Irish Journal of Psychological Medicine, (2021), **38**, 49–55. © College of Psychiatrists of Ireland 2020
doi:10.1017/ipm.2020.1

ORIGINAL RESEARCH

Physical health trajectories of young people commenced on clozapine

B. O'Donoghue[1,2,3,*], A. Mujanovic[4], S. Young[5], T. Bridson[6], L. Mora[3], M. Bismark[7], J. Cocks[3], D. Siskind[8,9] and P. McGorry[1,2]

[1] *Orygen, National Centre of Excellence in Youth Mental Health, Melbourne, Victoria, Australia*
[2] *Centre for Youth Mental Health, University of Melbourne, Melbourne, Victoria, Australia*
[3] *Orygen Youth Health, Melbourne, Victoria, Australia*
[4] *School of Medicine, Orebro University, Orebro, Sweden*
[5] *Department of Psychiatry, University of Manchester, Manchester, UK*
[6] *Cairns Hospital, Cairns, Queensland, Australia*
[7] *Centre for Health Policy, University of Melbourne, Melbourne, Victoria, Australia*
[8] *School of Medicine, University of Queensland, Brisbane, Queensland, Australia*
[9] *Metro South Mental Health Services, Brisbane, Queensland, Australia*

Objectives: Clozapine is the most effective antipsychotic medication, but it has the highest propensity for metabolic side effects. A clozapine clinic was established within an early intervention for psychosis service to facilitate the timely commencement of clozapine and to manage the associated adverse effects. This study describes the changes in the weight, body mass index (BMI), waist circumference and blood pressure after 6 months in young people commenced on clozapine.

Method: This was a prospective cohort study of all young people, aged 15–24 years, commenced on clozapine within an early intervention service in Melbourne, Australia, between 01.04.2016 and 30.06.2018. Continuous data were analyzed with paired *t*-test and categorical with Wilcoxon signed-rank test.

Results: Twenty-six young people received 6 months of treatment with clozapine, of whom the mean age was 19.8 years (S.D. ±3.1) and 66.7% were male. After 6 months, the mean weight gain was 5.1 kg (S.D. ±10.1 kg) and over half (53.8%) gained clinically significant weight. The proportion of young people classified as either overweight or obese rose from 69.2% to 88.5% ($p = 0.006$). The proportion of young people with a waist circumference above the recommended parameters increased from 57.9% to 78.9% ($p = 0.008$). Hypertension was present in 30%, and after 6 months, 45% had hypertension ($p = 0.64$). Metformin was prescribed to 34.6%, typically to those with the greatest and most rapid weight gain.

Conclusion: Among young people with treatment resistant psychosis, clozapine is associated with significant metabolic side effects in the early stages of commencement. More interventions aimed at attenuating this weight gain are needed.

Received 08 August 2019; Revised 28 November 2019; Accepted 20 December 2019; First published online 20 February 2020

Key words: Schizophrenia, psychosis, clozapine, metabolic syndrome, obesity.

Introduction

Around one-quarter of people with a first episode of psychosis (FEP) will experience persistent positive psychotic symptoms despite at least two adequate trials of antipsychotic medication (Demjaha *et al.* 2017). Clozapine is the most effective antipsychotic medication and the only medication licensed for the treatment of resistant schizophrenia (TRS) (Leucht *et al.* 2013; Siskind *et al.* 2016a). Furthermore, it is associated with shorter and fewer hospitalizations (Siskind *et al.* 2019) and lower rates of early mortality (Wimberley *et al.* 2017). However, it is recommended as a third-line treatment in individuals with a diagnosis of schizophrenia due to the risk of serious side effects, such as cardiac complications and agranulocytosis. In addition, clozapine has the highest propensity of all antipsychotic medications for weight gain (Leucht *et al.* 2013), as well as an increased risk of metabolic syndrome and diabetes mellitus type 2 (Larsen *et al.* 2018).

