Differences in Metabolic Side-effects of Typical and Atypical Antipsychotic Treatment in Elderly Individuals with Long-term Schizophrenia

典型及非典型抗精神病藥物對長期精神分裂症年長患者所產生的不同的代謝副作用

B Finkel, C Goodman, Y Melamed, M Naser, P Andreyev, Y Segev, A Bleich

Abstract

Objectives: To examine metabolic side-effects of year-long treatment with clozapine, risperidone, quetiapine, or olanzapine in comparison to treatment with haloperidol or perphenazine, among elderly individuals with long-term schizophrenia.
Participants and Methods: In a retrospective chart review, clinical records of 228 psychiatric inpatients with persistent schizophrenia were examined to determine any differences in metabolic side-effects of typical versus atypical antipsychotic treatment.
Results: There were no significant differences with respect to body mass index, body weight, blood glucose, and serum triglyceride, cholesterol, B12, and folic acid levels.
Conclusions: Elderly psychogeriatric patients may be less susceptible to the metabolic side-effects associated with atypical antipsychotic agents than younger populations. This finding warrants further investigation in prospective randomised controlled trials.

Key words: *Aged; Antipsychotic agents; Schizophrenia*

摘要

目的：探討及比較兩類抗精神病藥物對長期精神分裂症年長患者所產生的代謝副作用，這兩類藥物分別為：clozapine、risperidone、quetiapine、olanzapine及haloperidol、perphenazine。
參與者與方法：回顧228位有持續精神分裂徵狀的住院病人的醫院紀錄，以比較典型及非典型抗精神病藥物所產生的代謝副作用是否有不同。
結果：兩類抗精神病藥物在以下幾方面都沒有明顯分別：體重指數、體重、血糖量、血清三酸甘油脂、膽固醇、B12、和葉酸。
結論：與年青的精神病患者比較，年長精神病患者對非典型抗精神病藥物較不容易產生代謝副作用。需進一步進行預期性的抽樣對照試驗來確定此研究結果。

關鍵詞：*老年人、抗精神病藥物、精神分裂症*

Dr Boris Finkel, MD, Lev-HaSharon Mental Health Center, POB 90000, Netanya 42100, Israel.
Dr Craig Goodman, PhD, Lev-HaSharon Mental Health Center, POB 90000, Netanya 42100, Israel.
Dr Yuval Melamed, MD, MHA, Lev-HaSharon Mental Health Center; Sackler Faculty of Medicine, Tel-Aviv University, Israel.
Dr Mahmud Naser, MD, Lev-HaSharon Mental Health Center, POB 90000, Netanya 42100, Israel.
Dr Piter Andreyev, MD, Lev-HaSharon Mental Health Center, POB 90000, Netanya 42100, Israel.
Dr Yehoshua Segev, MD, Lev-HaSharon Mental Health Center, POB 90000, Netanya 42100, Israel.
Dr Avi Bleich, MD, MPA, Lev-HaSharon Mental Health Center; Sackler Faculty of Medicine, Tel-Aviv University, Israel.

Address for correspondence*: Dr Boris Finkel, Psycho-Geriatric Ward, Lev-HaSharon Mental Health Center, POB 90000, Netanya 42100, Israel.*
Tel: (972) 9898 1172; Fax: (972) 9898 0313;
E-mail: bfinkel@lev-hasharon.co.il

Submitted: *27 October 2008;* **Accepted:** *1 December 2008*

Introduction

Schizophrenia is one of the most serious chronic psychiatric disorders, which affects about 1% of the population. Although the disorder usually emerges before the age of 25 years, it may present in persons aged more than 45 years (late-onset schizophrenia).[1] A new era in the treatment of psychotic disorders, especially schizophrenia, began in the 1950s with the introduction of antipsychotic drugs. Due to only a partial response to this treatment, high relapse rates and adverse effects, new generations of drugs were synthesised.[2] Atypical antipsychotics, mostly clozapine, demonstrated better responses in the chronic schizophrenic populations, but were also reported to induce the metabolic syndrome (hypercholesterolemia, tryglyceridemia, and

elevation of blood glucose levels), and weight gain.[3]

