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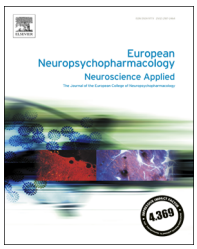

A systematic review and meta-analysis of randomised controlled trials of treatments for clozapine-induced obesity and metabolic syndrome

Jorge Zimbron[a,b,*,1], **Golam M. Khandaker**[a,b,1], **Chiara Toschi**[c], **Peter B. Jones**[a], **Emilio Fernandez-Egea**[a,b,d]

[a]*Department of Psychiatry, University of Cambridge, UK*
[b]*Elizabeth House, Fulbourn Hospital, Fulbourn, Cambridge, CB21 5EF, UK*
[c]*Department of Neuropsychiatry, University College London, Gower Street, London, WC1E 6BT, UK*
[d]*Behavioural and Clinical Neuroscience Institute (BCNI), University of Cambridge, UK*

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Abstract
Metabolic complications are commonly found in people treated with clozapine. Reviews on the management of this problem have generally drawn conclusions by grouping different types of studies involving patients treated with various different antipsychotics. We carried out a systematic review and meta-analysis of pharmacological and non-pharmacological treatments for clozapine-induced obesity or metabolic syndrome. Two researchers independently searched PubMed and Embase for randomised controlled trials (RCTs) of treatments for clozapine-induced obesity or metabolic syndrome. All other types of studies were excluded. We only included RCTs where more than 50% of participants were taking clozapine.
We identified 15 RCTs. Effective pharmacological treatments for clozapine-induced obesity and metabolic syndrome include metformin, aripiprazole, and Orlistat (in men only). Meta-analysis of three studies showed a robust effect of metformin in reducing body mass index and waist circumference but no effects on blood glucose, triglyceride levels, or HDL levels. In addition, there is limited evidence for combined calorie restriction and exercise as a non-pharmacological alternative for the treatment of clozapine-induced obesity, but only in an in-patient setting. Rosiglitazone, topiramate, sibutramine, phenylpropanolamine, modafinil,

Abbreviations: BMI, Body mass index; CHAOS, Coronary artery disease, hypertension, atherosclerosis, obesity, and stroke; HbA1c, Glycosylated haemoglobin; HDL, High-density lipoprotein; Kg, kilogram; LDL, Low-density lipoprotein; RCT, Randomised controlled trial; VLDL, Very-low-density lipoprotein

*Corresponding author at: Elizabeth House, Fulbourn Hospital, Fulbourn, Cambridge, CB21 5EF.
E-mail address: jz308@cam.ac.uk (J. Zimbron).

[1]Joint first authors.

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and atomoxetine have not shown to be beneficial, despite reports of efficacy in other populations treated with different antipsychotics.
We conclude that randomised-controlled trial data support the use of metformin, aripiprazole, and Orlistat (in men only) for treating clozapine-induced obesity. Calorie restriction in combination with an exercise programme may be effective as a non-pharmacological alternative. Findings from trials in different populations should not be extrapolated to people being treated with clozapine.

1. Introduction

Average life expectancy in people with schizophrenia is about 20 years shorter than the general population – this difference is largely attributed to increased mortality from chronic physical conditions such as heart disease and diabetes mellitus (Saha et al., 2007). Cardiometabolic complications such as weight gain, obesity, metabolic syndrome and diabetes mellitus are well recognised side effects of antipsychotics particularly the atypicals which are widely used today (De Hert et al., 2011).

Clozapine is generally regarded as the most efficacious antipsychotic drug (Leucht et al., 2013), but has been associated with the highest risk for developing obesity and metabolic complications compared with other atypical antipsychotics (Allison et al., 1999; Bodén et al., 2013; Gianfrancesco et al., 2002). It is estimated that the prevalence of metabolic syndrome in long-term clozapine users ranges from 28 to 45% (Bai et al., 2011; Bodén et al., 2013).

