The Association between Dyslipidaemia and Types of Antipsychotic Medications among Patients with Chronic Schizophrenia

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SUMMARY

This cross sectional study aimed to explore the association between dyslipidaemia and types of antipsychotics in 100 patients with chronic schizophrenia. Lipid profile, weight, height and waist circumference together with other relevant factors were measured. We found there was a high rate of dyslipidaemia among patients with chronic schizophrenia treated with antipsychotics (66%), however there was no significant difference found between typical or atypical antipsychotics (OR=1). All sociodemographic and clinical factors were not significantly associated with dyslipidaemia. Only non-Malays were found to have significant dyslipidaemia (p < 0.1). Effective management is needed to deal with the dyslipidaemia in this group.

KEY WORDS:
Dyslipidaemia, Schizophrenia, Antipsychotics

INTRODUCTION

Patients with schizophrenia have a higher risk of mortality compared to the general population [1, 2]. Physical illness and natural causes constitute major reasons for this excess in mortality other than suicide[3-5]. An association between severe mental illnesses, like schizophrenia and impaired glucose metabolism has been identified for many decades even before the introduction of antipsychotic medications. It was even found to be higher in drug naïve patients and patients with first episode psychosis [6].

Several studies suggested exposure to antipsychotics can elevate the risk of having dyslipidaemia in this group [7-9]. There is a growing clinical concern that some of the newer antipsychotic medications, called atypical antipsychotics may even contribute to increase further the risk of dyslipidaemia [7,8]. The differences between typical and atypical antipsychotics include the actions at the receptors, the tolerability and side effects profile. In Malaysia, one out of four patients with schizophrenia are on an atypical antipsychotic [10]. Even though both atypical antipsychotics [11-13] and typical antipsychotics [7-9] have been implicated in causing weight gain among patients with schizophrenia, higher rate of weight gain was found when they use atypicals [14-16]. Apart from that, higher rate of dyslipidaemia, metabolic dysregulation of glucose and lipid [17-19], and increased food intake [20] were found among patients on atypical as compared to typical.

As more patients with schizophrenia in Malaysia are currently being treated with the atypical antipsychotics, it is important to study whether there is a significant relationship between the atypical antipsychotic medications with dyslipidaemia. The hypothesis is patients who are on atypical antipsychotic medication are significantly associated with dyslipidaemia compared to patients who are on typical antipsychotics.

MATERIALS AND METHODS

This study was conducted in Hospital Bahagia Ulu Kinta (HBUK) in Perak. It was a cross-sectional study, conducted for duration of three months in 2009. This research project was submitted and obtained the approval from the Medical Research and Ethical Committee (MREC), Ministry of Health and Research & Ethics Committee, Medical Faculty, Universiti Kebangsaan Malaysia.

Study Population

The study population included all inpatients admitted in Hospital Bahagia Ulu Kinta during the study period with diagnosis of schizophrenia for more than 2 years.

Data Collection

Patients were selected using stratified random sampling. All in patients who fulfilled the criteria were first stratified according to the class of antipsychotic, i.e. typical and atypical. Patients on the atypical antipsychotics group were randomly selected through the stratification process. Patients who were on the typical antipsychotic group were matched with the patients on the atypical antipsychotics group according to age and gender. Patients who were on combination treatment of typical and atypical antipsychotics were not included as to ensure the main study factor was not contaminated.

The inclusion criteria include a diagnosis of schizophrenia using Mini International Neuropsychiatric Interview (M.I.N.I); aged 18 - 65 years old; receiving the same antipsychotic medication for at least 12 weeks; able to give consent. (BPRS score is less than 36). The Exclusion criteria include co-morbid mood disorder; history of illicit substance use within the last 1 month; pregnancy; patients with other endocrine disorders except diabetes mellitus and hyperlipidaemia that can affect the lipid profile. All patients who fulfilled the inclusion criteria were invited to participate in the study. Written informed consent was obtained from each selected subject before they entered the study.

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Patients' weight and height were in measurements of kilogram and centimeters. Patients also had their waist circumference measured using measuring tape. Waist circumference was taken at the midpoint between the anterior superior iliac crest and the costal margins during expiration phase. Patients were then fasted from midnight and were supervised by the ward staff in order to achieve accuracy in the fasting blood sample. Blood samples were taken at 8 am the next morning. Three milliliters of blood sample were taken for analysis.

Study Instruments

Mini International Neuropsychiatric Interview (M.I.N.I)

This is a short structured diagnostic interview with approximately 15 minutes administration. Even though it has not been validated in Malaysia, the M.I.N.I has been used widely in local studies prior to this study [21, 22].

