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Psychopharmacology
BULLETIN

Atypical Antipsychotic Drugs and Diabetes Mellitus in the US Food and Drug Administration Adverse Event Database: A Systematic Bayesian Signal Detection Analysis

Ross A. Baker; Andrei Pikalov; Quynh-Van Tran; Tatyana Kremenets; Ramin B. Arani; P. Murali Doraiswamy

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Abstract and Introduction

Abstract

Background: Prior literature suggests that the risk of diabetes-related adverse events (DRAEs) differs between atypical antipsychotics. The present study evaluated the potential association between atypical antipsychotics or haloperidol and diabetes using data from the FDA AERS database.

Methods: Analysis of AERS data was conducted for clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole or haloperidol with 24 DRAEs from the Medical Dictionary for Regulatory Activities using a Multi-item Gamma Poisson Shrinker (MGPS) data-mining algorithm. Using MGPS, adjusted reporting ratios (Empiric Bayes Geometric Mean or EBGM) and 90% confidence intervals (CIs; EB05–EB95) were calculated to estimate the degree of drug–event association relative to all drugs and events. Logistic regression odds ratios and 90% CIs (LR05–LR95) were calculated for diabetes mellitus events.

Results: All six atypicals had an EB05 \geq 2 for at least one DRAE. The most common event was diabetes mellitus (2,784 cases). Adjusted reporting ratios (CIs) for diabetes mellitus were: olanzapine 9.6 (9.2–10.0; 1306 cases); risperidone 3.8 (3.5–4.1; 447 cases); quetiapine 3.5 (3.2–3.9; 283 cases); clozapine 3.1 (2.9–3.3; 464 cases); ziprasidone 2.4 (2.0–2.9; 74 cases); aripiprazole 2.4 (1.9–2.9; 71 cases); haloperidol 2.0 (1.7–2.3; 139 cases). Logistic regression odds ratios agreed with adjusted reporting ratios.

Conclusions: In the AERS database, lower associations with DRAEs were seen for haloperidol, aripiprazole and ziprasidone, and higher associations were seen for olanzapine, risperidone, clozapine and quetiapine. Our findings support differential risk of diabetes across atypical antipsychotics, reinforcing the need for metabolic monitoring of patients taking antipsychotics.

Introduction

The risk of diabetes is markedly higher (two- to three-fold) in patients with schizophrenia compared with the general population,^[1] and evidence suggests a similar increased incidence of diabetes in patients with bipolar disorder and schizoaffective disorder.^[2,3] The main potential metabolic concerns in addition to the risk of developing type II diabetes are the risk for cardiovascular disease (CVD) and shorter life-expectancy. Mortality among patients with schizophrenia is higher than among the general population, and CVD accounts for a significant proportion of this excess mortality.^[4-6] Furthermore, metabolic syndrome (a constellation of obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and hypertension) is also highly prevalent in psychiatric patients^[7,8] and may further increase CVD risk. Early, effective monitoring of metabolic side effects is essential to minimize their long-term impact. To date, awareness and monitoring of these effects has been less than optimal;^[9] thus, a need exists to establish clearly the rate of such side effects and their association with various treatment paradigms.

Atypical antipsychotics are used to treat schizophrenia and bipolar disorder, and are under investigation for the treatment of many other mood and anxiety disorders. They have largely supplanted older typical agents in many settings because of some advantages over older antipsychotics, such as a reduced propensity for extrapyramidal symptoms.^[10] However, in recent years, suggestions of an increased occurrence of diabetes and other metabolic disturbances with some atypical antipsychotics agents, such as clozapine and olanzapine, have raised significant concerns.^[11-16] A number of prior studies have documented abnormal glucose metabolism (impaired glucose tolerance, diabetes and ketoacidosis) during treatment with clozapine, olanzapine, risperidone and quetiapine.^[11,17-22] Although prospective, controlled comparisons of multiple agents are limited, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study showed that olanzapine was associated with greater increases in weight gain and measures of glucose and lipids.^[23] Growing evidence indicates a lower likelihood of metabolic and diabetes-related adverse events with the newer atypical agents, ziprasidone and aripiprazole.^[14,22,24] In addition, both agents have shown a potential to reverse abnormal glucose metabolism related to treatment with other antipsychotics.^[24,25,26]

Although the underlying cause of abnormalities in glucose metabolism observed during antipsychotic treatment is unclear, one possible mechanism may be increased insulin resistance as a result of antipsychotic-induced weight gain.^[27] Indeed, the relationship between excessive weight gain and increased risk of diabetes in the general population is well established,^[28] and the atypical antipsychotics associated with the greatest risk of diabetes (clozapine and olanzapine) have been associated with the highest risk of weight gain.^[12] Moreover, direct effects of atypical antipsychotics on insulin secretion, as well as other mechanisms, have not been discounted.^[29,30]

Given the contribution of diabetes to CVD, and the observed excess mortality in patients with psychiatric disorders, there is great interest in further clarification of the differential effects of atypical antipsychotic agents on diabetes-related adverse events (DRAEs), ranging from new-onset hyperglycemia to life-threatening ketoacidosis. Therefore, the objective of this present study was to evaluate the potential association between the atypical antipsychotics or haloperidol and diabetes using data from the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS). The AERS database is a post-marketing surveillance safety database for all approved drugs and therapeutic biological products that aims to monitor and improve drug safety.

