The risk of metabolic disorders in patients treated with asenapine or olanzapine: a study conducted on real-world data in Italy and Spain.

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The risk of metabolic disorders in patients treated with asenapine or olanzapine: a study conducted on real-world data in Italy and Spain

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Abstract

Background: Atypical antipsychotics are the main treatment for a large number of psychiatric illnesses, with fewer extrapyramidal effects than conventional antipsychotics. However, it has been suggested that their use is associated with increased risk of dyslipidemia and type 2 diabetes mellitus.

Objective: The risk of metabolic adverse effects associated with asenapine was assessed in comparison with that associated with olanzapine using real-world data.

Methods: This study was a retrospective analysis based on data extracted from the Italian and Spanish Cegedim Strategic Data Longitudinal Patient-Data databases. Patients with asenapine or olanzapine prescriptions were retrieved from September 2010 to December 2012 using strict inclusion criteria to guarantee minimization of confounders. Patients with type 2 diabetes mellitus and dyslipidemia were identified by using ICD9 codes and by antidiabetic and dyslipidemic drug prescriptions. The presence or absence of the metabolic condition was compared before and after treatment, and between cohorts.

Results: The retrospective analysis showed a lower risk of developing type 2 diabetes with asenapine than with olanzapine (2.2 vs 3.5%, respectively; p value: 0.0002) and of developing dyslipidemia (2.8 vs 6.8%, respectively; p value: 0.0001).

Conclusions: Asenapine is associated with a lower risk of metabolic adverse effects than olanzapine, demonstrating its improved safety profile.

1. Introduction

Antipsychotic drugs remain the cornerstone of treatment for a number of psychiatric illnesses, including schizophrenia and bipolar disorder. However, these drugs can cause a wide range of adverse effects.

Adverse effects in general, and those of atypical antipsychotics (AAs) in particular, can impair quality of life, cause stigma, impact on morbidity and mortality and contribute to

poor adherence to medication or even discontinuation of therapy, which may lead to an increased relapse rate [1].

AAs have a lower risk of extrapyramidal symptoms when compared with conventional or 'typical' antipsychotics, but it has been suggested that the use of AAs is associated with substantial weight gain, and with an increased risk of dyslipidemia and of type 2 diabetes mellitus (T2DM) [2] In particular, weight increase has been reported for clozapine and olanzapine [3], while development of T2DM has been associated in varying degrees with the use of olanzapine, risperidone, clozapine and quetiapine [4]. For example, clozapine carries a risk of diabetes as much as seven times that of the conventional first-generation antipsychotic agents. These changes begin within 4 months after first exposure to the drugs and accrue over time [5]

It has been demonstrated that weight gain and increased risk of T2DM are often linked. Some studies also suggest that lipid profiles may be negatively affected by AAs [5,6].

A retrospective analysis showed a significantly higher prevalence of metabolic comorbidities in patients with bipolar disorder than in the general population. The same analysis also found that annual medical treatment costs for metabolic conditions in this patient population were twice as much as those incurred in the control group [7], thus emphasizing metabolic comorbidities as an important economic burden in severe mental illness.

Antipsychotic medications are associated with different levels of risk for adverse effects and a recent literature review indicated markedly different risks of developing most common adverse effects among atypical drugs [8].

Asenapine is a new AA drug developed for the treatment of schizophrenia and mania or mixed episodes associated with bipolar disorder [9]Asenapine summary of product characteristics. A recent post-hoc analysis of pooled data from all available asenapine placebo- or olanzapine-controlled clinical trials in patients with schizophrenia and bipolar disorder assessed the potential risk of weight gain and metabolic effects associated with the use of this drug [10]. Based on this analysis, asenapine has been shown to have a lower propensity than olanzapine in inducing weight gain or increasing triglycerides or serum lipids and glucose, indicating its more favorable metabolic profile.

The purpose of this study was to investigate whether the use of asenapine and olanzapine is associated with a potential risk of metabolic adverse events in a real-world context.

2. Materials and methods

A retrospective analysis was conducted on data extracted from Italian and Spanish Cegedim Strategic Data Longitudinal Patient-Data (LPD) databases, which contain anonymized patient-level data collected from a large sample of Spanish and Italian General Practitioners (GPs). Information on prescriptions, diagnoses, procedures, physician visits, hospitalizations, laboratory tests, and so on was gathered continually during the defined timeframe and in real time in doctors' offices using practice management software. This allowed tracking of data over time, and it provided real-world patient insight. These

databases are of value at National and Regional level, representing a wide patient-population visiting about 1300 primary care physicians in Italy and Spain, and reliability has been recognized by public institutions [11,12].