Brief Psychiatric Rating Scale (BPRS)

This is a clinician-based rating scale for severity of illness. It is one of the most frequently used scales in studies involving patients with schizophrenia and is generally found to have good inter-rater reliability [23]. Even though it is still not validated for local setting use, the BPRS has been widely used in local studies.

The other assessments including body weight, waist circumference and venous blood sampling was taken. All the blood samples were analyzed in the Chemical Pathology Laboratory in HBUK.

Definition of Variables

Chronic schizophrenia was defined as suffering from schizophrenia for more than 2 years duration. The BMI was calculated on the formula of Body Mass Index (BMI) equals to weight in kg divided by height in meters square. Body Mass Index= Weight (kg)/ Height^2 (m^2). Higher Body Mass Index was determined as more than 23 kg/ m^2. The value of waist circumference was determined according to gender based on the International Diabetes Federation recommendation [24]. Dyslipidaemia was defined as having either high total cholesterol, high LDL-cholesterol, low HDL-cholesterol, high triglyceride or a previously known case on lipid lowering medication. The values to determine dyslipidemia was according to Adult Treatment Panel III (NCEP ATP-III) recommendations. Normal total cholesterol level should be less than 5.2 mmol/l and was considered high if equaled or exceeded 5.2mmol/l. Normal HDL-Cholesterol for males should be at least 1.0 mmol/l and was considered low if it below 1.0 mmol/l. Normal HDL-Cholesterol for females should be at least 1.3 mmol/l and was considered low if it below 1.3 mmol/l. Normal LDL-Cholesterol should be less than 3.3 mmol/l and was considered high if it equaled or exceeded 3.3 mmol/l. Normal triglyceride (TG) level should be less than 1.7 mmol/l and was considered high if it equaled or exceeded 1.7 mmol/l.

Statistical Analysis

The data was analyzed using Statistical Package for Social Sciences (SPSS) version 16.0 which was licensed to UKM. The relationships between parameters were analyzed using appropriate statistical analysis. The relationship between the demographic as well as clinical variable, and lipid levels were analyzed using Chi-square (χ^2) statistics. Multiple significant variables were analyzed using log regression analysis.

RESULTS

Sociodemographic and clinical profiles

About half (44%) of the patients were aged above 45. The ethnic distribution does not reflect the proportion seen in the general population. Chinese was slightly over represented in this sample. About two third of patients were single, one third were married, and half had secondary education. Majority of the patients had more than one psychiatric hospitalization with mean illness duration of 19 years (Table I).

Body Mass Index

About half of the patients had higher BMI (>23). There were more female patients with larger waist circumference (44%) compared to the male patients (26%).

Clinical profiles

Eight out of eleven patients who had been diagnosed to have diabetes mellitus prior to the study were females. One out of ten patients had pre-existing hyperlipidaemia. About one third of them smoked, and they were all male patients. Fifty patients were on typical antipsychotics and the other fifty was on atypical. One out of five patients was treated with clozapine, 18% with perphenazine, 17% with sulpiride, and 15% with risperidone. About one fifth of them reported to have a family history of diabetes mellitus and 12% had family history of hyperlipidaemia.

Almost two thirds of the whole sample was detected to have dyslipidaemia with 56 (%) new cases. About half of them had high total cholesterol, one third had high triglyceride, and another third had high LDL-cholesterol. There were patients with overlapping conditions. It was interesting to note that only 1 female patient had low HDL-cholesterol and not a single male patient had low HDL-cholesterol.

Among all demographic and clinical variables, only two factors i.e. race and family history of hyperlipidaemia were statistically significant for presence of dyslipidaemia ($p < 0.05$). Typical and atypical antipsychotic medications were found to have similar risk for dyslipidaemia (OR= 1) (Table II).

Three factors i.e. duration of illness and family history of hyperlipidaemia from the univariate analysis were entered into logistic regression analysis. The result showed that only one factor i.e. being non-Malays remained statistically significant (Table III).

DISCUSSION

In this study, we found that 66% of the patients had dyslipidaemia. This finding is almost similar to the recent CATIE trial where 63% were found to have dyslipidaemia [25]. The rate of dyslipidaemia in this study is three fold higher than our general population [26]. Previous researchers from other parts of the world also found that there was a higher rate of dyslipidaemia in patients with schizophrenia compared to the general population [7-9, 25]. Other researchers

that focused more on the metabolic syndrome have also found similar findings [27-29].

