ORIGINAL ARTICLES

Obesity, metabolic syndrome and cardiovascular risk in patients attending clozapine clinic: a cross-sectional study

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ABSTRACT

Background: Patients with severe mental illness have higher cardiovascular mortality and shortened life span; this is at least partly attributed to medications although lifestyle plays a significant part.

Aim: To identify the role of lifestyle factors in contributing to weight gain and metabolic disturbances.

Method: We used a cross-sectional approach to measure physical health indices (Blood Pressure, Waist Circumference, Weight and BMI), laboratory indices (fasting sugar and lipid profile) and lifestyle measures using International Physical Activity Questionnaire-IV (IPAQ-IV) and a locally developed questionnaire to identify dietary patterns.

Results: We had a total of 45 patients; nearly half of our sample had metabolic syndrome and high Framingham Risk Score. 51% of our sample had high fast-food frequency and 40% used sugared drinks on a daily basis. High fast-food consumption, sugared drink use and low physical activity were significantly associated with obesity, which in turn was significantly associated with risk of metabolic syndrome.

Conclusions: It is important to monitor for metabolic parameters and also to identify the lifestyle factors in patients maintained on second generation antipsychotics that increases the risk for weight gain and metabolic syndrome.

Key words: Clozapine and metabolic syndrome, Clozapine and cardiovascular risk, Antipsychotic and metabolic risk, Antipsychotic agents and adverse effects, Metabolic syndrome X/chemically induced

INTRODUCTION

People with severe mental illness have reduced life-expectancy, [1] and a 3-fold greater chance of dying from natural causes compared to the general population, [2] the greatest contributor to this being cardiovascular disease. [3] Indeed, patients with severe mental illness have a higher prevalence of risk factors for CVS disease and higher prevalence of metabolic abnormalities. [4] A recent systematic review, [5] indicates that the overall rate of metabolic syndrome in patients with schizophrenia and other psychotic disorders is around 32% with very little differences between settings, country of origin, gender or definition used. Metabolic syndrome is associated with a two-fold increase in cardiovascular mortality and a 1.5 fold increase in all-cause mortality. [6]

Research has consistently demonstrated that second generation antipsychotics, particularly Clozapine and Olanzapine increase chances of weight gain and metabolic disturbances. [7-9] Others believe that schizophrenia per se increases the risk for diabetes mellitus and impaired Glucose Tolerance Test, [10-11] and obesity, [12] although this has been challenged. Lambert's 'hare and tortoise theory', [13] suggests that obesity, in the long run, is more likely related to behavioural factors than to specific medications.

Further, patients with severe mental illness are more likely to smoke, [14] exercise less, [15-16] and have unhealthy dietary habits. [16-18] There is however very little research done to delineate the role of these behavioural contributors in a cohort of patients maintained on medication known to cause obesity and metabolic disturbances such as Clozapine.

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Aims

This study has two aims, firstly to report the prevalence of obesity and metabolic disturbances in a cohort of patients attending Clozapine clinic and secondly to identify the role of lifestyle factors (including level of physical activity and dietary practices) in contributing to weight gain and metabolic disturbances.

MATERIALS AND METHODS:

Setting: This study was undertaken in the Hunter Valley Mental Health Service. Hunter valley mental health service provides mental heath service to a population of about 186,000 people spread over an area of about 3400 Sq. Km, that is largely rural. Services provided include care-coordination (case-management), intensive community care management (assertive or crisis intervention team), and allied health input to working age adults; ambulatory rehabilitation service; and mental health services for older persons.

Subjects: We included all patients who were maintained on Clozapine at the time of this study (N=45). Patients are generally commenced on Clozapine in the inpatient unit and their care transferred to the ambulatory care (community) team. As part of the service, patients on Clozapine are reviewed at periodic intervals (as per protocol) by the medical staff in addition to more frequent reviews by their care-coordinators.

Measures:

As part of the Clozapine clinic, all patients have their physical measures recorded (Blood Pressure, Waist circumference, Weight and BMI). In addition, we also administered the short-version of the IPAQ questionnaire, [19] which is a 4-item questionnaire that enquires about level of physical activity within the last week and has been validated for use in patients with schizophrenia. [20] We also used a locally developed 6-item questionnaire on dietary practices. This questionnaire helped to quantify fast-food frequency and sugared drink consumption.

