Metabolic parameters and long-term antipsychotic treatment: a comparison between patients treated with clozapine or olanzapine

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Abstract

OBJECTIVES: This study was undertaken to examine if patients exhibit more pronounced metabolic abnormalities after 8-year treatment with clozapine or olanzapine than before, and also to investigate whether there exist any differences between long-term clozapine and olanzapine therapies regarding metabolic side-effects.

METHODS: Fifty psychiatric outpatients diagnosed with schizophrenia or schizoaffective disorder and on treatment with clozapine or olanzapine were studied during 8 years. Fasting blood or serum samples for glucose, lipids, prolactin and antipsychotic drug concentrations were analyzed. In addition, body mass index was calculated.

RESULTS: More patients treated with olanzapine compared with those treated with clozapine ended with their medication, in most cases because of diabetes mellitus and/or hyperlipidemia, during the 8-year follow-up. Also more patients treated with olanzapine compared with those treated with clozapine developed manifest diabetes mellitus during the 8-year period. Prolactin levels were higher in the patients treated with olanzapine compared with in those treated with clozapine at study start, but there were no differences in the other parameters between the treatment groups at study start. In the patients remaining on their medication all 8 years, the glucose level increased over time in the clozapine group, but not in the olanzapine group, whereas body mass index and lipids were unchanged over time in both treatment groups.

CONCLUSIONS: Our findings point to that both olanzapine and clozapine long-term treatments cause development of hyperglycemia and/or hyperlipidemia. Furthermore, olanzapine long-term treatment seems to more often lead to development of manifest diabetes mellitus than long-term treatment with clozapine.

ORIGINAL ARTICLE

INTRODUCTION

Weight gain is an untoward effect of antipsychotic drugs, which contributes to non-compliance with treatment and may lead to medical morbidity (Goff & Shader 1995). The degree of weight-gain inducing ability varies by drug, there the atypical agents clozapine and olanzapine have been shown to have the greatest potential to induce weight gain (Allison *et al.* 1999), and also to associate with the highest metabolic risk (Melkersson & Dahl 2004; Raedler 2010). Patients treated with clozapine experience significant weight gain and lipid abnormalities and appear to be at increased risk for developing diabetes mellitus (DM) and cardiovascular disease (Henderson *et al.* 2000; 2005). Olanzapine therapy also is associated with significant increases in weight, fasting blood (B)-glucose and lipid levels (Melkersson *et al.* 2000; Meyer 2002).

However, there are few studies published which are long-term follow-up studies on antipsychotic drugs and metabolic parameters. There are also few studies published comparing long-term clozapine and olanzapine therapies regarding metabolic side-effects.

So, given the fact that metabolic side-effects have become a complication to antipsychotic drug treatment that have to be recognized and treated, we made a 8-year follow-up of patients on antipsychotic treatment with clozapine or olanzapine with special focus on body mass index (BMI) and metabolic parameters. The first aim of the study was to examine if patients exhibit more pronounced metabolic abnormalities after 8 years treatment with clozapine or olanzapine than before. The second aim was to investigate whether there exist any differences between long-term clozapine and olanzapine therapies regarding metabolic side-effects.

PATIENTS & METHODS

The study was approved by the Ethics Committee of Karolinska Institutet, Stockholm, Sweden and all patients participated after giving informed consent. Fifty psychiatric outpatients (28 men and 22 women) from the region of Stockholm, Sweden and with the diagnoses schizophrenia or schizoaffective disorder according to the DSM-IV criteria (American Psychiatric Association 1994) were included. The patients were investigated 2001/2002 and were then followed up during 8 years to 2009/2010. They had no actual substance-related disorder and were all chronically ill psychosis patients on treatment with either clozapine or olanzapine. Baseline characteristics of the patients in the two treatment groups are given in Table 1. The duration of therapy with current antipsychotic at study start was longer for the patients receiving clozapine than for those receiving olanzapine ($p<0.001$). Otherwise, there were no differences in gender distribution, age, subtype of diagnosis, frequency of smokers or duration of disease between the two treatment groups (Table 1). Concomitant medications used by the patients were benzodiazepine derivatives (N=11), anticholinergics (N=2), lithium (N=4) and/or other antipsychotic drugs (N=8), but the number of patients using the different concomitant medications did not differ between treatment groups. Whereas two patients were adoptees and lacked knowledge of their relatives,18 of the other 48 patients (38%) had a family history of psychosis, 17 (35%) had a family history of DM and 12 (25%) had a family history of cardiovascular disease. However, there were no differences found in frequencies of family history of these three diseases between the two treatment groups.