Despite offering the best outcomes for people with treatment resistant psychosis, there are often substantial delays in the commencement of clozapine, ranging from 19 weeks to 5.5 years (Thien and O'Donoghue, 2018). The requirement for frequent monitoring of blood tests was cited by clinicians as a barrier to the commencement of clozapine, as well as the metabolic side effects of the medication (Paranthaman, 2006). Psychiatrists have expressed a preference for polypharmacy of antipsychotic medication as opposed to

*Address for correspondence: B. O'Donoghue, Orygen, National Centre of Excellence in Youth Mental Health, 35 Poplar rd, Parkville, Melbourne, Victoria, Australia.
(Email: brian.odonoghue@orygen.org.au)

commencing clozapine (Nielsen *et al.* 2010), despite this non-evidence-based practice resulting in overall higher exposure to antipsychotic medication and adverse metabolic side effects (Connolly and Taylor, 2014). There has been a renewed call for the timely use of clozapine in eligible individuals (Kahn *et al.* 2018), and it is a recommendation within the Health Service Executive Early Intervention for Psychosis Model of Care in Ireland (Health Service Executive, 2019).

These current delays in the commencement of clozapine and the preference for polypharmacy mean that individuals with persistent psychotic symptoms are exposed to other anti-psychotic medications for a long period prior to commencing clozapine. Weight gain and other metabolic side effects are common in other antipsychotic medications (Leucht *et al.* 2013), and hence individuals who are being considered for clozapine may already have developed obesity or metabolic syndrome. At the Early Psychosis Prevention and Intervention Centre (EPPIC) in Melbourne, a 42 week delay to the commencement of clozapine in young people with TRS was observed (Thien *et al.* 2018). In order to reduce these delays, a clozapine clinic within the early intervention service was established.

This clozapine clinic within an early intervention for psychosis service provides the opportunity to examine the physical health trajectories of young people who commence clozapine in a timely manner. This study aimed to describe the changes in the weight, body mass index (BMI), waist circumference and blood pressure in young people commenced on clozapine after 6 months of treatment. Furthermore, this study aimed to describe the outcomes of those who were prescribed metformin in addition to clozapine.

Methods

This is a naturalistic, prospective cohort study of young people who attended the EPPIC at Orygen Youth Health (OYH) in Melbourne. The study included all young people with a FEP who were commenced on clozapine and who remained on the medication for at least 6 months.

Study setting

OYH is a youth mental health service for young people aged between 15 and 24 years in a catchment area of over 1 million residents. The EPPIC service provides care to approximately 200 new cases of FEP annually (Eaton *et al.* 2019). A previous cohort study at EPPIC estimated that approximately 10% of young people who initially present with a FEP will be eligible for clozapine within the 2 year episode of care within the early intervention service; however, less than 60% of these young people were actually commenced clozapine (Thien *et al.* 2018). Therefore, based on this, over the 27 month study period, we anticipated that 45 young people would have been eligible to commence clozapine. The clozapine service is led by experienced mental health nurses with support from psychiatrists and psychiatry registrars. Within the service, there is a dietician and exercise physiologist who offer individual and group sessions. Metformin, a medication which controls blood glucose levels, may also be prescribed due to its potential to reduce weight gain. At present, there is no algorithm for prescribing metformin, and the decision to prescribe metformin is made in consultation between the treating doctor, the young person and their caregivers if appropriate.

Participants

The study included all young people with a psychotic disorder who were commenced on clozapine between 1st of April 2016 and 30th June 2018 and for whom 6 months of outcomes data were available. All participants had persistent positive symptoms after an adequate trial of at least two other antipsychotic medications, including at least one second generation antipsychotic, taken regularly and at an adequate dose. The decision to commence clozapine was made by the patient and their treating psychiatrist, with input from a Treatment Resistance Early Assessment Team (TREAT) panel, which is a consultation team that provides assistance to clinicians at EPPIC.