Methods

Study Design

Data relating to DRAEs were extracted from the FDA AERS database up to 31 December 2006. The FDA AERS database, which replaced the earlier FDA Spontaneous Reporting System, contains more than 2.5 million spontaneously reported adverse events (AEs) submitted by patients, healthcare professionals and pharmaceutical manufacturers. In this extensive database, longitudinal data are available whereby one report of an event can be linked to follow-up reports. Submitted AE reports (using a MedWatch form) undergo clinical review by trained safety evaluators in the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research who assess each event according to defined principles.^[31] Events are subsequently entered into the AERS database using the Medical Dictionary for Regulatory Activities (MedDRA) coding system, which encompasses approximately 10,000 terms to define AEs within the database. MedDRA search terms for 24 DRAEs related to metabolic effects of atypical agents, as used in the current analysis, are listed in [Table 1](#).

Study Drugs

Seven widely used antipsychotics in the USA were analyzed for drug-event associations. These were the atypical antipsychotics, clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole. Haloperidol was also included in the analysis as a representative of the older, typical antipsychotic group. A separate analysis of the entire AERS database was also carried out to assess drug-event associations between diabetes mellitus and therapeutic agents using the Anatomical Therapeutic Chemical (ATC) Classification System. Drug-event associations by pharmacological subgroup (ATC Level 4, e.g., indole derivatives) and generic drug name (ATC Level 5, e.g., ziprasidone) were analyzed.

Statistical Analysis

Systematic disproportionality analysis (also referred to as data-mining analysis) is commonly used to extract information from large drug-safety databases.^[32] A commonly used measure of disproportionality of a targeted drug-DRAE combination is the Reporting Ratios (RRs) defined by $RR = \text{Observed Rates/Expected Rates}$, where Observed Rate = Number of reports of targeted DRAE with targeted drug/Number of all reports for targeted drug, and Expected Rate = Number of reports of targeted DRAE in AERS/Number of all reports in AERS. The further the RR is from 1, the stronger the indication of a degree of association.

It was observed that when the reports for a particular drug-event combination are few, the estimate of RR becomes unstable. However, more robust methods such as the Multi-item Gamma Poisson Shrinker (MGPS) data-mining algorithm have been developed to ascertain a stable estimate of RR for a particular drug-event combination in large safety databases. The MGPS method adjusts or shrinks the estimate of RR towards 1, which is referred to as 'adjusted' RR. Although this adjustment biases the estimate of RR, it provides a more precise estimate by reducing the volatility of the estimates when there are a low number of reported drug events. Generally, this approach is referred to bias-variance trade-off (see Hastie et al).^[33] Therefore, using the adjusted RR helps to focus on the drug-event combinations that have a stable adjusting ratio >1. The resulting adjusted RRs are denoted by the Empiric Bayes Geometric Mean (EBGM) and corresponding 90% confidence intervals (CI EB05-EB95). The EB05 is interpreted as a value such that there is about a 5% probability that the true value of RR (i.e., Observed/Expected) lies below it. Similarly, EB95 is a value such that there is about a 5% probability that the true value of RR (i.e., Observed/Expected) lies above it.

Typically, the identification of a potential signal is based on the EB05 values and corresponding pre-specified threshold value of 2 for identifying a potential signal, as described in previous studies.^[34,35]

In this study, stratified MGPS analysis of association between antipsychotic drugs' generic name and MedDRA search terms for 24 DRAEs was carried out to control for background differences in relative reporting rate by age, gender and FDA year. Additionally, in order to understand when drug-event combination first appeared as a potential signal, we performed the analysis of cumulative subsets of the data by year of report submission from January 1968 to December 2006.

MGPS analysis was performed utilizing WebVDME™, version 6.0 (Phase Forward, Lincoln Technologies).

In addition to MGPS analysis, logistic regression (LR) analysis was used to explore the association between antipsychotic drugs and the most commonly reported AE, diabetes mellitus. Logistic regression controls for other drugs showing association with diabetes mellitus.^[36] Multiple logistic regression is the standard statistical method for modeling the probability of occurrence of an event as a function of many covariates. Covariates considered in the LR model were: age group, gender, year of report, presence/absence of antipsychotic drug, and presence/absence of 100 other drugs showing association with diabetes mellitus and at least 10 reports in the database. The results are reported as logistic regression odd-ratios (LROR) and the corresponding 90% confidence interval (CI LR05-LR95). The identification of a potential signal is similar to EBGM with a threshold for LR05 of 2, which is chosen to indicate a potential signal.