Patients with at least one prescription of either asenapine (cohort 1) or olanzapine (cohort 2) between 1 September 2010 and 31 December 2012 were included in the study. For each patient, the date of the first asenapine or olanzapine prescription was considered as the Index Date. All patients being administered either asenapine or olanzapine for severe mental illness were entered into the analysis, independently from the associated diagnosis.

To avoid entering patients with only one prescription during the observation period, patients included in this analysis should have more than one prescription of the same AA drug (asenapine or olanzapine) during the 6 months following the Index Date. Patients should also have no prescriptions of the comparator medication during the 6 months following the Index Date to avoid co-administration of the two drugs, which could affect the analysis on treatment-emergent conditions.

While asenapine was first authorized in Europe on 1 September 2010 [9], olanzapine was already on the market for a few years, and it could have already been prescribed before the Index date. Therefore, in order to minimize the bias of including patients who had been prescribed the same drug previously, only patients without prescription of the same antipsychotic drug during the 6 months before the Index Date were entered into the study (Figure 1).

Demographic data (gender and birth date) for all included patients was collected. Age was calculated as the difference between the Index Date and the date of birth.

The risk of metabolic adverse events associated with the two cohorts was assessed by comparing the presence or absence of metabolic disturbances (i.e., diabetes and dyslipidemia) in the 12 months prior to the Index Date and in the 12 months following the Index Date. The timeframe of 12 months before and after the Index Date was selected to guarantee identification of adverse effects that could potentially have been caused by AAs use.

The presence/absence of T2DM was defined as the presence/absence of the relevant ICD9 codes 249.xx or 250.xx, that is, excluding 250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91 and 250.93, which are relevant to type 1 diabetes, and/or the presence/absence of prescriptions of antidiabetic drug, that is, anatomical therapeutic chemical (ATC) codes A10xx. Therefore, by convention, a patient with at least one prescription of A10xx drugs or a diabetes diagnosis in the year after the Index Date and no prescriptions of A10xx drugs or diabetes diagnosis in the year before the Index Date was considered as a subject with diabetes potentially due to antipsychotic use. Similarly, in order to assess AAs-treatment-emergent adverse effects in terms of dyslipidemia, the presence/absence of dyslipidemia diagnosis was defined as the presence/absence of 272.xx ICD9 code and the presence/absence of dyslipidemic drug prescription as C10xx ATC codes.

Furthermore, whenever available, requests for diabetology, dietology and internal medicine specialty visits by GPs were analyzed.

Statistical analysis included use of general statistical methods, such as frequencies and percentages for qualitative variables, mean value, standard deviation, median, minimum and maximum for quantitative variables. Two-tailed Pearson chi-square test was applied. To exclude potential bias due to a different age distribution, a direct method of standardization was used; calculated age-specific rates by cohort were applied to the age structure of the standard population, in this case defined as the overall study population. This approach eliminates differences in observed rates due to differences in age between the two cohorts. All the analyses were performed using SAS® software version 9.4.

3. Results

There were 658 eligible patients with at least one prescription of asenapine during the study period and 10,076 with at least one prescription of olanzapine. However, only 180 patients in the asenapine cohort and 3418 in the olanzapine cohort met the inclusion criteria, that is, did receive more than one prescription of the same medication during the 6 months after the Index date, did not receive any prescription of the comparator during the 6 months after the Index date, and were without previous prescriptions of the same antipsychotic medication in the 6 months prior to the Index date. The flow of patients into cohort 1 (asenapine-treated patients) and cohort 2 (olanzapine-treated patients) is described in Figure 1.

Table 1 presents demographic characteristics of the two cohorts. There were a slightly higher percentage of females in the asenapine than in the olanzapine cohort (54.4 vs 50.3%, respectively) and a younger population (mean age: 46 vs 50 years, respectively).

As reported in Table 2, 21 (11.7%) asenapine-prescribed patients and 166 (4.9%) olanzapine-prescribed patients had either a diabetes diagnosis and/or antidiabetic drug prescription already before the index date, while 4 (2.2%) asenapine-treated and 120 (3.5%) olanzapine-treated patients had a newly recorded post-treatment diagnosis of diabetes and/or antidiabetic drug prescription. The difference was statistically significant (p value: 0.0002). The statistical difference (p value: < 0.0001) was also confirmed after age-adjustment. Out of 3598 patients, there were 471 asenapine-treated (13.1%) and 173 (4.8%) olanzapine-treated patients with either a diabetes diagnosis and/or an antidiabetic drug prescription already before the Index date, while 71 (1.9%) and 126 (3.5%) of asenapine and olanzapine-treated patients, respectively, had a newly recorded post-treatment diagnosis of diabetes and/or antidiabetic drug prescription.