Instruments, measures and sources of information

Blood pressure, weight, height and waist circumference were measured during routine appointments with the clozapine service. Demographic and clinical data were extracted from patient electronic medical records. Clinically significant weight gain was defined as an increase of ≥7% of body weight. Waist circumference of greater than 94 cm in males and 80 cm in females was considered abnormal (International Diabetes Federation, 2006). Hypertension was defined as a blood pressure of ≥130 systolic or 85 diastolic or treatment for previously diagnosed hypertension. Participants were followed up for 6 months with data recorded within 4 weeks of this cut off included in the study.

Statistical analysis

Weight and waist circumference were treated as continuous ratio variables, while hypertension was classified as a categorical variable. We use descriptive statistics to describe baseline variables. We analyzed continuous variables with paired *t*-tests and categorical variables with Wilcoxon signed-rank test. Statistical significance was set at $p < 0.05$. BMI was calculated from weight/height^2 (kg/m^2)

https://doi.org/10.1017/ipm.2020.1 Published online by Cambridge University Press

Table 1. *Participant demographic and clinical characteristics at baseline*

	Total cohort ($N = 26$)		Male ($N = 17$)		Female ($N = 9$)			
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Statistical test of difference	*p*
Age	19.8	3.1	20.1	3.2	19.3	2.9	$t = 0.57$, df = 24	0.58
Diagnosis	*N*	%						
Schizophrenia	22	84.6	14	82.4	8	88.9	$X^2 = 1.3$, df = 3	0.73
Schizoaffective	2	7.7	1	5.9	1	11.1		
Major depressive disorder	1	3.8	1	5.9	0	0		
Bipolar disorder	1	3.8	1	5.9	0	0		
Substance abuse								
Present	11	42.3	10	58.8	1	11.1	$X^2 = 5.5$, df = 1	0.02
Not present	15	57.7	7	41.2	8	88.9		
Physical health	Mean	S.D.	Mean	S.D.	Mean	S.D.		
Weight (kg)	84.0	17.4	84.9	17.7	82.2	17.8	$t = 0.36$, df = 24	0.72
Waist (cm)[a]	94.2	17.3	95.4	13.2	92.4	23.5	$t = 0.38$, df = 19	0.71
	N	%	*N*	%	*N*	%		
Hypertension present[b]	9	36.0	7	43.8	2	22.2	$X^2 = 1.2$, df = 1	0.28
Normal blood pressure	16	64.0	9	56.3	7	77.8		
BMI categories								
Normal weight (18.5–24.9)	8	30.8	6	35.3	2	22.2	$X^2 = 1.3$, df = 2	0.53
Overweight (25–29.9)	10	38.5	7	41.2	3	33.3		
Obese (30+)	8	30.8	4	23.5	4	44.4		

[a]Data available for 80.8% ($N = 21$).
[b]Data available for 96.2% ($N = 25$).

Ethical approval

This study received ethical approval from the Melbourne Health Human Research Ethics Committee.

Results

Participants – baseline characteristics

During the study period, 26 young people completed 6 months of treatment with clozapine. Two-thirds, 66.7% ($n = 18$), were male, and the mean age of participants was 19.8 years (S.D. ±3.1). The most common diagnosis was schizophrenia (84.6%), followed by schizoaffective disorder (7.7%), major depressive disorder with psychosis (3.8%) and bipolar affective disorder (3.8%). A diagnosis of concurrent substance abuse was present in 42.3% ($N = 11$). The median dose of clozapine after 6 months was 400 mg (I.Q.R. 337.5–500 mg). Clozapine was commenced a median of 51 weeks (I.Q.R. 36.25–76.25) after presenting to the early intervention service (representing a delay of approximately 35 weeks, if each trial is assumed to take 8 weeks each). The clinical characteristics of the cohort are presented in Table 1.