Results

Overall Reports of Diabetes-related Adverse Events (DRAEs)

There were a total of 8,032 cases of the 24 MedDRA-defined DRAEs for individuals receiving atypical antipsychotics or haloperidol. Among the study drugs, olanzapine and clozapine demonstrated the highest frequencies of DRAEs (3,620 and 1,299 cases, respectively), followed by risperidone (1,163 cases), quetiapine (869 cases), haloperidol (546 cases), aripiprazole (295 cases) and ziprasidone (240 cases).

Diabetes mellitus (2,784 cases) was the most frequently reported DRAE, followed by hyperglycemia (1,347 cases), increased blood glucose (1,104 cases), diabetic ketoacidosis (782 cases), and non-insulin-dependent diabetes mellitus (707 cases). Insulin-dependent diabetes mellitus was reported in 234 cases, diabetic coma in 269 cases and glycosuria in 90 cases. [Table 2A](#) shows the number of DRAEs by each of the antipsychotics for the six most clinically relevant adverse events. The incidence of these six events per drug is similar to the incidence across all 24 DRAEs; olanzapine and clozapine demonstrated the highest frequencies, followed by risperidone, quetiapine, haloperidol, aripiprazole and ziprasidone. [Table 2B](#) shows the prescription volume for each antipsychotic from the time of launch to the end of 2006. It also shows the overall number of AEs reported for each drug in the AERS database.

Adjusted RRs for DRAEs

In total, 14 DRAEs had elevated EB05 values (≥ 2), indicating a 95% likelihood of DRAEs occurring at least two times more frequently than expected, including: diabetes mellitus (including insulin dependent or non-insulin dependent); diabetic coma (including hyperglycemic or hyperosmolar coma); diabetic ketoacidosis; gestational diabetes; glucose tolerance impaired; glucose urine present; glycosuria; hyperglycemia (including hyperosmolar nonketotic syndrome) and insulin resistance (Table 2A , Table 2B , Table 2C and supplementary Table 3). All seven study drugs demonstrated an EB05 score ≥ 2 for at least one DRAE. Overall, olanzapine was associated with the most DRAEs, with 13/24 DRAEs having elevated EB05 values. Furthermore, EB05 values were highest for drug-event combinations with olanzapine and five DRAEs had EB05 values ≥ 9 (non-insulin dependent diabetes mellitus; diabetic coma; diabetic ketoacidosis; glycosuria; and hyperglycemic hyperosmolar nonketotic syndrome).

In Figure 1a, adjusted RRs (EBGM values and 90% CIs) are plotted against logistic regression ORs for diabetes mellitus, which is the most frequently reported DRAE. Logistic regression odds ratios (and 90% CIs) for diabetes mellitus were: olanzapine 16.0 (15.3-16.8); clozapine 4.0 (3.7-4.3); risperidone 2.9 (2.6-3.2); quetiapine 2.9 (2.4-3.3); ziprasidone 1.7 (1.2-2.2); aripiprazole 1.3 (0.9-1.7) and haloperidol 1.3 (1.0-1.5). Based on both analytic methods, olanzapine separates with the highest risk; quetiapine, risperidone, and clozapine all demonstrate moderate risk; whereas ziprasidone, haloperidol, and aripiprazole demonstrate the least risk by falling at or below the threshold of 2 for both EB05 and LR05. The cumulative number of diabetes mellitus reports (Figure 1b) indicate that EB05 values of two or above for diabetes mellitus were evident from 1998 for clozapine and 1999 for olanzapine (the second year of its introduction in the AERS database).

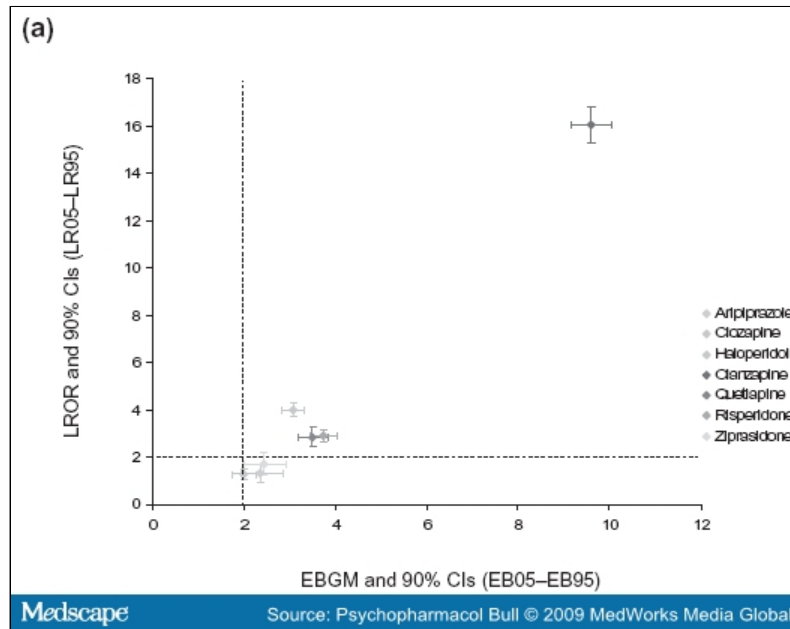


Figure 1A.

