Utilization of olanzapine and risperidone in Hungary with special concern to the treatment of schizophrenia in the psychiatric rehabilitation

Ph.D. Thesis

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SUMMARY
Because olanzapine and risperidone have similar efficacy and tolerability in the treatment of schizophrenia and these two agents are the most widely used atypical antipsychotics in Hungary, the utilisation of the drugs is a relevant consideration. The purpose of this study was to follow the utilisation trend of olanzapine and risperidone in Hungary and in the Gálfi Béla Hospital, which is a specialised institute on psychiatric rehabilitation. Data regarding dosages and psychiatrists' clinical preferences were collected through studying hospital charts in the Gálfi Béla Hospital during the period 1999-2007. Utilisation of the agents indicated that there was an increase of use for the whole examined period in the Gálfi Béla Hospital, although unambiguous growth began only in 2001. Hospital chart analysis shows that both drugs were used to a large extent and risperidone use is increasing more rapidly, which is justified by the gerontopsychiatric profile of the hospital.

The further aim of the study was to compare the risk of diabetes in a Hungarian schizophrenic population treated with atypical antipsychotics with that of the non-schizophrenic population. We wished to reveal the effects of gender and age. A schizophrenic population was examined by studying hospital charts in the Gálfi Béla Hospital. Data were given by the National Health Insurance Fund registry in the period of 2000-2006, while the Hungarian Central Statistical Office presented data on the prevalence of diabetes in the Hungarian population. Binomial distribution was used for the hypothesis testing. The examination shows higher prevalence of diabetes among schizophrenic patients (12.72%) in comparison with the Hungarian population (6.85%) in the age group of 18-64 among both sexes, while there was no higher risk of diabetes found in the age group of above 65 among both sexes. As a conclusion, we emphasize that continuous weight, glucose and lipid level monitoring should be considered during treatment with antipsychotics in all age groups, even if our study does not show higher risk of diabetes among elderly schizophrenic patients.
The results of my investigations did not show higher risk of diabetes among elderly schizophrenic patients treated with atypical antipsychotics, while continuous weight, glucose and lipid level monitoring should be indicated during treatment with antipsychotics in other age groups.

OBJECTIVES

I. Utilization study of olanzapine and risperidone in psychiatric rehabilitation within 1999-2007

Data showed that in accordance with the latest professional guidelines the use of novel antipsychotics is increasing. Based on analysis of the antipsychotic use in clinical practices there were characteristic patterns found that show that the conventional antipsychotic use is still notable.

Because olanzapine and risperidone have similar efficacy and tolerability in the treatment of schizophrenia and these two agents are the most widely used atypical antipsychotics in Hungary the utilization of the drugs becomes a relevant consideration.

The purposes of the thesis were to study retrospectively the use of olanzapine and risperidone between 1999 and 2007 and to have a clear view on their utilization with respect to the gerontopsychiatric profile of the Gálfi Béla Hospital which is a specialised institute on psychiatric rehabilitation and to follow the temporal development trends of use of olanzapine and risperidone in Hungary between 1999 and 2007.
II. Study of diabetes prevalence among elderly patients in psychiatric rehabilitation

Metabolic complications are a major issue in patients receiving antipsychotic therapy. Diabetes is known to occur occasionally with conventional antipsychotics, but has been more often associated with atypical antipsychotics. A body of evidence suggests that atypical antipsychotics, apart from clozapine, are more disadvantageous from the aspect of glucose regulation and diabetes than conventional drugs. Atypical antipsychotics should be administered with great care to patients with risk factors for diabetes. Diabetes is associated with increased morbidity and mortality for cardiovascular disease. An increasing number of reports concerning diabetes, ketoacidosis, hyperglycaemia and lipid dysregulation in patients treated with atypical antipsychotics have raised concerns about a possible association between these metabolic effects and treatment with these medications. Reports and clinical experience suggest that in the case of atypical antipsychotics associated diabetes, discontinuation of the antipsychotic agent may result in complete resolution of the hyperglycaemia.

Metabolic side effects have been increasingly noted during therapy with novel antipsychotics, but there is a dearth of comprehensive comparative data in this area. Weight gain is a common and troublesome side-effect, particularly associated with some of the atypical drugs, and probably related to 5-HT antagonism. Several mental illnesses including schizophrenia have been associated with impaired glucose regulation and elevated rates of diabetes mellitus. The purpose of the thesis were to study the relationship between the antipsychotic treatment and the prevalence of diabetes among elderly patients in psychiatric rehabilitation.
METHODS