All blood samples were collected in a fasting state in the morning, prior to breakfast and medication. The laboratory investigation included (B)-glucose and serum levels of triglycerides and cholesterol at study start and at 8-year follow-up, as well as serum level of prolactin (PRL) and serum concentrations of antipsychotic drugs at study start. B-glucose levels were determined by a glucose-oxidase method using the 950 Immunologic-Rate-Colorimetric system (Johnson and Johnson Clinical Diagnostics, Inc., NY, USA). Triglyceride concentrations were measured using an enzymatic method as described by Spayd *et al.* (1978) and choles-

Tab. 1. Age, diagnosis, smoking, duration of disease and duration of therapy with current antipsychotic for the patients in the two treatment groups at study start.

Treatment group	Age (year)	Diagnosis (DSM-IV)	Smoking N (%)	Duration of disease (year)	Duration of therapy with current antipsychotic (year)
Clozapine (N=23: 14 M, 9 W)	A: 43±10 M: 42±9 W: 44±12	Schizophrenia, paranoid type (N=7) disorganized type (N=2) undifferentiated type (N=11) Schizoaffective disorder (N=3)	A: 10 (43) M: 4 (29) W: 6 (67)	A: 20.4±9.7 M: 18.9±8.7 W: 22.8±11.2	A: 7.8±3.8[a] M: 7.8±4.5 W: 7.8±2.3
Olanzapine (N=27: 14 M, 13 W)	A: 41±10 M: 41±7 W: 41±12	Schizophrenia, paranoid type (N=10) disorganized type (N=0) undifferentiated type (N=12) Schizoaffective disorder (N=5)	A: 8 (30) M: 3 (21) W: 5 (38)	A: 15.6±10.7 M: 13.8±8.7 W: 17.5±12.6	A: 2.2±1.9 M: 2.0±1.8 W: 2.5±2.0

[a]Significantly different to the olanzapine group, $p<0.001$; Abbreviations: A=all; M=men; N=number; W=women

terol using an enzymatic method similar to that proposed by Allain *et al.* (1974). Prolactin was measured by a commercial fluoroimmunometric assay kit (Delfia Prolactin, Wallac Inc., Turku, Finland). Serum concentrations of clozapine and olanzapine were analyzed by high-performance liquid chromatography methods as previously described (Melkersson & Dahl 2003). Body mass index was calculated according to the formula BMI = kg/m^2, where kg = the body weight in kilograms and m = the height in meters (Labhart 1986).

Categorial data were summarized using frequency counts and percentages. Continuous data were presented as mean and standard deviation (SD). Data measured on a nominal scale were analyzed by Chi-square test or Fisher's exact test. In comparison between patients with different types of medication (clozapine or olanzapine) regarding baseline data, Mann-Whitney U test was used. To compare patients remaining on their clozapine or olanzapine medication after 8 years with respect to changes in BMI, B-glucose, triglycerides and cholesterol, two-way repeated measures analysis of variance was used. The variable B-glucose was positively skewed distributed and before the formal analyses reciprocal-transformed. A *p*-value of less than 0.05 was considered statistically significant. The statistical analyses were performed using the statistical program Statistica 10.0 (Statsoft, Inc., Tulsa, OK, USA).

RESULTS

More patients treated with olanzapine compared with those treated with clozapine ended with their medication during the 8-year follow-up (12/27 [44%] vs 3/23 [13%], p=0.03). The reasons why the patients ended with their medication are described in Table 2. The most common reason was development of DM and/or hyperlipidemia in one patient in the clozapine group and six patients in the olanzapine group (Table 2). Because of the development of DM and/or hyperlipidemia, these seven patients were prescribed a change of antipsychotics from clozapine or olanzapine to perphenazine (N=1), risperidone (N=4) or quetiapine (N=2), leading to normalization of fasting (B)-glucose and/or lipid levels in five of the seven patients (data not shown).

Additionally, two more patients treated with olanzapine developed DM during the 8-year follow-up and a third patient treated with clozapine had already at study start a known DM that was suspected to be clozapine-induced (Table 3). However, these three patients continued with clozapine (N=1) or olanzapine (N=2) in combination with only diabetic diet (N=1) or diabetic diet and antidiabetics (N=2) during the 8-year follow-up, since they earlier had tried, but got poor antipsychotic effect of several other antipsychotics.