Adjusted Reporting Ratio (EBGM Score) and 90% Confidence Intervals (EB05-EB95) Versus Logistic Regression Odd-ratios (LROR) and 90% Confidence Intervals (LR05-LR95) for Diabetes Mellitus

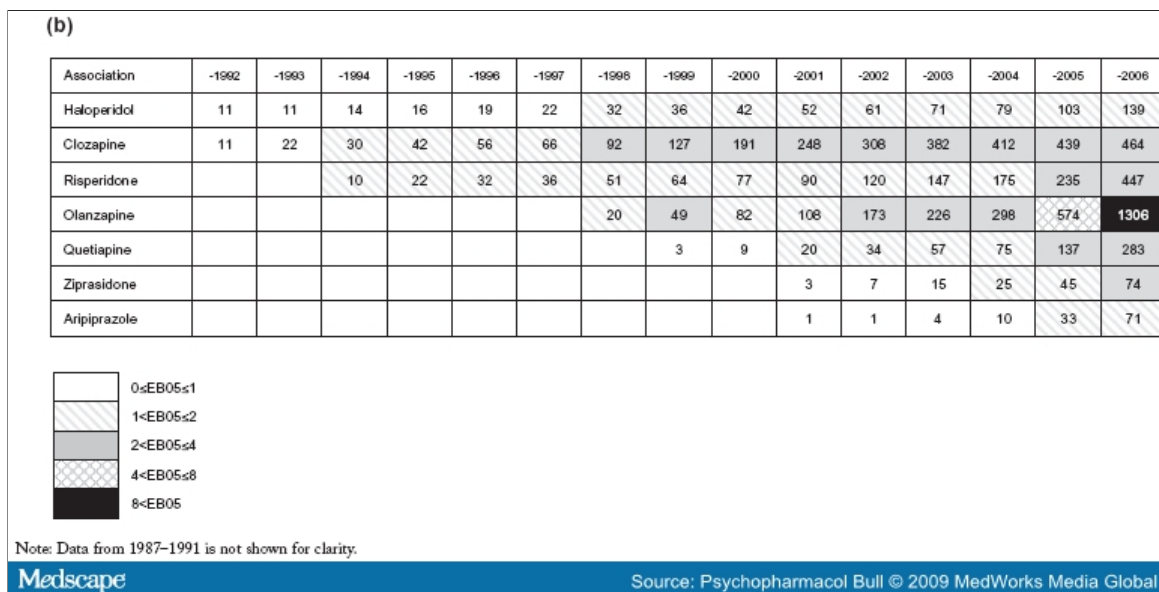


Figure 1B.

Cumulative Number of Drug–event Reports for Diabetes mellitus for Atypical Antipsychotic Drugs and Haloperidol

As observed with diabetes mellitus, olanzapine showed the highest EBGM value for hyperglycemia (supplementary Table 3). Whereas hyperglycemia was the second most reported DRAE, only olanzapine had an EB05 value >2, suggesting a potential signal. Haloperidol showed the lowest EBGM value. Blood glucose increase was the third most common DRAE; however, none of the atypical antipsychotics or haloperidol showed elevated EBGM values with EB05 >2, suggesting no association between agents and this DRAE (data not shown).

Although the cumulative frequencies for diabetic ketoacidosis and non-insulin-dependent diabetes mellitus were generally lower than for other DRAEs, EBGM EB05 values for these DRAEs exceeded the threshold of a potential signal (>2) for several agents (Table 2C). Haloperidol, risperidone, quetiapine, clozapine and olanzapine all exceeded the threshold for diabetic ketoacidosis; ziprasidone and aripiprazole did not. All agents had elevated EBGM values for non-insulin-dependent diabetes mellitus.

The cumulative number of reports of diabetic ketoacidosis (Figure 2) indicate that olanzapine demonstrated EB05 values >2 from the first years of inclusion within the database. By 2006, associations for olanzapine and diabetic ketoacidosis approached EB05 values of ≥8 (Figure 2). Neither aripiprazole nor ziprasidone showed elevated reports of diabetic ketoacidosis.



Figure 2.

Cumulative Number of Drug–event Reports for Diabetic Ketoacidosis for Atypical Antipsychotic Drugs and Haloperidol

Drug–diabetes Associations by Age Group

Children and Adolescents (Less Than or Equal to 17 Years). A total of 258 cases of the 24 DRAEs were identified for individuals, less than 17 years of age, receiving atypical antipsychotics or haloperidol. Among the study drugs, olanzapine and risperidone demonstrated the highest frequencies of DRAEs (82 and 56 cases, respectively).

Of the 24 DRAEs identified, hyperglycemia (61 cases) was the most frequently reported DRAE in this age group, followed by diabetes mellitus (58 cases) and increased blood glucose (37 cases). The number of diabetes events and events with EB05 values (≥2) are shown in Figure 3.

