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Cardio-metabolic risk and its management in a cohort of clozapine-treated outpatients

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ABSTRACT

Objective: To comprehensively assess cardio-metabolic risk factors and their management in a large sample of outpatients treated with clozapine.
Methods: Observational cross-sectional study of all clozapine users attending specialized clozapine monitoring outpatient clinics in three public hospitals in Sydney, Australia were approached to participate over the one-year period 01/10/2015–30/09/2016. Cardio-metabolic risk factors including metabolic syndrome, risk for future development of diabetes, smoking, physical activity, nutrition, and prescribed medications were assessed at face-to-face interview and through medical record review. Among patients who had cardio-metabolic risk factors, the proportion receiving appropriate management was assessed.
Results: Of 451 registered clozapine clinic attenders, 92.2% completed questionnaires and anthropometric measurements. 58.3% met criteria for metabolic syndrome. 79.6% were overweight or obese. 55.9% had blood pressure meeting metabolic syndrome criteria. 46.6% had elevated fasting blood glucose and 55.2% had elevated blood triglycerides. 43.6% were current smokers. Only 10% achieved recommended weekly physical activity levels. Unhealthy food categories were highly consumed. 32.1% were on additional antipsychotics. In the majority of individuals, cardio-metabolic risk factors were untreated or under-treated.
Conclusions: Clozapine use was associated with very high rates of cardiovascular and metabolic risk factors, which were frequently under-treated. Management of both physical and mental health should be prioritized. Polypharmacy should be rationalized. Future research should investigate the effectiveness of smoking cessation and lifestyle interventions in this high-risk population.

1. Introduction

Clozapine is an atypical antipsychotic used for treating refractory schizophrenia. Despite its efficacy, clozapine leads to significant weight gain (Allison et al., 1999), glucose dysregulation (Jin et al., 2004) and disorders of lipid and triglyceride metabolism (Meyer and Koro, 2004) that occur independently of weight gain in animal models (Skrede et al., 2012).

People with schizophrenia have been shown to have a mortality rate two to three times greater (Brown et al., 2010; Newman and Bland, 1991; Saha et al., 2007), and a life expectancy of 14.5 years shorter (Hjorthoj et al., 2017) than the general population. The increased risk of premature mortality in schizophrenia is most often due to natural causes of death (Colton and Manderscheid, 2006; Daumit et al., 2010; Druss et al., 2011; Osby et al., 2000). As in the general population, the leading causes are cardiovascular disease, cancer, cerebrovascular, and respiratory diseases (Colton and Manderscheid, 2006; Vancampfort et al., 2015) which are potentially modifiable by interventions targeting physical health comorbidities (Daumit et al., 2013).

Metabolic Syndrome (MetS) is a cluster of cardiac risk factors which places an individual at a 2- to 3-fold increase in cardiovascular mortality and a 2-fold increase in all-cause mortality (Lakka et al., 2002). Important sequelae of MetS include diabetes mellitus and dyslipidemia, which in turn increase cardiovascular risk and mortality (Bai et al., 2011; Henderson et al., 2005; Lamberti et al., 1992; Siskind et al., 2016a; Stratton et al., 2000). Older age and female gender are more commonly associated with MetS in the general population (Mozumdar and Liguori, 2011).

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Very high rates of MetS have been reported in individuals with psychoses (Galletly et al., 2012; McEvoy et al., 2005), including those treated with clozapine (Brunero et al., 2009; Tso et al., 2016). High rates of cardiovascular risk factors including smoking (Goff et al., 1992; Lohr and Flynn, 1992) and obesity are contributed to not only by modifiable risk factors including unhealthy diet and physical inactivity, but also by chronic exposure to antipsychotic medications (Brown et al., 2006; Daumit et al., 2003, 2005, 2008; McCreadie and Scottish Schizophrenia Lifestyle, 2003; Strassnig et al., 2003). Weight gain associated with antipsychotics, including clozapine, is greatest during the first 12 months of treatment (De Hert et al., 2011; Umbricht et al., 1994; Henderson et al., 2000, 2005). Clozapine-antipsychotic polypharmacy may be employed when clozapine alone provides inadequate symptomatic control or with the aim of reducing clozapine dose in order to minimize adverse effects (Sernyak and Rosenheck, 2004).

The aim of the study was to assess the prevalence of metabolic syndrome and of other cardiovascular risk factors, as well as the proportion of patients receiving appropriate management in a large sample of clozapine-treated outpatients. Additionally, we examined the role of gender, age, clozapine dose and duration, and exposure to polypharmacy as potential predictors of MetS.

2. Methods

An observational cross-sectional study of metabolic parameters was conducted in all individuals registered with clozapine monitoring clinics across three hospital sites in South Eastern Sydney Local Health District, Australia. Anthropometric measures, presence of metabolic syndrome, risk for later development of diabetes, smoking, physical activity, diet, and prescription of psychotropic and additional medications were assessed at face-to-face interview and medical record review. Clients were asked to rate their interest in participating in smoking cessation and lifestyle interventions. Metabolic blood measures were obtained *via* pathology services.