Our main focus for this study was to study the rate of dyslipidaemia among two groups of patients who were either on typical or atypical antipsychotics. In this study, the typical antipsychotics were haloperidol, chlorpromazine, perphenazine, trifluoperazine and sulpiride whereas atypical antipsychotics consisted of risperidone, olanzapine, quetiapine, clozapine, aripiprazole and palliperidone. We found patients with schizophrenia have similar rates of dyslipidaemia regardless whether they were taking typical or atypical antipsychotics. In fact, we were surprised to find that both the groups had similar prevalence with 66% of each group having dyslipidaemia. This was in contrast to previous findings that found higher rate of dyslipidaemia among patients taking atypical antipsychotics [11, 12, 14, 30-32].

One of the reasons that could have caused the equal prevalence seen here was the homogeneity of the patients in both groups. One fifth of the patients who are currently on typical antipsychotics had been exposed before to atypical antipsychotics in their treatment history. Grouping the patients into 2 large groups namely the typical and atypical antipsychotics probably did not really differentiate the study factor. There were limited resources to study each type of antipsychotics with an adequate number of samples. We acknowledge that each antipsychotic medication has its unique chemical structures and mechanism of actions [33] and may exert different effects on lipid profile. Grouping the antipsychotics together may mask their individual effects.

However, it has been suggested before that patients with schizophrenia who are exposed to either both atypical or typical antipsychotics have a higher risk of developing hyperlipidaemia [34]. Among typical antipsychotics, it was suggested that high potency ones conferred a lower risk for developing hyperlipidaemia as compared to the lower potency [34].

Studied showed the odds ratio of developing dyslipidaemia were not markedly different between these two groups of treatment except for clozapine (16),(9).Several studies that focused on metabolic syndrome also found that metabolic syndrome was prevalent in both typical and atypical antipsychotics (27, 35).

Several mechanisms on how antipsychotics can induce dyslipidaemia were postulated. One of those is indirectly through weight gain and obesity. Obesity is a known risk factor for dyslipidaemia as well as cardiovascular diseases. Weight gain has been demonstrated on patients with schizophrenia taking antipsychotics [36]. Since our study was a cross sectional one, we could not determine any weight gained during their treatment with antipsychotics. BMI could indirectly represent the weight problem. However, we found higher BMI was not statistically associated with dyslipidaemia.

Other factors that associated with dyslipidaemia were also explored in this study. The mean age for the sample was 47 years old, representing a higher age group. This could

Table I: Sociodemographic characteristics of the sample

	Total (N=100)
Sociodemographic	
Age Mean, S.D	47.01(8.49)
N (%)	
Sex	
Male	50(50)
Female	50(50)
Race	
Malay	37(37)
Chinese	55(55)
Indian	8(8)
Marital status	
Single	67(67)
Married	28(28)
Divorced	4(4)
Widowed	11(0)
Religion	
Islam	37(37)
Buddhist	53(53)
Hindu	7(3)
Others	3(3)
Education	
Primary	42(42)
Secondary	52(52)
Tertiary	6(6)
Clinical profile	
Mean (S.D)	
No of admission	10.21(9.14)
Duration of illness (months)	223.3(133.4)
Height (cm)	159.5(9.6)
Weight (cm)	59.3(13.1)
Waist circumference (cm)	82.6(11.9)
BMI (N,%)	
Normal (<23)	54(54)
High (>23)	46(46)
Waist Circumference (No,%)	
Male	
Normal	37(74)
High (>90cm)	13(26)
Female	
Normal	22(44)
High (>80cm)	28(56)
Confirmed Diabetes	
Yes	11(11)
No	89(89)
Pre-existing Hyperlipidaemia	
Yes	10(10)
No	90(90)
Menopause	
Yes	23(46)
No	27(54)
Smoking	
Yes	28(28)
No	72(72)
Currently smoking	
Yes	7(7)
No	93(93)
Family history of Diabetes	
Yes	19(19)
No	81(81)
Family history of Hyperlipidaemia	
Yes	12(12)
No	88(88)

Table II: Univariate analysis of relationship between socio-clinical factors with Dyslipidaemia using Chi- square (X2)