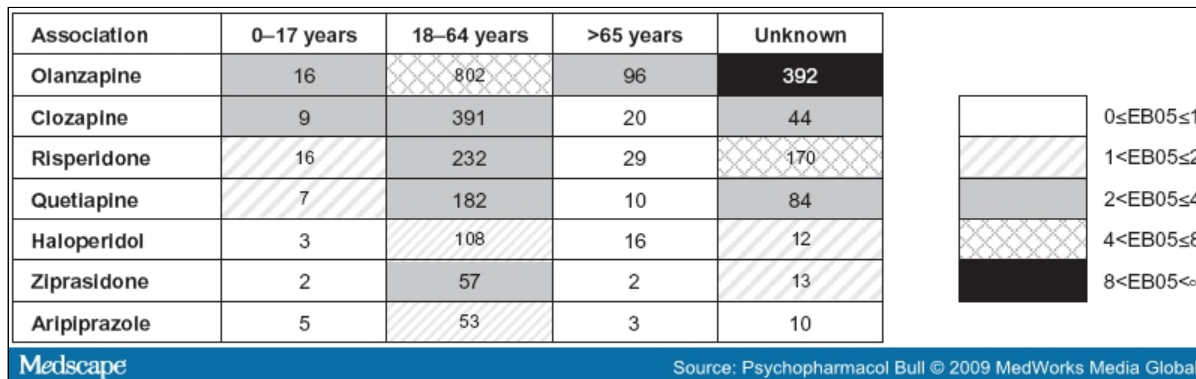


Figure 3.

Association of Diabetes Mellitus With Age for Atypical Antipsychotic Drugs and Haloperidol

In this age group, three DRAEs had elevated EB05 values (≥ 2), indicating a 95% likelihood of DRAEs occurring at least two times more frequently than expected, including: diabetes mellitus (olanzapine and clozapine); non-insulin-dependent diabetes mellitus (olanzapine and quetiapine); and diabetic coma (olanzapine).

Adults (18-64 Years). A total of 5,764 cases of the 24 DRAEs were identified for individuals, aged 18-64 years, receiving atypical antipsychotics or haloperidol. Results for this group were similar to the total population; olanzapine and clozapine demonstrated the highest frequencies of DRAEs (2,500 and 1,115 cases, respectively) and all seven study drugs demonstrated an EB05 score ≥ 2 for at least one DRAE.

Of the DRAEs, diabetes (1,825 cases) and hyperglycemia (955 cases) were the most frequently reported DRAEs in this age group. Olanzapine, quetiapine, risperidone, clozapine and ziprasidone all demonstrated elevated EBGM values for diabetes mellitus (Figure 3), whereas only olanzapine demonstrated $2 \leq \text{EB05} < 4$ for hyperglycemia in this age group (Figure 4).

Association	0-17 years	18-64 years	>65 years	Unknown
Olanzapine	17	376	50	110
Clozapine	7	257	12	30
Risperidone	13	124	28	29
Quetiapine	10	72	14	11
Haloperidol	10	88	16	16
Ziprasidone	0	23	0	5
Aripiprazole	4	15	2	8

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Figure 4.

Association of Hyperglycemia With Age for Atypical Antipsychotic Drugs and Haloperidol

Elderly (Over 65 Years). A total of 529 cases of the 24 DRAEs were identified for individuals, over 65 years of age, receiving atypical antipsychotics or haloperidol. Among the study drugs, olanzapine and risperidone demonstrated the highest frequencies of DRAEs (243 and 99 cases, respectively).

Of the 24 DRAEs identified, diabetes (176 cases) was the most frequently reported DRAE in this age group, followed by hyperglycemia (122 cases) and increased blood glucose (116 cases). The number of events and events with EB05 values (≥ 2) for diabetes are shown in Figure 3.

In this age group, three DRAEs had elevated EB05 values (≥ 2), indicating a 95% likelihood of DRAEs occurring at least two times more frequently than expected, including: diabetes mellitus; non-insulin-dependent diabetes mellitus; and diabetic coma (all with olanzapine only).

Diabetes Mellitus Associations in AERS

Among more than 4,000 drugs in the entire AERS database (analyses using generic drug names, ATC Level 5), olanzapine had the second highest frequency of diabetes reports (1,306 cases) and the highest EBGM adjusted RR (9.59) and 90% CIs (9.16-10.03). Clozapine was the fifth highest.

Discussion

Pharmacovigilance studies provided an early signal, and subsequent epidemiological or clinical studies have mostly suggested a higher incidence of DRAEs and/or increased diabetes risk with clozapine and olanzapine, and, to a lesser extent, risperidone and quetiapine. The results from this study suggest that ziprasidone and aripiprazole are associated with the lowest risk of DRAEs among atypicals, although these products were introduced relatively more recently than the other atypical antipsychotics, which may have resulted in less data available for analysis. However, in agreement with the results from this study, clinical evidence to date has shown a lower risk of metabolic AEs with these agents than with older atypicals.^[14,22] Of particular interest is the emerging evidence that both agents can reverse metabolic AEs related to treatment with other antipsychotics.^[25,26,24] Furthermore, cumulative AE reporting showed that diabetes associations for clozapine and olanzapine were evident within 2 years of introduction, whereas the time from introduction to association is longer with the other agents. This might also explain why an earlier pharmacoepidemiological study failed to show a significantly greater risk of diabetes with olanzapine than with haloperidol.^[37] Interestingly, the reports of diabetes increased sharply around 2003-2004, following warnings issued by Japan and the UK and influential case series published by Drs. Szarfman and Doraiswamy;^[19,11] subsequently, the FDA warning language was introduced to the label of antipsychotics and the American Diabetes Association (ADA) published their consensus on metabolic monitoring in psychiatry. This is of relevance because awareness of these important AEs is crucial to encourage physicians to monitor and manage them appropriately. The impact of more recent events, such as changes to the label of olanzapine^[16] and publicity around litigation, are yet to be determined.