Totally, it was more patients treated with olanzapine compared with those treated with clozapine who developed manifest DM during the 8-year follow-up (7/27 [26%] vs 0/23 [0 %], p=0.01). On the other hand, it was more common with slight hyperglycemia among the clozapine-treated patients at the 8-year follow-up (Table 4B).

Serum PRL levels were higher in the patients treated with olanzapine compared with in those treated with clozapine at study start (Tables 4A and 4B; p=0.01 and p=0.008, respectively). However, there were no differences in BMI, B-glucose, triglycerides or cholesterol at study start between the treatment groups (Tables 4A and 4B).

In the patients remaining on their clozapine or olanzapine medication all 8 years, glucose levels increased over time in the clozapine group, but not in the olanzapine group, whereas BMI, triglycerides and cholesterol neither changed over time nor differed between treatment groups at the 8-year follow-up (Table 4B).

Regarding the medication, patients' daily doses of clozapine or olanzapine did not differ between at study start and after 8 years (Tables 4A and 4B).

DISCUSSION

In this study, it was found that treatment with olanzapine or clozapine may lead to increased glucose and/or lipid levels. It was also seen that more patients treated with olanzapine developed manifest DM compared

Tab. 2. Reasons why the patients ended with their medication during the 8-year follow-up.

Reasons why the patients ended with their medication	Clozapine group (N)	Olanzapine group (N)
Died due to physical illness or unknown cause	2	2
Poor antipsychotic effect	1[a]	2
Diabetes mellitus		5
Hyperlipidemia	1[a]	1
Self-discontinued medication		2

[a] The same patient ended with the medication because of both poor antipsychotic effect and hyperlipidemia

Tab. 3. Somatic diseases in the patients treated with clozapine or olanzapine all 8 years.

Treatment group	Somatic diseases	
	at study start	at 8-year follow-up
Clozapine (N=20)	Diabetes mellitus (N=1)	Diabetes mellitus (N=1) Chronic obstructive lung disease (N=1) Hypertension (N=1)
Olanzapine (N=15)	Muscle disease (unknown cause; N=1)	Muscle disease (unknown cause; N=1) Diabetes mellitus (N=2) Hypertension (N=2)

Tab. 4A. Body mass index (BMI) and metabolic parameters as well as daily dose and serum concentration of antipsychotic in all patients at study start. Reference values are put in brackets.

	All patients at study start				
	Clozapine group mean±SD	**N**	**Olanzapine group mean±SD**	**N**	**Δ between groups *p*-value**
BMI, kg/m^2 (M ≤27, W ≤25)	29±6	22#	28±4	27	0.30
f(B)-glucose, mmol/L (3.0–6.0)	5.7±0.7	23	5.7±0.8	26#	0.90
Triglycerides, mmol/L (≤50 years 0.3–1.8, >50 years 0.4–2.2)	2.2±1.2	23	1.9±1.1	25#	0.35
Cholesterol, mmol/L (<40 years <5.5, 40–59 years <6.0, >60 years M <6.0, W <6.5)	5.7±1.1	23	5.8±0.9	25#	0.70
Prolactin, pmol/L (M and menopausal W <10, fertile W <20)	9.7±14.6	19#	10.3±5.4	16#	**0.01**
Daily dose of antipsychotic, mg	401±146	23	12±5	27	---
Serum concentration of antipsychotic, nmol/L	1519±879	23	118±63	27	---

#Data was missing in one or more patients
Abbreviations: Δ=difference; M=men; N=number; W=Women

Tab. 4B. Body mass index (BMI) and metabolic parameters as well as daily dose and serum concentration of antipsychotic in the patients who were treated with clozapine or olanzapine all 8 years. Reference values are put in brackets.