In the general population, weight gain and obesity are common and can be serious health risks contributing to hypertension, diabetes mellitus, and cardiovascular disease.[4] Some studies reported higher rates of medical illnesses in schizophrenic patients than the general population.[1] Antipsychotic therapy for schizophrenic patients sometimes contributes to the exacerbation of these health risks, though studies have shown that weight gain can be attenuated in medicated patients with mental illness.[5-7] Atypical antipsychotic drugs have been widely used in the treatment of elderly psychiatric patients, especially those with long-term and late-onset schizophrenia.[8,9] Currently, approximately 90% of elderly schizophrenic patients are treated with atypical antipsychotics, but it is unclear how these affect body weight, and the metabolism of glucose and lipids in comparison to first-generation agents. Barak et al[10] investigated whether elderly patients with persistent schizophrenia or schizoaffective disorder might improve clinically if switched from older antipsychotic treatment to olanzapine. In these elderly patients with persistent schizophrenia, no significant change in body weight was reported after the switch. To our knowledge, there are no other studies in the literature examining differences in metabolic side-effects of typical and atypical medications used to treat elderly patients with long-term schizophrenia. This is particularly of interest considering the abundance of corresponding data reported in the literature about such antipsychotic treatment in younger and middle-aged schizophrenic patients. Moreover, the apparent lack of studies examining metabolic side-effects linked to antipsychotic treatment of elderly schizophrenia patients is particularly important, considering the profound physiological changes that accompany ageing. In this retrospective chart review, we therefore compared data regarding the metabolic side-effects of typical versus atypical antipsychotics, after year-long treatment of elderly individuals with long-term schizophrenia.

Methods

Participants

The medical charts of 228 psychiatric inpatients with long-term schizophrenia and hospitalised in the psychogeriatric department of Lev-Hasharon Mental Health Center (a university-affiliated government hospital) for more than 2,000 days were examined (covering a duration of 12 months). Each patient's diagnosis was recorded using the Diagnostic and Statistical Manual of Mental Disorders – 4th edition (DSM-IV) Axis I criteria for psychiatric disorders by consensus between the treating and research clinicians, after a clinical interview, and recourse to observational and case note information. Exclusion criteria were: first episode of schizophrenia; concomitant medications affecting glucose levels, triglycerides, or body mass index (BMI); having medical conditions such as diabetes, acute ischaemic heart disease, renal insufficiency, and thyroid dysfunction; as well as a current or previous DSM-IV diagnosis of drug or alcohol dependence.

All patients were able to eat and received regular fixed meals. They were treated with either typical (108 patients) or atypical (120 patients) antipsychotic medications; none received a combination of such therapy, and all of them had to have received the same medication for at least 3 months with no change in dosage for at least 4 weeks prior to the 1-year evaluation. Moreover, patients included in the sample had no change in concomitant medications. Mean (standard deviation [SD]) daily typical antipsychotic treatment dosages included either: haloperidol 10.1 (9.3) mg, perphenazine 31.2 (5.5) mg, zuclopenthixol depot 257.1 (97.6) mg. Corresponding values for atypical antipsychotic treatments included either risperidone 3.3 (1.8) mg, olanzapine 16.7 (7.3) mg, or clozapine 270.8 (109.7) mg. Data were obtained by retrospective review of medical records and assigned to atypical or typical antipsychotic treatment groups. Physiological data were based on monthly blood samples taken regularly from each patient over 1 year.

The study was approved by the hospital's Internal Review Board, and the data were analysed anonymously.

Statistical Analysis

Univariate analysis of variance was used to compare variables between groups. An average of all physiological data derived from monthly examinations was used for the analysis. Spearman's bivariate correlation analysis was used to examine association between variables and a partial correlation analysis was performed to assess the effects of potential confounding and socio-demographic variables. Statistical analysis was performed using the Statistical Package for the Social Sciences (Windows version 12.0; SPSS Inc, Chicago [IL], US).