Physical health trajectories

The physical health trajectories, in regards to weight, BMI, waist circumference and blood pressure, of the young people commenced on clozapine are presented in Table 2. The mean weight of participants on commencement of clozapine was 84.0 kg (S.D. ±17.4 kg). This increased to 89.1 kg (S.D. ±17.6 kg) after 6 months of treatment with clozapine, representing a statistically significant increase of 5.1 kg ($t = 1.256$, df = 25, $p = 0.02$). The mean weight gain was similar in males and females (5.3 kg for males and 4.8 kg for females). Over half (53.8%) of young people commenced on clozapine gained clinically significant weight (≥7% of weight). However, around one in ten (11.5%) experienced clinically significant weight loss of a similar proportion of body weight (i.e. ≥7% of weight). The difference in weight from commencement to 6 months was not correlated with the dose of clozapine (rs = –0.004, $N = 26$, $p = 0.98$). In regards to BMI, at the time of commencement of clozapine, 38.5% ($N = 10$) of young people were overweight (BMI 25–29.9) and 30.8% ($N = 4$) were classified as obese, and there was no difference in males or females ($X^2 = 1.3$, df = 2, $p = 0.53$). After 6 months of treatment of clozapine, the proportion of young people who were classified as overweight or obese rose from 69.2% to 88.5% ($X^2 = 7.63$, df = 1, $p = 0.006$) and this increase was significant in both males and females (Table 2).

Waist circumference data were available for 73.1% ($N = 19$) of participants. For males, the mean waist

https://doi.org/10.1017/ipm.2020.1 Published online by Cambridge University Press

Table 2. *Physical health trajectories for young people commenced on clozapine after 6 months*

	Commencing		26 weeks		
Weight (kg)	*N*	Mean (S.D.)	Mean (S.D.)	Paired *t*-test	*p*
Total cohort	26	84.0 (17.4)	89.1 (17.6)	−2.56	0.02
Male	17	84.9 (17.7)	90.2 (16.4)	−2.11	0.05
Female	9	82.2 (17.8)	87.0 (20.5)	−1.37	0.21
	Commencing		26 weeks		
BMI – % classified as overweight or obese	*N*	*N* (%)	*N* (%)	X^2 (df)	
Total cohort	26	18 (69.2)	23 (88.5)	7.63 (1)	0.006
Male	17	11 (64.7)	15 (88.2)	4.16 (1)	0.04
Female	9	7 (77.8)	8 (88.9)	3.94 (1)	0.047
Waist circumference (cm)	*N*	Mean (S.D.)	Mean (S.D.)	Paired *t*-test	*p*
Total cohort	19	94.7 (17.8)	97.9 (14.4)	−1.50	0.15
Male	11	96.4 (13.4)	99.0 (8.5)	−1.16	0.27
Female	8	92.4 (23.5)	96.4 (20.7)	−0.95	0.37
	Commencing		26 weeks		
Hypertension present	*N*	*N* (%)	*N* (%)	*Z*	*p*
Total cohort	20	6 (30.0)	9 (45.0)	−0.91	0.47
Male	12	5 (41.7)	6 (50.0)	−0.33	0.74
Female	8	1 (12.5)	3 (37.5)	−1.41	0.16

circumference at the time of commencement of clozapine was 96.4 cm (S.D. ±13.4 cm) and 45.5% ($N = 5$) had a waist circumference above the recommended parameters. After 6 months of treatment with clozapine, the mean waist circumference of males was 99.0 cm (S.D. ±8.5 cm), representing a non-significant mean increase of 2.6 cm (S.D. ±7.5 cm) ($t = -1.16$, df = 10, $p = 0.27$). The proportion with a waist circumference greater than the recommended parameters increased from 45.5% to 72.7% ($X^2 = 3.44$, df = 1, $p = 0.06$). For females, the mean waist circumference at the time of commencement of clozapine was 92.4 cm (S.D. ±23.5 cm) and 75% ($N = 6$) had a waist circumference above the recommended parameters. After 6 months of treatment with clozapine, the mean waist circumference of females was 96.4 cm (S.D. ±20.7 cm), representing a non-significant mean increase of 4.0 cm (S.D. ±11.8 cm) ($t = -0.95$, df = 7, $p = 0.37$). The proportion with a waist circumference greater than the recommended parameters increased from 75.0% to 87.5% ($X^2 = 3.43$, df = 1, $p = 0.06$). For the total cohort, the proportion of young people with a waist circumference above the recommended parameters increased from 57.9% ($N = 11$) to 78.9% ($N = 15$) after 6 months of treatment with clozapine ($\chi^2 = 7.0$, df = 1, $p = 0.008$).