	Patients who were treated with clozapine (N=20) or olanzapine (N=15) all 8 years									
	at study start					at 8-year follow-up				
	Clozapine group mean±SD	**N**	**Olanzapine group mean±SD**	**N**	**Δ between groups *p*-value**	**Clozapine group mean±SD**	**N**	**Olanzapine group mean±SD**	**N**	***Δ over time* Δ between groups regarding change *p*-value**
BMI, kg/m^2 (M ≤27, W ≤25)	29±6	19#	27±4	15	0.54	28±6	18#	28±4	14#	*0.73* 0.29
f(B)-glucose, mmol/L (3.0–6.0)	5.7±0.7	20	5.5±0.7	15	0.29	6.5±1.5	17#	5.5±0.5	15	*clozapine:* ***0.01*** *olanzapine: 0.94* **0.004**
Triglycerides, mmol/L (≤50 years 0.3–1.8, >50 years 0.4–2.2)	2.2±1.3	20	1.7±0.9	15	0.37	1.8±0.8	16#	1.4±0.7	14#	*0.09* 0.74
Cholesterol, mmol/L (<40 years <5.5, 40–59 years <6.0, >60 years M <6.0, W <6.5)	5.7±1.0	20	5.9±0.9	15	0.68	5.4±1.3	16#	5.7±0.9	14#	*0.45* 0.71
Prolactin, pmol/L (M and menopausal W <10, fertile W <20)	6.4±4.5	16#	10.7±5.5	10#	**0.008**	---	---	---	---	---
Daily dose of antipsychotic, mg	401±141	20	13±6	15	---	405±119	19#	12±6	15	*clozapine: 0.75 olanzapine: 0.74*
Serum concentration of antipsychotic, nmol/L	1409±861	20	120±58	15	---	---	---	---	---	---

#Data was missing in one or more patients
Abbreviations: Δ=difference; M=men; N=number; W=Women

with those treated with clozapine. However, glucose levels increased over time also in the clozapine group, although this was not found in the olanzapine group, probably because more patients in the olanzapine group than in the clozapine group changed antipsychotics due to DM and hyperlipidemia during the 8-year follow-up. As known, clozapine is usually prescribed to patients who have schizophrenia or schizoaffective disorder and are resistant to several other antipsychotics, so it was easier to change antipsychotic from olanzapine than from clozapine. One exception to this rule was the patient in the clozapine group who was prescribed a change of antipsychotic because of hyperlipidemia and poor antipsychotic effect from clozapine (500 mg daily) to risperidone (8 mg daily), leading to better antipsychotic effect and decreased lipid levels.

A patient treated with clozapine had already at study start a known DM that was suspected to be clozapine-induced. Moreover, it was more common with slight hyperglycemia among the clozapine-treated patients at the 8-year follow-up. Fasting glucose level ≥7.0 mmol/L is one of the diagnostic criteria of DM (Mayfield 1998) and a number of patients who were treated with clozapine in this study developed hyperglycemia which was on the verge of DM, but did not meet this criterion at the 8-year follow-up. The hyperglycemia in the clozapine-treated patients developed over time during the 8 years, but seems not to be explained by increased doses of clozapine in the patients, since the mean clozapine doses did not differ between at study start and at the 8-year follow-up.

Serum PRL levels were higher in the patients treated with olanzapine compared with in those treated with clozapine at study start. Antipsychotic drugs exert their main effect on PRL secretion through blockade of the D_2 receptors on the lactotrophs in the pituitary (Reichlin 1998). It is therefore reasonable to assume that it is because of clozapine having weaker D_2 blocking effect (Farde *et al.* 1992), it is associated with less PRL elevation than olanzapine in this study. Since hyperprolactinemia has been reported to be associated with abnormalities of glucose and lipid metabolism (Ben-Jonathan *et al.* 2006), and even slight hyperprolactinemia due to antipsychotics may decrease insulin sensitivity (Melkersson *et al.* 2011), we may speculate that the PRL elevation possibly is related to why more patients in the olanzapine group developed manifest DM compared with those in the clozapine group. However, serum PRL levels were not investigated at the 8-year follow-up, so we do not know whether the difference in PRL level between the two treatment groups at study start remained after 8 years.

To compare, our findings that long-term treatment with olanzapine or clozapine may lead to development of hyperglycemia, hyperlipidemia and DM are fully consistent with previously published literature, suggesting that olanzapine and clozapine have higher propensity to induce metabolic abnormalities and DM compared with other atypical antipsychotics (Gianfrancesco *et al.* 2002; Scheen & De Hert, 2007).

According to this study, both olanzapine and clozapine long-term treatments cause development of hyperglycemia and/or hyperlipidemia which are signs of the metabolic syndrome (Reaven 1988). Furthermore, olanzapine long-term treatment seems to more often lead to development of manifest DM than long-term treatment with clozapine. Therefore, patients on long-term treatment with antipsychotics, especially olanzapine and clozapine, ought to be evaluated regarding metabolic abnormalities. Body mass index and metabolic parameters including fasting B-glucose and lipids as well as serum PRL should be followed up every year. It is also important to either change antipsychotic agent and/or treat the diabetes and hyperlipidemia immediately when such states are revealed.

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