This screening was conducted over the one-year period 01/10/2015–30/09/2016 by the Keeping Body in Mind (KBIM) clinical team, comprised of clinical nurse consultants, dieticians, exercise physiologists, and youth peer wellness coaches (Curtis et al., 2016). The information was collected as part of routine care at an initial KBIM appointment to determine the health status of each individual and the clinical interventions that were required. Individuals were advised by the clozapine clinical co-ordinator during their routine clozapine appointment that a new team (KBIM) was offering lifestyle interventions. Individuals were encouraged to attend the additional service but could opt out without it impacting on their usual care. The study received ethical approval from the South Eastern Sydney Local Health District Human Research Ethics Committee (Reference no: 17/030; LNR/17/POWH/49).

2.1. Definitions and research measures

2.1.1. Metabolic syndrome

International Diabetes Federation (IDF) definition criteria were applied (Alberti et al., 2006):

Central Obesity, defined as waist circumference ≥94 cm for Europid men and ≥80 cm for Europid women, with ethnic-specific values of ≥90 cm for Asian men and ≥80 cm for Asian women;

Plus two of the following four factors:

1. Serum triglycerides ≥1.7 mmol/L or on drug treatment for this lipid abnormality.
2. Serum high-density lipoprotein (HDL) cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women, or on drug treatment for this lipid abnormality.
3. Systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥ 85 mmHg, or treatment of previously diagnosed hypertension.
4. Fasting plasma glucose (FPG) ≥5.6 mmol/L or previously diagnosed type 2 diabetes.

2.1.2. Waist circumference

Waist circumference measurements were conducted by three Clinical Nurse Consultants trained in the method below, outlined by Tolonen et al. (2002):

1. Use a measuring tape that is checked monthly for stretching (replace if stretched). 2. Ask the person to remove heavy outer garments, loosen any belt and empty pockets. 3. Ask the person to stand with their feet fairly close together (about 12–15 cm) with their weight equally distributed and to breathe normally. 4. Holding the measuring tape firmly, wrap it horizontally at a level midway between the lower rib margin and iliac crest (approximately in line with the umbilicus). The tape should be loose enough to allow the measurer to place one finger between the tape and the person's body. 5. Record the measurement taken on an exhalation. Consistency of measurement was checked during training.

2.1.3. Risk for type 2 diabetes

The AUS-D risk questionnaire is a validated tool for identification of Australian adults at high risk of type 2 diabetes (Chen et al., 2010). Participants had waist measurement recorded and completed nine questions related to demographic characteristics, family history of diabetes, history of high blood sugar, smoking, diet, blood pressure, physical activity, ethnicity, and Aboriginal and Torres Strait Islander heritage (indigenous Australian population known to be at high risk for the development of diabetes). Scores were categorized as follows:

- *Low risk* (5 or less) [approximately one person in 100 will develop diabetes].
- *Intermediate risk* (6–11) [6–8: approximately one person in 50 will develop diabetes; 9–11: approximately one person in 30].
- *High risk* (12+) [12–15: approximately one person in 14 will develop diabetes; 16–19: approximately one person in seven; 20 and above: approximately one person in three].

2.1.1. Nicotine dependence

The Fagerstrom Test for Nicotine Dependence (Fagerstrom, 1978) is a six-item questionnaire, with demonstrated reliability and validity (Pomerleau et al., 1994). Scores of 1–2 indicate low dependence; 3–4 low to moderate dependence; 5–7 moderate dependence; and 8+ high dependence. Additionally, clients were asked to rate out of ten how important quitting smoking was to them (one, not important at all; ten, of utmost importance).

2.1.2. Physical activity

Previous seven-day physical activity was assessed using the International Physical Activity Questionnaire – Short Form (IPAQ-SF) (Craig et al., 2003). The IPAQ asks participants to recall time spent in vigorous and moderate intensity physical activity, time spent walking, and time spent sitting. A continuous indicator of physical activity of each intensity was calculated as a sum of minutes per week. The percentage of clients achieving the WHO guidelines (World Health Organization, 2010) of 150 minutes of moderate to vigorous physical activity (MVPA) per week was included as a categorical variable. The IPAQ has demonstrated reliability as a surveillance tool to assess levels of physical activity in people with schizophrenia (Faulkner et al., 2006).

2.1.3. Diet

Diet was assessed through use of a targeted semi-structured ten-question, picture-guided, food intake questionnaire. The dietary assessment tool was developed by three mental health dietitians and a researcher experienced in validation of dietary assessment tools. Early drafts of the questionnaire were piloted with a sample of people with severe mental illness who completed a food diary to compare accuracy to foods reported in the dietary assessment tool (unpublished). The

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