As reported in Table 3, there were more patients with a recorded diagnosis of dyslipidemia and/or dyslipidemic drugs already before the Index date in the asenapine- (30 patients; 16.7%) than in the olanzapine-cohort (285 patients, 8.3%), whereas more patients had a newly recorded dyslipidemia and/or dyslipidemic drug treatment following olanzapine (n = 232; 6.8%) than asenapine (n = 5; 2.8%). The difference was statistically significant (p value: 0.0001). Again, the statistical difference (p value: < 0.0001) was also observed after age-adjustment. Out of 3598 patients, there were 678 asenapine-treated (18.9%) and 299 (8.3%) olanzapine-treated patients with either a dyslipidemia diagnosis and/or an anti-dyslipidemic drug prescription already before the Index date, whereas 109 (3.0%) and 243

(6.8%) of asenapine- and olanzapine-treated patients, respectively, had a newly recorded post-treatment diagnosis of dyslipidemia and/or anti-dyslipidemic drug prescription (Table 3).

The majority of patients had no record of diabetology, dietology and internal medicine specialty visit requests, therefore no reliable analysis could be performed (data not shown).

4. Discussion

The results of this retrospective analysis from real-world data of the prescription pattern of asenapine and olanzapine in Italy and Spain substantiate the results from the recent post-hoc analysis conducted by Kemp *et al.* [10] on comparative clinical trials. Findings suggest a better safety profile of asenapine showing a lower risk of developing T2DM and dyslipidemia associated with asenapine than with olanzapine. Indeed, the risk of developing T2DM was statistically higher (p value: 0.0002) in the olanzapine-treated patients (n = 120; 3.5%) than in the asenapine-treated patients (n = 4; 2.2%). Likewise, the risk of developing dyslipidemia was statistically higher (p value: 0.0001) in the olanzapine-treated patients (n = 232; 6.8%) as compared to the asenapine-treated patients (n = 5; 2.8%).

A considerably higher percentage of patients treated with asenapine when compared with olanzapine had T2DM and dyslipidemia before Index date (11.7 vs 4.9%; p value: 0.0002 and 16.7 vs 8.3%; p value: 0.0001, respectively). This suggests that the presence of T2DM and/or dyslipidemia may also influence which antipsychotic drugs were prescribed over time. Clinicians might have been favoring asenapine over olanzapine for patients with pre-existing metabolic conditions, given the known risk of olanzapine to develop T2DM. The fact that a lower risk of developing metabolic conditions is observed in the asenapine patients, even though it might have been prescribed in a more prone population, further strengthens the safety profile of asenapine.

Results were confirmed also after adjustment for age, that is, excluding potential bias due to the different age distribution in the two cohorts.

This study has some limitations. The use of data derived directly during the consultation by GPs may only partly represent patients' clinical history. However, LPD database reliability has been recognized by the pharmaceutical industry and Medicine Agencies [11,12] The assumptions made in selecting the population and in defining the methodology of identifying adverse effects possibly caused by medication therapy constitute an additional potential limitation. However, when using real-world data, assumptions are essential to define and assess the outcomes of interest. Stringent additional selection criteria and analyses, along with adjustment for confounders, were applied to reasonably warrant consistency of cohort characteristics.

Development of metabolic comorbidities in patients with severe mental illness under AAs treatment could be also due to a range of factors, and not just medications; the confounding effect of the mental illness and its associated genetics and different lifestyle should be taken into consideration [13]. The higher prevalence of metabolic disturbances (e.g., 10 − 15% for diabetes) in people with mental illness has a number of clinical implications for care [14]. A number of National and International bodies have recommended screening for diabetes in people with severe mental illness [15-17]. It is recommended that symptoms of diabetes and

blood glucose concentration should be assessed at baseline, 3 – 4 months after initiation of, or changes in, antipsychotic medication, and annually thereafter. Many mental health services achieved positive results with weight management programs in patients with severe mental illness, and this supports the hypothesis that weight loss, and possibly a decrease in metabolic comorbidities in mental illnesses, can be achieved using a simple behavioral intervention in motivated psychiatric patients [14].

The identification of the potential risk of adverse effects arising from AAs facilitates informed prescribing decisions by the clinician and should minimize the burden of adverse effects.

In conclusion, clinicians can beneficially modify patient risk through medication choice, regular monitoring of weight, body mass index, waist circumference, fasting plasma glucose level and lipid profiles, and with active interventions for identified risk, including ongoing encouragement of healthy lifestyle choices.

Article highlights.

- Antipsychotic drugs are the main treatment for a large number of psychiatric illnesses, but it has been reported that atypical antipsychotics lead to metabolic adverse effects.

- The object of this article is to assess the risk of metabolic adverse effects associated with asenapine in comparison with those associated with olanzapine.

- The study is a retrospective analysis based on data extracted from Italian and Spanish Cegedim Strategic Data Longitudinal Patient Data databases.

- The results indicate that asenapine is associated with a lower risk of metabolic adverse events than olanzapine.

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