

Review of Glycemic Related Studies

March 2002

Prepared for MHLW

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1. Introduction

This report was prepared at the request of a fax received on 06-Mar-2002 from MHLW to provide analysis of Eli Lilly global trial data on weight gain and hyperglycemia associated with the use of olanzapine.

Diabetes and diabetes related events are frequently associated with schizophrenia and related disorders. A number of factors may explain this phenomenon. These include an unknown genetic link, obesity, sedentary lifestyles and impulsive eating behavior.

2. Request

MHLW inquiry for hyperglycemic/diabetic SAE:

- all expedited reports concerning hyperglycemia (Japan case reports)
foreign hyperglycemia SAE case line-listing

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3. Epidemiological Studies

3.1. *AdvancePCS Study*

A Pharmacoepidemiological Study of Diabetes Mellitus and Antipsychotic Treatment in the United States

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Purpose: To compare the odds of developing diabetes mellitus (DM) during exposure to various antipsychotics

Background: Cases of treatment-emergent DM have been reported for both conventional and atypical antipsychotics. However, large epidemiological studies are needed to determine the existence and extent of any association between development of DM and antipsychotic medications and to resolve whether there is a substantial difference in the risk of developing DM among different antipsychotic therapies.

Method: This is a retrospective cohort study based on the prescription claim data of AdvancePCS Inc. in the US covering the period of 12/01/1997 to 8/31/2000. Prescription claims for antipsychotics were used to identify and select adult subjects that began antipsychotic monotherapy between 12/1/1998 and 2/29/2000. The antipsychotic cohorts studied were combined conventional antipsychotics (N= 19,782), haloperidol (N= 8,476), thioridazine (N=3,133), combined atypical antipsychotics (N= 38,969), olanzapine (N=13,863), risperidone (N=20,633), quetiapine (N=4,196), and clozapine (N=277). The AdvancePCS general patient population (N=5,816,473) included all adult AdvancePCS members who had made at least one prescription claim (other than an antipsychotic) between January 1, 2000 and February 29, 2000. Prescription claims for diabetes medications were used to identify subjects with DM. Those with antipsychotic prescription claim(s) 6 months prior to starting anti-diabetic therapy or those with anti-diabetic prescription claims any time prior to starting antipsychotic therapy were

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excluded. Cox Proportional Hazards regression was used to adjust for differences in age, gender, and duration of antipsychotic exposure between cohorts in the estimation of risk of developing diabetes. Hazard ratios (HRs) of DM in antipsychotic cohorts, were determined relative to the AdvancePCS general patient population and between selected antipsychotic cohorts.

Results: Compared to the general PCS patient population, the incidence of diabetes mellitus was significantly increased in both the conventional and atypical groups (Figure 1). The relative risk of developing DM during treatment with conventional and atypical antipsychotics cohorts compared to the AdvancePCS general population were HR=3.5; CI: 3.1-3.9; p<.001 and HR=3.1; CI: 2.9-3.4; p<.001, respectively. The relative risk of developing DM during treatment with individual antipsychotics compared to the AdvancePCS general population were haloperidol HR=3.1; CI: 2.6-3.7; p<.001, thioridazine HR=4.2; CI: 3.2-5.5; p<.001, olanzapine HR=3.0; CI: 2.6-3.5; p<.001, risperidone HR=3.4; CI: 3.1-3.8; p<.001, quetiapine HR=1.7; CI: 1.2-2.4; p=.002, and clozapine HR=3.3; CI:1.4-8.0; p=.007. The combined conventional and atypical cohorts were compared and there was no significant difference in risk of developing DM (HR=0.97; CI: 0.8-1.1; p=0.6). Compared to the haloperidol cohort, a statistically significant increase in risk of developing DM was observed in the risperidone cohort HR=1.2; CI: 1.0-1.5; p= 0.04. There was no statistically significant difference between the risk of developing DM in the olanzapine and risperidone cohorts HR=0.9; CI: 0.8-1.1; p= 0.2.

As shown in Table 1, the risk of DM for the combined conventional cohort was not significantly different from that of the combined atypical cohorts (HR=1.0; CI: 0.8-1.1; p=0.6). No significant increase in the risk of DM was observed for either the olanzapine (HR=1.1; CI: 0.9-1.4; p=0.5) or the clozapine (HR=1.3; CI:0.6-2.9; p=0.5) cohort when compared to the haloperidol cohort. The clozapine sample was very small (N=277), and lacked sufficient power to detect a significant difference in the risk of DM. The HR for the quetiapine cohort was 0.7 (CI: 0.5-0.97; p=0.03), suggesting a statistically significant lower risk of DM compared to the haloperidol cohort. The risk of DM in the risperidone cohort, relative to the haloperidol cohort, was 1.2 (CI: 1.0-1.5; p=

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.04). On comparison of the two largest atypical antipsychotic cohorts, olanzapine and risperidone, the HR was 0.9 (CI: 0.8-1.1; p= 0.2).