I. Utilization study of olanzapine and risperidone in psychiatric rehabilitation within 1999-2007

Data regarding dosages and psychiatrists’ clinical preferences were collected through studying hospital charts in the Gálfi Béla Hospital which is specialized on gerontopsychiatric attendance with a main profile of rehabilitation. The location of the Gálfi Béla Hospital is in Pest County with a distance of 25 km from Budapest. In the examined period there was psychiatric attendance on 420 beds. As a first step of the examination all diagnosed schizophrenic disorders (ICD-10 F20xx – F29) were surveyed between 1999 and 2007 in the Gálfi Béla Hospital including over 2000 hospital charts. Hospital charts are electronically registered documents that can be filled out only by the prescribing doctors. There were 14 psychiatrists’ prescriptions surveyed in the period of 1999-2007. Patients show a view of a typical polymorbid population. All charts refer to some cases of schizophrenia - including paranoid, disorganized, undifferentiated or residual types - or schizoaffective disorder of unknown type receiving antipsychotic treatment - conventional neuroleptics or atypical antipsychotics (n=2545). A smaller number of charts (n=1472) indicate when patients received antipsychotic medication of olanzapine (OLA) or risperidone (RIS). The defined daily dose of olanzapine (DDD\textsubscript{OLA}) is 10 mg/day (ATC\textsubscript{OLA} N05AH03) and risperidone (DDD\textsubscript{RIS}) is 5 mg/day (ATC\textsubscript{RIS} N05AX08), while PDDs for olanzapine and risperidone are 15 mg and 4-6 mg, respectively. Polynomials have been fitted to both sets of data and analysis of variance has also been applied to check the results. The statistical program package SPSS 13.0 (SPSS Inc., Chicago, IL, USA) has been used.
Utilization study of clozapine, olanzapine and risperidone

The utilization data of the country study were obtained by the National Health Insurance Fund registry in the period of 1999-2003. Data were given in the Gálfi Béla Hospital by hospital chart analysis. Olanzapine and risperidone were the most widely used atypical antipsychotics in Hungary between 1999 and 2003, while the special indication of clozapine indicated its participation in the utilization study.

II. **Sample selection for the study of the diabetes prevalence among elderly patients in psychiatric rehabilitation**

Data regarding dosages and psychiatrists’ clinical preferences were collected through studying hospital charts in the Gálfi Béla Hospital which is specialized on gerontopsychiatric attendance with a main profile of rehabilitation. In the examined period there was psychiatric attendance on 420 beds. As a first step of the examination, all diagnosed schizophrenic disorders (International Classification of Diseases ICD-10 F20xx – F29) were surveyed between 2000 and 2006 in the Gálfi Béla Hospital including over 2,500 hospital charts. Hospital charts are electronically registered documents that can be filled out only by the prescribing doctors. There were 14 psychiatrists’ prescriptions surveyed in the period of 2000-2006. As a result of the hospital chart analysis we admitted a population of schizophrenic patients (n = 245). The examined population came together with fulfilling the following criteria. Each patient was treated continuously with antipsychotics between 2000 and 2006. There would be a near number of the male and female patients in the examination. All ages should have been represented. All patients were diagnosed as schizophrenic (according to ICD-10 F20xx – F29).
Patients preferably would come from all parts of Hungary. Patients were not diagnosed as diabetics before 2000 in the Gálfí Béla Hospital. We aimed to compare the risk of diabetes in a Hungarian schizophrenic population treated with atypical antipsychotics with that of the non-schizophrenic population. We wished to reveal the effects of gender and age. A schizophrenic population (n = 135 male and n = 110 female patients of different age groups) was examined by studying hospital charts in the Gálfí Béla Hospital. Data were given by the National Health Insurance Fund registry in the period of 2000-2006, while the Hungarian Central Statistical Office presented data on the prevalence of diabetes in the Hungarian population. Binomial distribution was used for the hypothesis testing.

Hypothesis testing

Binomial tests were made, with the zero hypothesis that there is no difference between the schizophrenic and normal Hungarian population in diabetes rates and with the alternative hypothesis that the diabetic rate is higher in the schizophrenic group. In cases of all female and male groups, the age-adjusted population prevalence data (based on census information, 2001) were applied in the binomial tests. Microsoft Excel software was used for the calculations. Level of significance was taken as 5%.

RESULTS AND DISCUSSION

I. *Results of the utilization study of olanzapine and risperidone in psychiatric rehabilitation within 1999-2007 in comparison with the country data*

There was an increase in the use of both atypical antipsychotics over the examined period. Although there was a stagnancy of the use in 2000 and 2001 for olanzapine
and in 2001 for risperidone, there was a gross increase in the use of both agents over the whole surveyed period. An increase of 1.142 mg/day/year (p = 0.0004) was found for olanzapine and 1.6483 mg/day/year (p = 0.002) for risperidone. Therefore, it might justly be concluded that risperidone use increased more rapidly. An increase of 0.507 mg/day/year (p = 0.0002) was found for olanzapine and 0.130 mg/day/year (p = 0.0001) for risperidone. Even if the use of both agents shows a dynamic accession, the growth with olanzapine was significantly higher (p=0.026) in the examined period on a country level, while the gerontopsychiatric profile of the hospital supports more use of risperidone.

Utilization study of clozapine, olanzapine and risperidone
The use of olanzapine and risperidone was increasing in the Gálfi Béla Hospital and Hungary in the examined period, while the use of clozapine was decreasing in the country study. Although the daily therapy costs of clozapine are much lower than that of olanzapine and risperidone, the reason of the decrease could be the serious side-effect profile of clozapine. In the Gálfi Béla Hospital the use of clozapine showed a small increase, what could be indicated by the relative big number of therapy resistance.