Fast-food frequency has been shown to have a positive association with obesity, [21] and has been used in previous studies. [22] We defined fast-food frequency as:

- High: consuming fast-foods (Hungry-Jacks, Kentucky Fried Chicken, Pizza Hut etc.) more than once a week and
- Low: less than once a week
- Never

Sugared drinks consumption has also been associated with weight-gain and diabetes; [23] we modified the definition for our study as:

- Monthly or less
- Weekly or less
- Less than daily, but more than weekly
- Weekly

The measures were taken and the questionnaires administered by co-authors KW and CS.

Statistical Analysis: Descriptive analyses (frequencies, percentages, means and standard deviations) were used to describe key socio-demographic and clinical data. The prevalence of obesity (as defined by BMI), metabolic syndrome (NCEP criteria), and Framingham risk score were calculated. Pearson's X^2 and independent-t-test were used to identify association between clinical variables to these risk factors. Logistic regression analysis was conducted to determine whether these risk factors were associated with obesity, metabolic syndrome or Framingham risk score.

Ethics :

Hunter New England Research Ethics exempted the need for ethics application as this was part of a service audit.

RESULTS

Table 1 shows the socio-demographic and clinical variables and Table 2 depicts the risk factors for obesity, metabolic syndrome and Framingham risk score in the study sample.

Table 1: Socio-Demographic and Clinical Variables

Variable	Response (%)
Socio-demographic Variables	
Mean Age (years)	39.76
Gender	
Males	31 (69 %)
Females	14 (31 %)
Marital Status	
Single or separated	36 (80 %)
Married or de facto	9 (20 %)
Living conditions	
Living with partner or family	25 (55.6 %)
Living alone	20 (44.4 %)
Clinical Variables	
Diagnosis	
Schizophrenia	43 (95.6 %)
Schizo-affective disorder	2 (4.4 %)
Duration of illness	
< 5yrs	4 (8.9%)
5-10yrs	10 (22.2%)
10-20yrs	9 (42.2%)
>20yrs	12 (26.7%)

Treatment Details:	
Mean Clozapine Dose	361.67 MG (Range; 75-725 MG)
Mean duration of Clozapine treatment	79.49 months (Range; 1-228 months)
Frequency of Review	
Weekly review	1(2.2%)
Monthly Review	25 (55.6%)
6-monthly Review	19 (42.2%)
History of Substance Misuse	
Past Illicit Drug use	17/45 (37.8%)
Current Illicit Drug Use	4 (8.9%)
Past Alcohol Use	27(60%)
Current Alcohol Use	24 (53.3%)
Past Smoking	33 (73.3%)
Current Smoking	27 (60%)
Co-prescription of other Psychotropics	
Yes	25 (55.6%)
Antipsychotics (oral)	8 (17.8%)
Antipsychotics (depot)	4 (8.9 %)
Antidepressants	12 (26.7%)
Mood Stabilisers	9 (20%)

Table 2: Risk factors for Obesity, Metabolic Syndrome and Framingham Risk Score

Variable	P-value
Obesity	
Gender	0.247
Fast-food	0.039*
Sugar-drinksconsumption	0.004*
Physical Activity	0.000*
Waist Circumference	
Fast-food	0.036*
Sugar-drinks	0.10
Metabolic Syndrome	
Gender	
Living with family	0.013*
Clozapine Dose	0.631
Duration of Clozapine treatment	0.174
BMI	0.003*
Sugar Drinks	0.26
Framingham Risk Score	
Gender (Males)	0.008*
Current Smokers	0.023
BMI	0.344
Fast-food	0.393
Sugar drinks	0.53
Physical Activity	
Blood Pressure	0.037*
Total Cholesterol	0.87
Glucose	0.33
HDL	0.61
LDL	0.95
Triglycerides	0.11
Waist Circumference	0.000*
Metabolic Syndrome	0.32
Framingham Risk Score	0.21

*Statistically significant

DISCUSSION

All 45 patients of the service who were currently on clozapine were included in the study; the assessments for this study were taken between July 2010 and December 2010. Majority of our sample (69%) were males and the mean age was 39 years; majority were single (80%) and lived alone (44%). This was not different to other studies. [24-26] The mean clozapine dose was 361.67 mg and the mean duration of treatment on Clozapine was 79.5 months.

We found that 51% of our sample fulfilled the IDF criteria for metabolic syndrome. Our finding is similar to previous reports. [24] 37 patients (82%) were either overweight or obese, with 10 of the 45 (22%) being morbidly obese. Nearly half of our patients had a high Framingham Risk Score. We also found that a majority of our patient population engaged in unhealthy lifestyle habits; thus 60% were current smokers, 53% used alcohol, 51% had high fast-food frequency and 40% used sugared drinks on a daily basis. High fast-food consumption, sugared drink use and low physical activity were significantly associated with obesity, which in turn was significantly associated with risk of metabolic syndrome.