Blood pressure data were available for 76.9% ($N = 20$) of participants. The proportion of young people with hypertension prior to commencement of clozapine was 30% ($N = 6$) and after 6 months of treatment, 45% ($N = 9$) had hypertension, which was non-significant ($X^2 = 0.47$, df = 1, $p = 0.64$), and this result was consistent in males and female.

Interventions for physical health

Metformin (1000 mg) was prescribed to over one-third (34.6%) of the young people who were commenced on clozapine. Metformin was prescribed a median of 18 weeks (I.Q.R. 9–27.5) after the commencement of clozapine. The mean weight gain after 6 months of treatment in clozapine in those who were also prescribed metformin was 8.4 kg (S.D. ±14.1 kg) compared to 3.4 kg (S.D. ±7.3 kg) in those who were not prescribed metformin. As metformin was prescribed a median of 18 weeks after the commencement of clozapine, post-hoc analysis was performed to examine the physical health trajectories from week 18 to 26 according to whether metformin was prescribed (data were available for 80.7% of participants at week 18 and 26). In those prescribed metformin, there was a mean weight *loss* of 0.46 kg (S.D. ±3.8) between week 18 and

https://doi.org/10.1017/ipm.2020.1 Published online by Cambridge University Press

26 compared to a mean weight *gain* of 0.44 kg (S.D. ±3.1) in those who were not prescribed metformin; however, this was not significant ($t = -0.58$, df = 19, $p = 0.57$).

Discussion

Summary of findings

This study found that over half of young people commenced on clozapine experienced clinically significant weight gain (≥7% of body weight). Furthermore, after 6 months, the majority of young people was classified as either overweight or obese and had a waist circumference greater than the recommended parameters. There was no significant change in rates of hypertension; however, nearly half of the young people had hypertension. Metformin was used in approximately one-third of young people prescribed clozapine, and it tended to be used in those with the most pronounced initial weight gain.

Clinical implications

Alongside this renewed call for the timely use of clozapine (Kahn *et al.* 2018), there is a need for greater attention of managing side effects, including metabolic, gastrointestinal, cardiac and hematological side effects. Lifestyle factors, including diet and exercise, have been demonstrated to be effective in preventing weight gain in individuals with a FEP (Curtis *et al.* 2015) and therefore these interventions should have already been trialed in individuals who are being considered for clozapine. However, it has been demonstrated that there are high rates of sedentary behavior, poor dietary intake and smoking among people taking clozapine, and hence there is still a need for lifestyle interventions in this group and research evaluating their effectiveness (Lappin *et al.* 2018).

In addition to lifestyle interventions, due to the severity of the rapid weight gain, it is likely that pharmacotherapy could have a role in addressing the cardiometabolic side effects of clozapine. There is evidence supporting the use of metformin adjunct to clozapine, and it appears that metformin is more effective at preventing weight gain as opposed to reversing the gains in weight (Siskind *et al.* 2016b). However, there is not yet good evidence on whether metformin should be routinely prescribed at the same time as the commencement of clozapine (Siskind *et al.* 2018). In our study setting, metformin was prescribed in those with the most pronounced weight gain and tended to be prescribed late, usually after 4 months of clozapine treatment. While non-significant finding, there was a suggestion that metformin may have slowed or reversed the trajectory of those who had rapid, significant and initial weight gain. The practice of only commencing metformin after significant weight gain leads to a concern that opportunities for early prevention of weight gain may be missed.