Results

Patient demographic data and laboratory test results are presented in the Table. There were no significant differences in demographic and ancillary factors (age, length and frequency of hospitalisations) between the two treatment groups. Metabolic blood test results were similar in both groups, and were within normal ranges. The mean blood glucose level in the group that received atypical antipsychotics was 96.6 (SD, 29.6) mg/dl as compared to 107.6 (SD, 114.6) mg/dl in those who received typical antipsychotics. There were no between-group or between-gender differences in weight, BMI, and respective glucose, cholesterol, triglyceride, prolactin, folic acid, or vitamin B12 levels. Although an average of all physiological data derived from monthly examinations was used for the analysis, we also examined monthly changes and found no significant differences for month-to-month changes.

Discussion

This study was conducted to discover any differences

Table. Demographic and physiological data of elderly schizophrenia patients receiving typical versus atypical antipsychotics for 1 year: univariate analysis of variance.

Data	Mean (SD)		*f*	*df*	p Value
	Typical	Atypical			
Demographic data					
Age (years)	74.5 (10.4)	73.8 (9.2)	0.05	226	0.82
Number of hospitalisations	7.7 (6.0)	9.4 (8.0)	1.38	225	0.24
Cumulative days of hospitalisation	5072.6 (2925.3)	4382.0 (2397.1)	1.37	225	0.24
Weight (kg)	66.2 (15.4)	69.5 (13.8)	2.95	226	0.09
Body mass index (kg/m^2)	26.7 (5.5)	27.6 (6.0)	1.57	225	0.21
Physiological data					
Blood glucose (mg/dl)	107.6 (114.6)	96.6 (29.6)	1.04	224	0.31
Cholesterol (mg/dl)	193.0 (44.7)	189.5 (41.8)	0.377	217	0.54
Triglyceride (mg/dl)	133.1 (62.8)	145.2 (71.2)	1.82	224	0.18
Prolactin (ng/ml)	265.1 (115.8)	268.4 (306.4)	0.008	212	0.93
Vitamin B12 (pg/ml)	383.0 (281.0)	433.9 (283.2)	0.415	222	0.52
Folic acid (ng/ml)	21.6 (31.2)	19.9 (26.2)	0.041	224	0.84

Abbreviation: *SD = standard deviation.*

in metabolic side-effects in typical versus atypical antipsychotics among elderly patients with persistent schizophrenia on long-term antipsychotic treatment. Contrary to the findings of Schneider et al,[11] in the CATIE – Alzheimer's Disease study, who revealed statistically significant increases in weight gain, BMI, and glucose levels in Alzheimer's patients treated with atypical antipsychotic drugs (olanzapine, quetiapine, risperidone) versus placebo, we did not find any significant differences with respect to BMI, weight, levels in blood glucose, triglyceride, cholesterol, B12, and folic acid in our 2 treatment groups. We acknowledge that second-generation antipsychotic drugs are not a homogenous group. Nevertheless, our study did not reveal any differences between the elderly patients with persistent schizophrenia receiving different individual atypical (risperidone, olanzapine, clozapine) and typical (haloperidol, perphenazine, zuclopenthixol depot) antipsychotic drugs.

There is considerable literature regarding antipsychotic drug–induced weight gain and associated health problems in psychiatric patients, particularly those with schizophrenia. They include a high risk of weight gain, obesity, impaired glucose tolerance, and diabetes mellitus.[12,13] Although second-generation antipsychotic drugs have been reported to induce metabolic syndromes, including diabetes, dyslipidemias, and coronary heart disease in individuals with schizophrenia,[14] data concerning these effects in elderly patients are scarce. Thus, we examined the metabolic side-effects of such treatment in an elderly patient population with persistent schizophrenia. Comparison of physiological data for the 2 groups of treated elderly receiving typical versus atypical antipsychotics did not reveal notable differences with respect to metabolic side-effects. These findings suggest that treatment with second-generation antipsychotics appears appropriate for such elderly patients. In addition, since this age-group generally has a higher rate of chronic conditions such as diabetes and cardiovascular disease, these findings may have even greater relevance to treatment options. Nevertheless, there are Food and Drug Association warnings concerning the use of second-generation antipsychotic agents among elderly patients with diabetes and increased risk of stroke.[15] In view of the many reports in the literature concerning younger schizophrenia patients, our findings warrant further study regarding the possible metabolic side-effects of these agents in elderly patients.

