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 mortality 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

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.\textsuperscript{7} This mortal-
ity gap is driven largely by avertable cardiometa-
bolic illness including bodyweight gain and met-
abolic syndrome.\textsuperscript{6} Clozapine is associated
with the highest rate of bodyweight gain and met-
abolic syndrome of all antipsychotics.\textsuperscript{8} As such,
monitoring of metabolic parameters among
patients on clozapine is important.\textsuperscript{9}

Beyond monitoring is the need to identify effective
treatments to ameliorate clozapine-induced
weight gain (CIWG) at time of clozapine initi-
tion. Metformin has previously been shown to
reduce bodyweight in obese patients who are sta-
ble on clozapine.\textsuperscript{10} This is due partly to its effect
on glucagon-like peptide 1 (GLP-1) – an intestinal
peptide that modulates glucose regulation.\textsuperscript{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.\textsuperscript{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 clo-
zapine initiation. Secondary outcomes included
the difference in proportion of patients with clin-
ically 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 clozap-
ine/norclozapine ratio on percentage change in
bodyweight.\textsuperscript{11}

\section*{Methods}

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

\subsection*{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.

\subsection*{Data collection}
Everyone initiated on clozapine at the four hospi-
tals 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 initia-
tion, weight (at baseline and 12 months), clozap-
ine dose, clozapine levels, presence of tobacco
smoking, use of metformin and presence of
T2DM, where available. However, data on antip-
sychotics 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 distrib-
uted with a rightward skew. To normalise distri-
bution, we excluded patients with extreme
body-weight change (greater than 22% change in
bodyweight over 12-months) from the dataset.

\subsection*{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 \textit{t} tests and chi-square
tests, as appropriate. The primary analysis was
the difference in 12-month percentage body-
weight change by use of metformin. Our second-
ary 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 \geq 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 body-
weight 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.
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 1000 mg (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/

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**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                    |              |           |              |
| 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                       |              |           |              |
| 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 (110–580) |
| 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.
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 body-weight \( (p = 0.025) \), 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 2. Percentage weight gain at 12 months by predictors and moderators of CIWG.

| Predictor                                      | 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                                            |                 |        |                     |                |              |
| \( \leq \) 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                                 |                 |        |                     |                |              |
| \( \leq \) Median (300 mg)                     | 2.77            | 47     | 1.49                | −2.85 to 5.82  | 0.497        |
| \( > \) Median (300 mg)                        | 4.26            | 43     |                     |                |              |
| Clozapine levels\(^b\)                         |                 |        |                     |                |              |
| \( \leq \) 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\(^c\)             |                 |        |                     |                |              |
| \( \leq \) 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.
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 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

| 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%) |
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.\(^\text{20}\) 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.\(^\text{21}\) 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 initiation 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.\(^\text{22}\) 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.\(^\text{23}\)

Despite these findings on CIWG, all-cause mortality remains much lower among people on clozapine,\(^\text{5}\) and this agent remains the most effective medication for treating the positive symptoms of TRS and reducing hospitalisations.\(^\text{3,4}\)

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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