This analysis of the extensive FDA AERS database revealed that all seven antipsychotics were associated with at least one DRAE (as demonstrated by EB05 values ≥ 2). However, there were noticeable differences in the number of DRAEs reported for each agent, and the degree of association observed. Overall, olanzapine demonstrated the highest frequencies of DRAEs (13 DRAEs) and five of these associated drug-event combinations were well above the threshold (EB05 values >10) of a potential signal (>2) defined in this study. Clozapine, quetiapine and risperidone were also more frequently associated with DRAEs, whereas drug-event associations with DRAEs were generally low for aripiprazole, haloperidol and ziprasidone. Adjusted reporting ratios and odds ratios for diabetes mellitus support this grouping and suggest three clusters of drug associations: a) olanzapine, b) clozapine, quetiapine and risperidone, and c) aripiprazole, haloperidol and ziprasidone. Although the mechanism of action of antipsychotic-related DRAEs requires further elucidation, antipsychotic-induced weight gain with consequent insulin resistance has been implicated as a potential mechanism. Thus, the high frequency

of DRAEs with clozapine and olanzapine observed in this study may reflect the increased risk of weight gain associated with both agents.^[12] Conversely, lower drug-event associations between aripiprazole or ziprasidone and DRAEs may correlate with their lower weight-gain risk profiles.^[38,39] There may also be other mechanisms at play and, as such, AERS analyses cannot determine causal mechanisms.

Of the 24 DRAEs investigated in this study, diabetes mellitus was the most frequently reported DRAE, with olanzapine, clozapine, quetiapine, risperidone and ziprasidone showing drug-event associations. Comparison of these findings to the entire AERS database shows that olanzapine and clozapine have some of the highest number of reports of diabetes among all 4,000 plus drugs, giving these findings some context. Hyperglycemia was the second most frequently reported DRAE; however, only olanzapine showed a drug-event association.

The present findings are broadly consistent with recent epidemiological^[22] and pharmacovigilance^[19,20,11,21] studies, as well as monitoring guidance^[12] and an earlier analysis of data from the AERS database.^[36] The present study extends this analysis to include more information on the recently introduced atypicals aripiprazole and ziprasidone, and allows for the impact of 2004 updated warning language. For example, in the present analysis, a total of 2,784 cases of diabetes mellitus were reported, versus 955 in the earlier analysis.^[36]

Despite the smaller relative number of DRAEs reported in juvenile patients (<17 years) and older patients (>65 years), drug-event associations were still evident in these populations. Olanzapine showed drug-event associations with three DRAEs in both juvenile and older patients (diabetic coma; diabetes mellitus; and non-insulin-dependent diabetes mellitus). This is an important finding given that there is increasing use of atypical antipsychotics in juvenile patients^[40-44] and evidence suggests that this population is less likely to be monitored for metabolic AEs.^[9] Ultimately, clinicians need to be aware of the risk of diabetes in juveniles receiving atypical antipsychotic agents and take precautions, including using these agents judiciously and routinely monitoring patients for metabolic AEs in line with current guidelines.^[12]

The notable advantage of safety databases such as the AERS is their ability to provide warning signals of drug-event combinations, which may not necessarily become apparent until the post-marketing stage when therapeutic agents become available to a larger population than those participating in clinical studies. Analyses of these databases are strengthened with the use of systematic disproportionality methods (for example, the MGPS algorithm and logistic regression of the odds ratio), which are able to provide adjusted estimates of association between drugs and AEs in the absence of large, long-term, controlled, comparative trials of multiple agents. However, there are limitations in the quality and/or scope of these databases as a result of uncertainties in establishing causality between the suspected drug and the AE, incomplete drug and medical histories, and inconsistencies in the use of diagnostic terms between reporters. Reporting and detection biases can also arise based on differences in dates of drug launch, prescription volume and publicity. However, our analyses of the data by year suggests that diabetes signals were evident with olanzapine in the first 2 years of its launch. Furthermore, prescription volume for olanzapine is lower than that for risperidone (and also quetiapine in recent years). Differences in the rates of total adverse events between individual antipsychotic drugs can dilute or amplify the relative reporting of diabetes signals. For example, clozapine can be used only within the context of a registry -its overall higher rate of all adverse events probably dilutes individual diabetes signals (since the denominator is larger) and result in an underestimate of diabetes reporting ratios. This should be borne in mind when comparing drugs with overall higher rates of events to drugs with lower rates of events. Haloperidol was launched prior to the introduction of modern safety reporting practices and hence is underestimated. Thus, our results must be interpreted in this context. Reporting patterns of metabolic as well as other types of adverse effects of drugs can change over time due to various factors and hence periodic updates of such data may prove useful to inform clinicians.