Conclusions: An increased risk of developing diabetes compared to a general reference population was observed in the AdvancePCS prescription-database cohorts during treatment with either conventional or atypical antipsychotics. Though the risk of developing diabetes was significantly greater for patients in the risperidone cohort than in the haloperidol cohort, this analysis did not demonstrate a generally elevated risk between the atypical and conventional antipsychotic cohorts. It remains unclear whether the observed increases are related to factors intrinsic or extrinsic to those psychiatric conditions commonly treated with antipsychotic drugs.

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FIGURE 1: ANNUALIZED INCIDENCE OF DIABETES MELLITUS DURING ANTIPSYCHOTIC TREATMENT

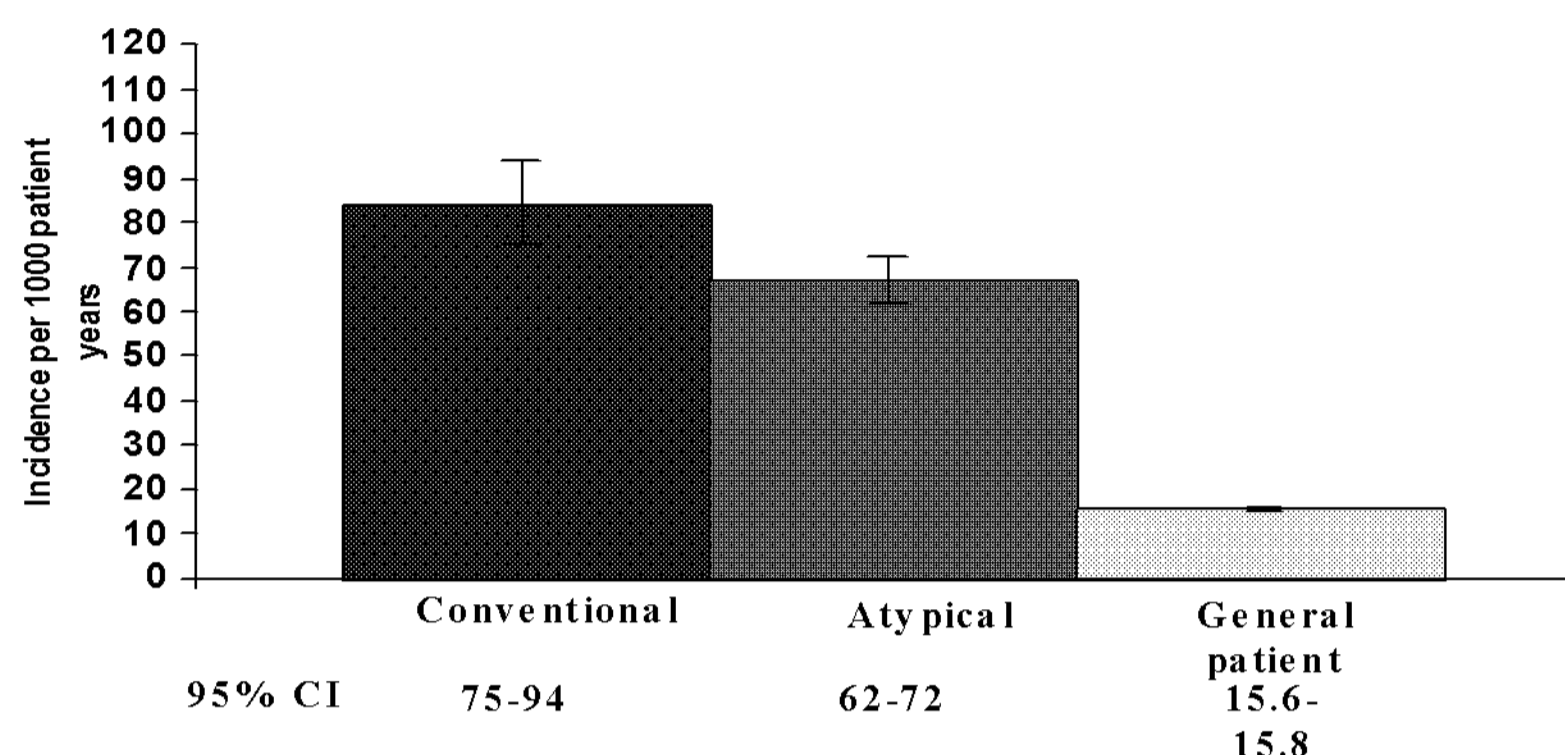


Table 1. Hazard Ratio of Developing Diabetes Comparing Selected Antipsychotic Cohorts to other Antipsychotic Cohorts

TREATMENT COHORT	Number of new Cases	Number of subjects in cohort	Hazard ratio*		
			Ratio	95% CI	p-value
Atypical	641	38,969	0.97	0.84 - 1.11	0.626
vs. Typical	307	19,782	-	-	-
Clozapine	7	277	1.31	0.60 - 2.86	0.496
Olanzapine	194	13,863	1.09	0.86 - 1.37	0.479
Quetiapine	40	4,196	0.67	0.46 - 0.97	0.033
Risperidone	400	20,633	1.23	1.01 - 1.50	0.040
vs. Haloperidol	133	8476	-	-	-

*Cox Proportional Hazards regression analysis adjusted for age, gender and duration of antipsychotic exposure.