The retrospective nature of this study was a major limitation. The broad exclusion criteria may also limit generalisation of the results. There was no intervention with regard to medical decisions, and none of the patients received a combination of typical and atypical antipsychotic agents. The mean age of the study population was 74 years, which is more than the average lifespan of patients with schizophrenia (of around 65 years). Our sample was therefore not representative of most geriatric patients with persistent schizophrenia, and perhaps individuals predisposed to metabolic problems had already died.

Acknowledgement

The authors thank Rena Kurs for assistance in preparation of the manuscript.

References

1. Breier A, Schreiber JL, Dyer J, Pickar D. National Institute of Mental Health longitudinal study of chronic schizophrenia. Prognosis and predictors of outcome. Arch Gen Psychiatry 1991;48:239-46.
2. Kane JM. Schizophrenia. N Engl J Med 1996;334:34-41.
3. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, et al. Antipsychotic-induced weight gain: a comprehensive

research synthesis. Am J Psychiatry 1999;156:1686-96.
4. Allison DB, Saunders SE. Obesity in North America. An overview. Med Clin North Am 2000;84:305-32,v.
5. Sharpe JK, Hills AP. Atypical antipsychotic weight gain: a major clinical challenge. Aust N Z J Psychiatry 2003;37:705-9.
6. Poyurovsky M, Fuchs C, Pashinian A, Levi A, Faragian S, Maayan R, et al. Attenuating effect of reboxetine on appetite and weight gain in olanzapine-treated schizophrenia patients: a double-blind placebo-controlled study. Psychopharmacology (Berl) 2007;192:441-8.
7. Melamed Y, Stein-Reisner O, Gelkopf M, Levi G, Sivan T, Ilievici G, et al. Multi-modal weight control intervention for people with persistent mental disorders. Psychiatr Rehabil J 2008;31:194-200.
8. Jano E, Johnson M, Chen H, Aparasu RR. Determinants of atypical antipsychotic use among antipsychotic users in community-dwelling elderly, 1996-2004.Curr Med Res Opin 2008;24:709-16.
9. Gareri P, De Fazio P, Stilo M, Ferreri G, De Sarro G. Conventional and Atypical Antipsychotics in the Elderly : A Review. Clin Drug Investig 2003;23:287-322.
10. Barak Y, Shamir E, Mirecki I, Weizman R, Aizenberg D. Switching elderly chronic psychotic patients to olanzapine. Int J Neuropsychopharmacol 2004;7:165-9.
11. Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 2006;355:1525-38.
12. Luft B, Taylor D. A review of atypical antipsychotic drugs versus conventional medication in schizophrenia. Expert Opin Pharmacother 2006;7:1739-48.
13. Wirshing DA. Schizophrenia and obesity: impact of antipsychotic medications. J Clin Psychiatry 2004;65 Suppl 18:S13-26.
14. Henderson DC, Cagliero E, Copeland PM, Borba CP, Evins E, Hayden D, et al. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents: a frequently sampled intravenous glucose tolerance test and minimal model analysis. Arch Gen Psychiatry 2005;62:19-28.
15. Carson S, McDonagh MS, Peterson K. A systematic review of the efficacy and safety of atypical antipsychotics in patients with psychological and behavioral symptoms of dementia. J Am Geriatr Soc 2006;54:354-61. Erratum in: J Am Geriatr Soc 2006;54:1479.