Conclusion

This database analysis suggests a low association with DRAEs for aripiprazole, haloperidol and ziprasidone, and more frequent associations with DRAEs for olanzapine, clozapine, quetiapine and risperidone. However, as spontaneous reporting of AEs cannot determine causality or definitely determine the relative risk with each agent, the results must be interpreted with caution. Nevertheless, these results are indicative of differential effects of atypical antipsychotics in their propensity to cause DRAEs, are consistent with previously published epidemiological studies and reinforce guidance on the need for metabolic monitoring in patients taking antipsychotic drugs.

Table 1. Study Drugs and Medical Dictionary for Regulatory Activities (MEDDRA) Search Terms for Diabetes-related Adverse Events

	DRUG-EVENT COMBINATIONS	
Study drugs	Aripiprazole	Clozapine
	Haloperidol	Olanzapine
	Quetiapine	Risperidone
	Ziprasidone	
MedDRA terms	Blood glucose abnormal	Gestational diabetes
	Blood glucose fluctuation	Glucose tolerance impaired
	Blood glucose increased	Glucose tolerance test abnormal
	Blood insulin decreased	Glucose urine
	Diabetic coma	Glucose urine present
	Diabetic hyperglycemic coma	Glycosuria
	Diabetic hyperosmolar coma	Hyperglycemia
	Diabetic ketoacidosis	Hyperglycemic hyperosmolar nonketotic syndrome
	Diabetes mellitus	Insulin-requiring type II diabetes mellitus
	Diabetes mellitus, inadequate control	Insulin resistance
	Diabetes mellitus, insulin dependent	Insulin resistance syndrome
	Diabetes mellitus, non-insulin dependent	Insulin-resistant diabetes

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Table 2A. Overall Reports of Diabetes-related Adverse Events (DRAEs)

DRAE	ARIPIPRAZOLE	OLANZAPINE	CLOZAPINE	HALOPERIDOL	QUETIAPINE	RISPERIDONE	ZIPRASIDONE	TOTAL
Diabetes mellitus	71	1306	464	139	283	447	74	2784
Diabetes mellitus, insulin-dependent	8	82	55	14	19	49	7	234
Diabetes mellitus, non-insulin-dependent	33	349	97	32	80	83	33	707
Diabetic coma	6	169	32	17	20	19	6	269
Diabetic ketoacidosis	24	406	100	56	81	98	17	782
Glycosuria	3	41	8	9	12	14	3	90

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Table 2B. Prescription Volume* and Overall Reports of Adverse Events With Each of the Antipsychotics According to IMS Data

DRAE	ARIPIPRAZOLE	OLANZAPINE	CLOZAPINE	HALOPERIDOL	QUETIAPINE	RISPERIDONE	ZIPRASIDONE
Date of launch	2003	1996	1991	1967	1997	1994	2001
Prescriptions from launch to end 2006 (n)	11,495,122	69,434,963	27,242,628	99,204,718	53,132,463	92,928,016	8,565,697
AERS reports to end 2006 (n)	5,662	21,271	30,529	17,221	11,855	24,733	4,470

*Prescription data are adapted from Szarfman et al (45).

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Table 2C. Adjusted Reporting Ratios (RRs; EBGM Scores) and 90% Confidence Intervals (EB05-EB95) for Six Clinically Relevant Diabetes-related Adverse Events Showing a Higher Than Expected Drug-event Association (EB05 Values ≥ 2) (Shaded Boxes Represent EB05 Values ≥ 2). For example, the adjusted RR for olanzapine-diabetes mellitus is 9.69, which suggests that this association is 9.69 times higher than predicted as the background rate for drugs in this database. See text for details

DRUG NAME	ADVERSE EVENT					
	DIABETES MELLITUS	DIABETES MELLITUS INSULIN-DEPENDENT	DIABETES MELLITUS NON-INSULIN-DEPENDENT	DIABETIC COMA	DIABETIC KETOACIDOSIS	GLYCOSURIA
Haloperidol	2.0 (1.7–2.3)	2.6 (1.7–3.8)	3.2 (2.4–4.2)	2.9 (2.0–4.2)	3.9 (3.2–4.9)	1.8 (1.1–2.9)
Aripiprazole	2.4 (1.9–2.9)	1.4 (0.8–2.3)	3.6 (2.7–4.8)	1.9 (1.0–3.2)	2.3 (1.7–3.2)	1.6 (0.7–3.1)
Ziprasidone	2.4 (2.0–2.9)	1.7 (1.0–2.9)	4.2 (3.1–5.6)	2.0 (1.1–3.5)	1.9 (1.3–2.8)	1.8 (0.8–3.5)
Risperidone	3.8 (3.5–4.1)	4.1 (3.2–5.2)	4.3 (3.6–5.1)	2.3 (1.6–3.3)	3.9 (3.3–4.6)	2.7 (1.7–4.0)
Quetiapine	3.5 (3.2–3.9)	2.1 (1.5–3.0)	4.1 (3.4–4.9)	3.1 (2.2–4.4)	4.3 (3.6–5.1)	3.6 (2.2–5.6)
Clozapine	3.1 (2.9–3.3)	4.7 (3.7–5.9)	4.0 (3.4–4.7)	3.1 (2.3–4.1)	3.2 (2.7–3.7)	1.3 (0.8–2.1)
Olanzapine	9.69 (9.2–10.0)	6.4 (5.2–7.9)	14.0 (12.8–15.3)	20.9 (18.4–23.6)	13.8 (12.7–15.0)	13.4 (10.3–17.3)