A number of studies have looked at metabolic disturbances in patients receiving Clozapine. [24-33] These studies have helped to establish that Clozapine is associated with metabolic disturbances, the prevalence of which varies from 7.5%, [27] to 64%; [30] most studies report a prevalence of 44% to 54%. [24-26] The differences in rates may be related to differences in methodology (such as definitions used) or to sample characteristics. [26] Obesity (or high BMI) has been identified as a consistent correlate for metabolic syndrome among patients on Clozapine, [24; 26] we found this association among our sample. Other associations include age, [24] and being Caucasian. [27]

Our study is different in that we also studied the lifestyle habits of our patient group and explored association between activity levels, and unhealthy dietary patterns with the risk of metabolic syndrome. We found that low physical activity levels and poor dietary habits (increased fast food frequency and sugared drink consumption) was significantly associated with BMI, which in turn was significantly associated with metabolic syndrome. Based on our results we developed the

following model (Figure 1) to best explain the risk of metabolic syndrome in our cohort of patients; this also helps to identify where to intervene.

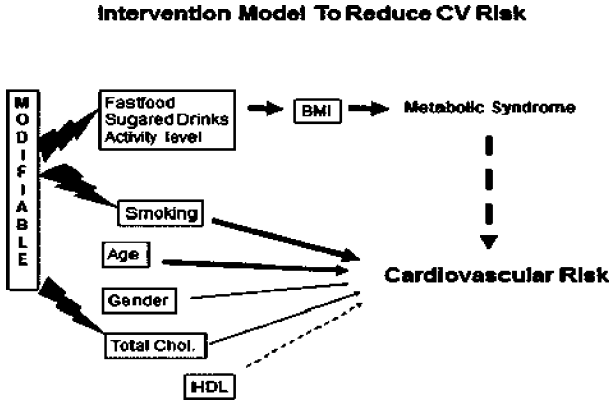

Figure 1 Intervention model to reduce cardiovascular risk

It is therefore important to monitor for and address any unhealthy behavioural patterns that emerge. A recent systematic review of the available guidelines / recommendations for cardiovascular risk in people with schizophrenia using the AGREE (Appraisal of Guidelines for Research and Evaluation) tool recommended lifestyle advise be provided alongside regular monitoring; accordingly, physical health measures (weight, waist circumference, BMI, and blood pressure), biochemistry (fasting glucose and lipids) and targeted interventions (diet and lifestyle advice) should be undertaken at baseline, 6 weeks (of commencing treatment), 12 weeks (of commencing treatment), and thereafter annually at a minimum. [34]

Our study is not without limitations. The cross-sectional nature of the study, absence of a comparison group and lack of random assignments are all limitations. Further, although we used measures to identify the dietary patterns, these were not validated instruments. That said, it must be borne in mind, that there are no short and user-friendly instruments that can be employed in routine clinical practice.

There is no doubt that clozapine has a definitive role in treatment resistant or refractory psychosis; however, its use is associated with significant limiting side effects. More recently, the focus has shifted to cardiovascular risks with clozapine rather than the haematological side effects. While evidence for the risk of myocarditis is becoming clearer, [35-38] the same cannot be said about other cardiovascular mortality. Although, research indicates that clozapine increases the risk for metabolic syndrome and therefore cardiovascular morbidity and mortality, this should be considered alongside other available evidence. A recent retrospective cohort study indicates that in patients for whom treatment was commenced before 55 years, the risk of CVD mortality does not differ between clozapine and Risperidone in adults despite known differences in risk profiles for weight gain and metabolic side effects. [39] Further, the Fin-11 study, [40] indicates that long-term use of antipsychotics (particularly clozapine) is associated with lower mortality compared with no antipsychotic use; in fact a modelling study has indeed shown that wider use of clozapine could save an average of 53 lives per year world-wide as it reduces the risk of suicide. [41]

Long-term effects of differences between individual antipsychotics on overall mortality and cardiovascular mortality are not well established. [42] For this reason, there is a need for prospective cohort studies of patients maintained on Clozapine. Future research should also identify the long-term impact of routine metabolic screening and lifestyle interventions in this group of patients.

CONCLUSION:

Patients with severe mental illness are at higher risk of cardiovascular morbidity and a shortened life span. While antipsychotics, particularly second generation antipsychotics increase risk for metabolic syndrome and cardiovascular morbidity, it is also important to explore for lifestyle factors that contributes to this risk in this patient population. A recent meta-analysis of lifestyle interventions, [43] demonstrates that these interventions improve anthropometric measures that are sustained at the end of twelve months.

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