Clozapine has affinities for many receptors from multiple neurotransmitter systems. These include the dopamine (D1-D5), serotonin (5-HT1A/1D, 5-HT2A/2C, 5-HT3, 5-HT6, and 5-HT7), histaminergic (H1-H3), muscarinic (M1-5), adrenergic (α1-2 and β1-3), and GABAA receptors (Meltzer, 1994). The difference in the receptor binding profiles of different antipsychotics is thought to account for the different weight gain liabilities associated with them (Reynolds and Kirk, 2010). The weight gain induced by clozapine is highly variable and a twin study by Theisen and colleagues has shown that it is more highly correlated in monozygotic twins than in siblings, suggesting that genetic factors may play a major role (Theisen et al., 2005). More than 200 genes or markers have been linked to human obesity and many of them could be important in clozapine-induced obesity (Basile et al., 2001).

It has been hypothesised that clozapine causes obesity via its actions on the serotonergic and histaminergic systems. Rat studies have shown that 5-HT1A agonists and 5-HT2C/2A antagonists cause a marked increase in feeding (Yamada et al., 1996). Clozapine is a potent 5-HT2C/2A antagonist and a 5-HT1A partial agonist. H1 antagonism is known to be associated with increased feeding and weight gain, and antipsychotics with a high propensity for weight gain, like clozapine, have strong affinities for the H1 receptor (Wirshing et al., 1999). Two meta-analyses (De Luca et al., 2007; Sicard et al., 2010) have linked polymorphisms in the serotonergic system to clozapine-induced obesity, making it the most robust pharmacogenetic mechanism to date that could explain some of the variation in weight gain amongst these patients. Despite the evidence, it must be noted that some studies have not found such association (Basile et al., 2001; Rietschel et al., 1997; Yevtushenko et al., 2007). Results in studies looking at the histaminergic system have shown positive (Vehof et al., 2011) and negative (Hong et al., 2002) findings. Reviews of the literature (Basile et al., 2001; Lett et al., 2012; Müller et al., 2004; Reynolds, 2012) highlight many other targets that have been investigated in order to try to explain the variation in weight gain seen in people taking clozapine. The results of this research provide clues to the mechanisms behind clozapine-induced weight gain, but our understanding of this complex phenomenon is still limited and further research is warranted.

Clozapine is the gold standard for managing treatment-resistant schizophrenia, which comprises approximately 25% of all patients with this condition (Brenner et al., 1990). Clozapine is the only antipsychotic approved by the US Food and Drug Administration (FDA) for treatment-resistant schizophrenia (Novartis, 2002). Similarly, the UK national institute for health and care excellence (NICE) recommends clozapine as the treatment of choice for patients who do not respond to two antipsychotics (NICE, 2014). Clinicians, therefore, are faced with a difficult choice between efficacy and long-term cardiometabolic complications when choosing clozapine.

We present a systematic review and meta-analysis of pharmacological and non-pharmacological treatments for clozapine-induced obesity and metabolic syndrome. Previous reviews have considered the effect of weight loss treatments for patients who take antipsychotics (Faulkner et al., 2007, 2003; Maayan et al., 2010), but these have included studies of various different antipsychotics. Different antipsychotics have very different effects on weight gain and metabolic risk (Leucht et al., 2013), so there is a need to focus on particular antipsychotics in order to reduce heterogeneity. Given the different mechanisms of action of different antipsychotics, and their different metabolic effects, it is reasonable to suggest that treatments that may work with one antipsychotic, may not work with another. Whitney and colleagues have focused on clozapine (Whitney et al., 2015), but the review presented here is distinct in two ways. We report an up-to-date, systematic review and a meta-analysis (for metformin) of randomised controlled trials (RCTs) of pharmacological and other treatments for clozapine induced obesity and metabolic syndrome.

2. Experimental procedures

2.1. Search strategy

The PubMed and Embase electronic databases were searched from their inception until the 30th July, 2015 for all studies (without any filters) involving the management of obesity or metabolic syndrome in people taking clozapine using the following search terms: (clozapine OR norclozapine OR clozaril OR gen-clozapine OR analeptic OR leponex