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Table 3 (Supplementary). Empiric Bayes Geometricmean (EBGM) Scores for Additional Parameters With at Least One Antipsychotic Showing a Drug–event Association (EB05 Values ≥ 2) for Diabetes-related Adverse Events (Shaded Boxes Represent EB05 Values ≥ 2)

PARAMETER	EBGM (EB05-EB95)						
	ARIPIPIRAZOLE	HALOPERIDOL	ZIPRASIDONE	RISPERIDONE	QUETIAPINE	CLOZAPINE	OLANZAPINE
Diabetic hyperglycemic coma	1.3 (0.5–3.0)	-	1.3 (0.5–3.0)	1.3 (0.6–2.8)	1.5 (0.6–3.1)	3.9 (2.1–9.0)	1.9 (0.9–3.5)
Diabetic hyperosmolar coma	2.1 (1.0–4.0)	2.4 (1.3–4.2)	1.1 (0.4–2.6)	3.2 (2.0–4.9)	3.5 (2.1–5.8)	1.3 (0.6–2.4)	11.6 (8.5–15.5)
Gestational diabetes	-	1.3 (0.5–2.7)	-	1.1 (0.5–2.2)	1.4 (0.7–2.5)	1.8 (1.0–3.2)	4.3 (3.0–6.3)
Glucose tolerance impaired	1.5 (0.8–2.9)	1.7 (0.9–3.0)	2.7 (1.5–4.5)	2.4 (1.5–3.6)	1.9 (1.1–3.0)	2.1 (1.4–3.2)	4.8 (3.5–6.5)
Glucose urine present	1.1 (0.5–2.4)	2.6 (1.6–4.0)	1.5 (0.7–3.0)	1.2 (0.7–2.0)	1.8 (1.1–3.0)	2.1 (1.4–3.0)	3.1 (2.2–4.1)
Hyperglycemic hyperosmolar nonketotic syndrome	1.2 (0.4–2.9)	2.0 (0.9–3.9)	1.2 (0.4–2.9)	1.7 (0.8–3.3)	3.4 (1.8–7.6)	1.2 (0.5–2.6)	21.8 (15.7–29.5)
Hyperglycemia	1.7 (1.2–2.2)	0.9 (0.8–1.0)	1.6 (1.2–2.2)	1.1 (1.0–1.24)	2.2 (1.9–2.6)	1.2 (1.1–1.3)	4.0 (3.7–4.3)
Insulin resistance	1.9 (0.9–3.5)	1.2 (0.5–2.6)	1.4 (0.6–2.9)	2.8 (1.8–4.4)	1.4 (0.7–2.6)	1.2 (0.6–2.2)	10.2 (7.3–13.6)

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Abbreviation Notes

AE = adverse event; AERS = Adverse Event Reporting System; ATC = Anatomical Therapeutic Chemical Classification System; CVD = cardiovascular disease; DRAEs = diabetes-related adverse events; EBGM = Empiric Bayes Geometric Mean; FDA = US Food and Drug Administration; MGPS = Multi-item Gamma Poisson Shrinker; MedRA = Medical Dictionary for Regulatory Activities; RR = reporting ratio.

Reprint Address

Ross A. Baker PhD, MBA, Associate Director, Neuroscience, Bristol-Myers Squibb, 777 Scudders Mill Road, Plainsboro, NJ, 08536, USA. Tel: +1 609 897 4191; Fax: +1 609 897 6042; Email: ross.a.baker@bms.com

Baker, PhD, MBA, Bristol-Myers Squibb, Princeton, NJ, USA.

Pikalov, MD, PhD, Tran, PharmD, Otsuka America Pharmaceutical, Inc., Rockville, MD, USA.

Kremenets PhD, Arani, PhD, Bristol-Myers Squibb, Pennington, NJ, USA.

Doraiswamy, MD, Departments of Psychiatry and Medicine, Duke University Medical Center, Durham, NC, USA.

Author Contributions: Study design (all authors), analysis (Ross A Baker, Andrei Pikalov, Quynh-Van Tran, Tatyana Kremenets and Ramin Arani), interpretation of data (all authors), drafting, editing, and approving manuscript (all authors).

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