HR and 95% CI values were rounded to first decimal place except where such rounding obscured significance cut-off points.

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3.2. GPRD Study

A Retrospective Cohort Study of Diabetes Mellitus and Antipsychotic Treatment in the United Kingdom

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Objective: In this retrospective cohort study, we explored the UK General Practice Research database (GPRD) to determine the hazard ratio of diabetes mellitus for patients prescribed antipsychotics compared with the GPRD general patient population in the UK.

Methods: The retrospective cohorts studied included a GPRD general patient population cohort, a combined antipsychotic cohort, and individual antipsychotic monotherapy cohorts. The GPRD general patient population cohort (N=266,272) consisted of a random sample of subjects registered continuously during January 1, 1996 and December 31, 1997 who had received at least one prescription for any medication other than an antipsychotic during this two-year period. The study population was comprised of adults 18 years of age or older as of 1994, which were registered in standard general practices, and were prescribed an antipsychotic between January 1, 1994 and December 31, 1999. The combined antipsychotic cohort included patients exposed to either conventional or atypical antipsychotics (N= 46,111). Individual antipsychotic cohorts were comprised of patients exposed to a single antipsychotic during the study period.

Any patient who had a recorded diagnosis of type 1 or type 2 diabetes mellitus (as defined by one or more of the Oxford Medical Information System diagnostic codes for diabetes mellitus) or who was prescribed any antidiabetic agent was considered as having diabetes. Patients with a personal history of diabetes prior to the first prescription of antipsychotic(s) were excluded from the analysis.

A Cox proportional hazard regression model was used to determine the hazard ratio (HR) of diabetes development between the GPRD general patient population,

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combined antipsychotic, and individual antipsychotic cohorts. The covariates included in the model were age, gender, and the presence or absence of obesity.

Results: Compared to the GPRD general patient population cohort, patients in the combined antipsychotic cohort had a higher risk of developing diabetes (HR=1.5; CI=1.1-1.9; p=.007). The risk of developing diabetes during exposure to thioridazine (HR=1.5; CI=1.009-2.3; p=.045) and risperidone (HR=3.2; CI=1.4-7.1; p=.006) was significantly higher than that of the GPRD general patient population. Assessment of other individual antipsychotics was limited by sample size of the cohorts.

Conclusions: This study is consistent with previous observations of elevated risk of diabetes in patients treated with antipsychotic drugs. It remains unclear to what extent the increased risk of diabetes is related to treatment factors or factors related to the underlying psychiatric conditions commonly treated with antipsychotic drugs such as biological vulnerability or lifestyle.

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4. Study HGIM

Study F1D-MC-HGIM sought to determine whether olanzapine or risperidone has a direct effect to impair insulin secretion. The study assessed insulin secretory capability as measured by changes (baseline to endpoint) in insulin levels during a hyperglycemic clamp in healthy subjects treated (15 to 17 days) with olanzapine 10mg/day, in comparison to risperidone 4mg/day or placebo. Weight increased significantly ($p < 0.01$) in both the olanzapine (2.8 ± 1.7 kg) and risperidone (3.1 ± 2.1 kg) treatment groups. Fasting insulin levels were also increased significantly ($p < 0.05$) compared to placebo during treatment with olanzapine (40%) or risperidone (36%). Fasting glucose was not changed in either active treatment group. Using the hyperglycemic clamp, a similar increase (~25%) in the total insulin response (weighted mean insulin level, 0 to 240 minutes) and a decrease (~18%) in the insulin sensitivity index (steady state $M/I = \text{glucose infusion rate} / \text{ambient insulin concentration}$) was observed during treatment with olanzapine or risperidone. The change in clamp insulin response was correlated ($r=0.5576$, $p=0.019$) with change in body mass index (BMI). When the impact of weight change was accounted for by multivariate regression analyses, no significant change in total insulin response, insulin sensitivity index, or fasting insulin was detected following treatment with olanzapine or risperidone. Results of the study found similar weight related changes in fasting insulin, insulin secretion during hyperglycemia, and insulin sensitivity measured during the clamp during treatment with olanzapine or risperidone. Treatment with olanzapine or risperidone was not, however, associated with impaired (decreased) insulin secretion during the hyperglycemic clamp.

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