Despite the rapid onset of weight gain and high prevalence of obesity and other physical health complications, there is consistent evidence that people with TRS who are not treated with clozapine have an earlier mortality compared to those treated with clozapine (Tiihonen *et al.* 2009; Wimberley *et al.* 2017; Cho *et al.* 2019). It was previously assumed that the mandatory, regular monitoring for clozapine that involves frequent contact with healthcare staff could be one of the reasons for preventing earlier mortality; however, a study in the UK demonstrated that this was not the determining factor (Hayes *et al.* 2015). Therefore, alongside developing and evaluating further interventions to address the cardiometabolic effects of clozapine, we also need to understand the reasons for the better mortality outcomes in those treated with the medication.

Strengths and limitations

The strengths of this study include that it was undertaken in a 'real world setting' and therefore includes a representative cohort of young people who were commenced on clozapine. Furthermore, as a result of aiming to start clozapine as early as indicated, it reduced the exposure to other antipsychotic medications that can also cause weight gain and other metabolic side effects. However, the findings of this study need to be considered within the limitations, first there was a small sample size and there was missing data for a proportion of the cohort at follow-up, which was confined to only 6 months. A further limitation is that height was not measured at follow-up, and therefore, there could have been an increase in the height over the 6 month follow-up, and this would have resulted in the changes in BMI being over-estimated.

Conclusions

Clozapine is associated with significant, rapid weight gain in the early stages of commencement, and more interventions aimed at attenuating this weight gain are needed. The risk of these metabolic side effects needs to be assessed in the context of the important mental health benefits offered by clozapine. Further research into potential interventions aimed at preventing, reducing or reversing the metabolic side effects of clozapine is urgently needed.

Financial support

This work did not receive any financial support.

Conflicts of interest

The authors Dr B.O., A.M., S.Y., T.B., L.M., M.B., J.C., D.S. and P.M. have no conflicts of interest to disclose.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008.

The study protocol was approved by the ethics committee of each participating institution.

References

Cho J, Hayes RD, Jewell A, Kadra G, Shetty H, MacCabe JH, Downs J (2019). Clozapine and all-cause mortality in treatment-resistant schizophrenia: a historical cohort study. *Acta Psychiatrica Scandinavica* **139**, 237–247.

Connolly A, Taylor D (2014). Factors associated with non evidence-based prescribing of antipsychotics. *Therapeutic Advances in Psychopharmacology* **4**, 247–256.

Curtis J, Watkins A, Rosenbaum S, Teasdale S, Kalucy M, Samaras K, Ward PB (2015). Evaluating an individualized lifestyle and life skills intervention to prevent antipsychotic-induced weight gain in first-episode psychosis. *Early Intervention in Psychiatry* **10**, 267–276.

Demjaha A, Lappin JM, Stahl D, Patel MX, MacCabe JH, Howes OD, Heslin M, Reininghaus UA, Donoghue K, Lomas B, Charalambides M, Onyejiaka A, Fearon P, Jones P, Doody G, Morgan C, Dazzan P, Murray RM (2017). Antipsychotic treatment resistance in first-episode psychosis: prevalence, subtypes and predictors. *Psychological Medicine* **47**, 1981–1989.

Eaton S, Harrap B, Downey L, Thien K, Bowtell M, Bardell-Williams M, Ratheesh A, McGorry P, O'Donoghue B (2019). Incidence of treated first episode psychosis from an Australian early intervention service and its association with neighbourhood characteristics. *Schizophrenia Research* **209**, 206–211.

Hayes RD, Downs J, Chang CK, Jackson RG, Shetty H., Broadbent M., Hotopf M, Stewart R. (2015). The effect of clozapine on premature mortality: an assessment of clinical monitoring and other potential confounders. *Schizophrenia Bulletin* **41**, 644–655.

Health Service Executive (2019). Early intervention for psychosis model of care (https://www.hse.ie/eng/about/who/cspd/ncps/mental-health/psychosis/resources). Accessed June 2019.

