greater bodyweight gain.[20] Although we have no reason to believe prior antipsychotic was associated with metformin use, this cannot be discounted as a confounder. Similarly, there was no information on concomitant medications such as topiramate that could independently influence weight.[21] However, topiramate is used rarely at the hospitals in this study due to concerns about cognitive impairments and funding barriers to off-label prescribing.

Metformin dose was not available for all participants, nor was time and reason for metformin imitation or discontinuation. It is therefore possible that metformin was initiated in patients who were already showing bodyweight gain, thereby underestimating its true effect on preventing weight gain. Among patients for whom metformin dose was available, the median dose was in keeping with doses that had been found to be associated with bodyweight loss in other non-diabetic populations.[22] In addition, we were unable to collect data on other potential confounders such as diet and physical activity levels as this information was rarely recorded, and, if recorded, was not measured objectively. Data on illness acuity and cognitive impairment was not available. These factors may affect patient's ability to attend to activities of daily living, and their impact on weight. Finally, our sample size was relatively small, with only 90 patients included. This lack of study power may explain why some findings, such as proportion with >5% or >7% change in bodyweight did not consistently show difference in statistical significance. As such, these findings should be treated with caution.

Clinical implications

Given the high propensity for bodyweight gain associated with clozapine initiation, it is important to monitor the metabolic health of all people with TRS newly initiated on clozapine, especially those who are younger. Metabolic measures, including bodyweight, height, BMI, blood pressure, fasting glucose, triglycerides and high and low density lipoprotein cholesterol should be collected prior to clozapine commencement. Physical observations should be collected weekly for the first 18 weeks, then 4-weekly for the first year. Metabolic blood testing should be done every 6 months. Lifestyle interventions, including diet and exercise, should be initiated wherever possible.[23]

Despite these findings on CIWG, all-cause mortality remains much lower among people on clozapine,[5] and this agent remains the most effective medication for treating the positive symptoms of TRS and reducing hospitalisations.[3,4]

Although we found that initiation of metformin was associated with amelioration of CIWG, these results need to be tested in other clinical cohorts, or ideally in an RCT of metformin *versus* placebo. Further research is required before advising whether metformin be initiated routinely at time of clozapine commencement.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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