II. Diabetes prevalence among elderly patients in psychiatric rehabilitation

The examination shows higher prevalence of diabetes among schizophrenic patients (12.72%) in comparison with the Hungarian population (6.85%) in the age group of 18-64 among both sexes, while there was no higher risk of diabetes found in the age group of above 65 among both sexes. Diabetes prevalence in the sample population shows almost a double value (12.72%) in comparison to the Hungarian population prevalence (6.85%). The Hungarian Central Statistical Office and the National Institute for Strategic Health Research presented data on the prevalence of
diabetes in the Hungarian population. The hypothesis test shows that in the age
group of 18-64 significantly higher diabetic rates were found among both sexes. In
the age group above 65 there was no significant difference between the treated and
the normal population rates neither among the male nor the female patients. We
could miss the effect because of the small number of patients (n = 245) fulfilling
the criteria in those groups. Schizophrenic patients have higher mortality and the
population prevalence of diabetes is higher in the age group of 18-65, while in the
non-schizophrenic population the prevalence of diabetes is higher over the age of
65. Sex differences in schizophrenia can be caused by the disease process itself, by
genetic and hormonal differences, by differences in the maturation and
morphology of the brain and in age- and gender-specific behavioural patterns.
However, in our study no significant differences were observed between the two
sexes.

Calculations on the all, male and female groups are made with age adjusted
prevalence based on 2001 Census.

The study is based on a survey of hospital charts in the Gálfí Béla Hospital and the
National Health Insurance Fund registry. Country data give a clear view on the
growing utilization trend of atypical antipsychotics in Hungary. A large study of
38,600 patients with schizophrenia suggested that patients on atypical treatment
were 9% more likely to have diabetes than conventionally treated patients.
Risperidone however was not associated with an increased risk across the entire
age group, just in patients under 40 years old.

The examination shows higher prevalence of diabetes among schizophrenic
patients treated with antipsychotics (12.72%) in comparison with the Hungarian
population (6.85%) while there was no higher risk of diabetes found in the age
group of 65+ among both sexes. Nevertheless the difference was found significant;
the latent diabetes prevalence of the Hungarian non-schizophrenic population is
higher than the officially published value.
Based on the results it would seem prudent to monitor patients’ weight, glucose and lipid levels, especially in the age group of 18-64, whatever antipsychotics are prescribed for them.

Limitation of this study was the relatively small number of schizophrenic patients in the examined sample (n = 245).

**CONCLUSIONS**

Analysis on the data sources showed a clear accession for olanzapine and risperidone in the examined term. There was a growth in use of the agents over the whole study term, although an unambiguous increase started only in 2001. In general, the clinical preferences as revealed by the study are consistent with the literature, which suggests that the drugs have similar indications and are equally effective. The use of olanzapine and risperidone show a dynamic accession between 1999 and 2007 in the Gálfí Béla Hospital and in Hungary. Country data clearly show the growing utilisation trend of atypical antipsychotics in Hungary. Even if the use of olanzapine shows a greater growth at a country level, the gerontopsychiatric profile of the hospital supports more use of risperidone.

Our results did not show higher risk of diabetes among elderly schizophrenic patients treated with atypical antipsychotics. Nevertheless it would seem prudent to monitor patients’ weight, glucose and lipid levels, especially in the age group of 18-64, whatever antipsychotics are prescribed for them. Although there is a growing trend in the use of atypical antipsychotics in the medication of schizophrenia in Hungary, no relevant data can be found in the literature considering the metabolic effects of these drugs in the Hungarian population. Atypical antipsychotics, which have a better side-effect profile are more suitable for elderly people. This paper includes an assessment of the potential contributory
role of treatment-induced ATC-A10A parenteral and ATC-A10 B oral antidiabetic use during treatment with atypical antipsychotics in psychiatric rehabilitation among elderly patients in Hungary.

**Practical conclusions of the results**

Daily therapy costs of olanzapine and risperidone as the most often ordered atypical antipsychotics and of all other atypical agents are higher in comparison with typical agents. Whereas drug costs are the smaller part of therapy costs of psychotic diseases, hospitalization can take the half of all costs. With the use of atypical antipsychotics all costs of the therapy can be decreased and the quality of life of the treated patient is significantly better than in patients treated with classical agents.

Country data show growing utilisation trend of atypical antipsychotics in Hungary, while the use of clozapine is decreasing. Clozapine remains the antipsychotic agent of therapy resistant schizophrenic patients.

The incidence of hyperglycaemia and lipid abnormalities can be higher among patients treated with atypical antipsychotics. Therefore schizophrenic patients with one or more risk factors of diabetes should be regularly controlled in point of weight, blood pressure, blood sugar and lipid levels.
PUBLICATIONS AND LECTURES

Publications


Lectures


3. **Klebovich A.**: Antipszichotikumok alkalmazása a gerontopszichiátriai gyakorlatban. 

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