	Dyslipidaemia			
	No	Yes	p value	OR (95% CI)
Age				
Less than 45	13 (30.2)	30 (69.8)	0.49	0.74(0.32- 1.73)
45 and more	21 (36.8)	36 (63.2)		
Sex				
Male	19 (38)	31 (62)	0.40	1.43(0.62- 3.29)
Female	15 (30)	35 (70)		
Race				
Malay	18 (48.6)	19 (51.4)	0.02 *	2.78(1.18- 6.57)
Non-Malay	16 (25.4)	47 (74.6)		
Educational level				
Lower	12 (28.6)	30 (71.4)	0.33	0.66(0.28- 1.54)
Higher	22 (37.9)	36 (62.1)		
Duration of illness				
Up to 20 years	15 (26.8)	41 (73.2)	0.09	0.48(0.21- 1.12)
More than 20 years	19 (43.2)	25 (56.8)		
Waist circumference				
Normal	22 (37.3)	37 (63.7)	0.41	1.44(0.61- 3.38)
Large	12 (29.3)	29 (70.7)		
BMI				
Normal (<23)	22 (40.7)	32 (59.3)	0.43	1.41(0.60- 3.37)
Higher (>23)	12 (26.1)	34 (73.9)		
Smoking (Males)				
Yes	9 (32.1)	19 (67.9)	0.81	0.89(0.35- 2.26)
No	25 (34.7)	47 (65.3)		
Currently Smoking				
Yes	2 (28.6)	5 (71.4)	0.75	0.76(0.14- 4.15)
No	32 (34.4)	61 (65.6)		
Menopause (Females)				
Yes	8 (34.8)	15 (65.2)	0.50	1.52(0.45- 5.14)
No	7 (25.9)	20 (74.1)		
Family History of Diabetes				
Yes	5 (26.3)	14 (73.7)	0.43	0.64(0.21- 1.96)
No	29 (35.8)	52 (64.2)		
Family History of Hyperlipidaemia				
Yes	1 (8.3)	11 (91.7)	0.045*	0.15(0.02- 1.23)
No	33 (37.5)	55 (62.5)		
Antipsychotics				
Typical	7 (34)	33 (66)	1.00	1.00(0.44- 2.29)
Atypical	17 (34)	33 (66)		

Table III: Logistic regression analysis of relationship of socio-clinical factors with Dyslipidaemia

Variable	Adjusted OR	p value	95% CI
Race			
Malay*	2.85	0.02	1.15- 7.00
Non-Malay			
Duration of illness			
More than 20 years *	1.78	0.20	0.73- 4.31
Less than 20 years			
Family History Hyperlipidaemia			
No *	7.00	0.07	0.83- 58.70
Yes			

contribute to the high rate of dyslipidaemia as older age is a known non-modifiable risk factor for dyslipidaemia. In fact, most physicians screen their patients for cardiovascular risk factors including fasting lipid profiles if they are above the age of 45. We found relatively low rate of smoking among study sample. This is in contrast with reports that showed high rate of smoking among patients with schizophrenia [37, 38]. About 60% of Malaysian males reported to have ever smoked and 47.2% were current smokers whereas, the females reported 4.7% have ever smoked and 2.6% were current smokers [39]. The low rate of smoking among study patients was probably due to recall bias, underreporting, or also may be due to the fact that the hospital forbids patients smoking during their stay in the hospital. Surprisingly, there was no significance difference in proportion between smokers and non-smokers on dyslipidaemia. Smoking may be a risk factor for cardiovascular diseases but may not serve as a risk factor for developing dyslipidaemia.

The non-Malay group had significantly higher rate of dyslipidaemia compared to the Malay group. The Indian males in our local population were quoted to have a lower HDL-cholesterol [40]. This again may need a wider and more representative population as our sample did not reflect the general population.

Menopause is a known factor for developing dyslipidaemia [41]. However, this was not statistically found to be associated with dyslipidaemia in our study. This may be due to small number of female patients recruited (n= 50) in this study and was not able to generate a significant result. Menopause in female patients with schizophrenia should be explored in more detail as amenorrhea can be a side-effect of antipsychotics. Blockage at the Dopamine D2 receptor in the tubero-infundibular pathway may result in hyperprolactinaemia which may in turn cause amenorrhea [33]. In our current study, there were 8 patients who had menopause before the age of 50.

The small percentage of patients with pre-existing diabetes in this study might explain why we could not find any significant association with dyslipidaemia. Assesment of the latest glycaemic status of patients would probably more useful in this study as impaired glucose tolerance was hypothesized as one of the mechanisms in antipsychotic-induced dyslipidaemia [34].

Duration of illness was also not found to be significantly associated with dyslipidaemia. However, we think that a careful approach must be taken when interpreting this result as a longer duration generally reflects on an older age. Advancing age is a risk factor for developing dyslipidaemia.

Even though positive family history of hyperlipidaemia was found not to be statistically associated with dyslipidaemia, we think a larger sample may be more representative and may be able to yield a positive result. There may be an element of recall bias on that aspect. Furthermore, patients who were admitted to the current mental institution for a long period of time may not have the latest information on their physical health status of their family members. We were not able to get any corroborative history to confirm the negative report of no family history of dyslipidaemia.

Future study in this area needs to gather larger sample size to possibly achieve statistically significant results. The effect of antipsychotic on lipid profile perhaps can be better detected at a longer duration of follow up. A prospective follow up study would be able to have a clearer picture of a causal effect.

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