International Diabetes Federation (2006). The IDF consenus worldwide definition of the metabolic syndrome (https://www.idf.org/e-library/). Accessed June 2019.

Kahn RS, Winter Van Rossum I, Leucht S, McGuire P, Lewis SW, Leboyer M, Arango C, Dazzan P, Drake R, Heres S, Diaz-Caneja CM, Rujescu D, Weiser M, Galderisi S, Glenthoj B, Eijkemans MJC, Fleischhacker WW, Kapur S, Sommer IE (2018). Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE): a three-phase switching study. *Lancet Psychiatry* **5**, 797–807.

Lappin JM, Wijaya M, Watkins A, Morell R, Teasdale S, Lederman O, Rosenbaum S, Dick S, Ward P, Curtis J (2018). Cardio-metabolic risk and its management in a cohort of clozapine-treated outpatients. *Schizophrenia Research* **199**, 367–373.

Larsen JR, Svensson CK, Vedtofte L., Jakobsen ML, Jespersen HS, Jakobsen MI, Koyuncu K, Schjerning O, Nielsen J, Ekstrom CT, Holst JJ, Correll CU, Vilsboll T, Fink-Jensen A (2018). High prevalence of prediabetes and metabolic abnormalities in overweight or obese schizophrenia patients treated with clozapine or olanzapine. *CNS Spectrums*, 1–12. Published online ahead of print. doi:10.1017/S1092852918001311.

Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lassig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* **382**, 951–962.

Nielsen J, Dahm M, Lublin H, Taylor D (2010). Psychiatrists' attitude towards and knowledge of clozapine treatment. *Journal of Psychopharmacology* **24**, 965–971.

Paranthaman R, Baldwin RC (2006). Survey of clozapine use by consultant old age psychiatrists. *Psychiatric Bulletin* **30**, 410–412.

Siskind D, Friend N, Russell A, McGrath JJ, Lim C, Patterson S, Flaws D, Stedman T, Moudgil V, Sardinha S, Suetani S, Kisely S, Winckel K, Baker A (2018). CoMET: a protocol for a randomised controlled trial of co-commencement of METformin as an adjunctive treatment to attenuate weight gain and metabolic syndrome in patients with schizophrenia newly commenced on clozapine. *BMJ Open* **8**, e021000. doi: 10.1136/bmjopen-2017-021000.

Siskind D, McCartney L, Goldschlager R, Kisely S (2016a). Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. *British Journal of Psychiatry* **209**, 385–392.

Siskind D, Reddel T, MacCabe JH, Kisely S (2019). The impact of clozapine initiation and cessation on psychiatric hospital admissions and bed days: a mirror image cohort study. *Psychopharmacology (Berl)* **236**, 1931–1935.

Siskind DJ, Leung J, Russell AW, Wysoczanski D, Kisely S (2016b). Metformin for clozapine associated obesity: a systematic review and meta-analysis. *PLoS One*, **11**, e0156208.

Thien K, Bowtell M, Eaton S, Bardell-Williams M, Downey L, Ratheesh A, McGorry P, O'Donoghue B (2018). Clozapine use in early psychosis. *Schizophrenia Research* **199**, 374–379.

https://doi.org/10.1017/ipm.2020.1 Published online by Cambridge University Press

Thien K, O'Donoghue B (2018). Delays and barriers to the commencement of clozapine in eligible people with a psychotic disorder: a literature review. *Early Intervention in Psychiatry*, **13**, 18–23.

Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, Haukka J (2009). 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* **374**, 620–627.

Wimberley T, MacCabe JH, Laursen TM, Sorensen HJ, Astrup A, Horsdal HT, Gasse C, Stovring H (2017). Mortality and self-harm in association with clozapine in treatment-resistant schizophrenia. *American Journal of Psychiatry* **174**, 990–998.

https://doi.org/10.1017/ipm.2020.1 Published online by Cambridge University Press