Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

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To: Lisa L. Mathis MD, Associate Director
Pediatric and Maternal Health Staff (PMHS)
Office of New Drugs (OND), CDER
and
M. Dianne Murphy, MD, Director
Office of Pediatric Therapeutics (OPT), OC

Through: Mark Avigan, MD, CM, Director
Division of Pharmacovigilance (DPV) I

From: Allen Brinker, M.D. Medical Officer Team Leader
Division of Pharmacovigilance (DPV) I
and
Ida-Lina Diak, Pharm.D., Safety Evaluator Team Leader
Division of Pharmacovigilance (DPV) I

Subject: Pediatric Advisory Committee Follow-Up

Drug Name(s): Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone

Application Type/Number: See table below

Applicant/sponsor: Otsuka, Lilly, Astra Zeneca, Ortho McNeil Janssen, Pfizer

OSE RCM #: 2009-1004

DRUG	**NDA OR ANDA #**
Aripiprazole	21436, 21713, 21729, 21866
Olanzapine	20592, 21253, 21086
Quetiapine	20639, 22047, 22172
Risperidone	20272, 20588, 21444, 21346, 76228, 76288, 76440, 76879, 76904, 77328, 77494, 77719, 77769, 77860, 77953, 78040, 78071, 78269, 78516, 78707, 78740, 78828, 78871, 78909, 79088
Ziprasidone	20825, 20919, 21483

CONTENTS

EXECUTIVE SUMMARY

A November 18, 2008 Pediatric Advisory Committee (PAC) recommended that the FDA provide additional follow-up to address concerns of extrapyramidal symptoms, hyperprolactinemia, metabolic effects, and precocious puberty in association with olanzapine and risperidone. The Division of Pharmacovigilance (DPV) was asked by the Office of Pediatric Therapeutics (OPT) to provide a pediatric-focused safety review of reports from the Adverse Event Reporting System (AERS) database to address the concerns of the PAC and to specifically focus on five atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone). With a large volume of reports generated from the AERS database concerning these issues, a disproportionality analysis of reports from the AERS database was performed. The objective of this review was to assess whether further analyses of spontaneous reporting data may generate hypotheses with interest in differential risk between products or age groups. A focused review of the medical literature was also performed.

Note that there are many limitations in using spontaneous reporting data to compare multiple drug products. Of particular concern is the fact that all voluntary, spontaneous reporting systems are subject to incomplete reporting of adverse events; variations in volume of reporting occur, and typically, most adverse event reporting occurs early in marketing of the product. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, spontaneous reports cannot be used to calculate the absolute incidence of an adverse event in the U.S. populations or be used to measure quantifiable differences in known risk among products.

Spontaneous reports of extrapyramidal symptoms (EPS), hyperprolactinemia, and metabolic effects have been reported among the pediatric population in association with the use of aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone; however, often the number of reports are highly variable from drug product to drug product. Precocious puberty was only reported in association with risperidone among the pediatric population.

DPV conclusions / recommendations:

This review identifies a study from the medical literature that reports a direct association between adverse metabolic effects of treatment with atypical antipsychotics and younger age groups. Although observational studies have limitations, this hypothesis should nonetheless be subject to some further evaluation by the Agency. If substantiated by well-designed clinical trial data, this finding would be important information for product labeling.

The disproportionality analyses presented herein show increased reporting for metabolic effects in association with olanzapine and quetiapine, hypothesis-generating findings, which by themselves may not reflect true agent-specific differences in risk. These findings are consistent with differences identified in a published analysis of clinical trials and in approved labeling for olanzapine. The quetiapine finding should be the subject for further review of data similar to that have been used to analyze and label olanzapine.

1 BACKGROUND

1.1 INTRODUCTION

DPV was asked by OPT to provide a pediatric focused safety review concerning extrapyramidal symptoms, hyperprolactinemia, metabolic effects, and precocious puberty in association with aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone in response to concerns raised by the PAC at the November 18, 2008 meeting. This report does not include a hands-on review of reports due to the volume of reports for some of the adverse events of interest. Rather, it is primarily focused on presentation of report counts and hypothesis-generating disproportionality analyses. Importantly, and as noted above, disproportionality analyses are similar to other data-mining exercises conducted by OSE and CDER and thus are ***hypothesis-generating.*** Importantly, based on experience with datamining in OSE, further review of quantifiable measures of datamining "signals" suggesting an apparent difference between two products may not be reflected by true differences in the incidence of adverse events associated with different members of a therapeutic class. Typically, potential safety signals generated through data mining efforts are insufficient in and of themselves for regulatory action prior to further review.

A second issued considered by DPV in assessment of the study issue was current labeling status for the adverse events of interest for the five agents of interest. As noted below in section 1.3, except for precocious puberty which appears in the label for risperidone, the adverse events of interest are generally well described in current approved labeling for these agents. Spontaneous reporting data is most adept at identification of new safety information. The data have limitations in assessment of differential risk between products all associated with some level of risk. This is especially important in the assessment of labeled events, which could have been the subject of notoriety.

In addition to the caveats noted above, only a selected minority of comparative adverse drug events lend themselves to reporting rate analyses. Reporting rates (based on division of the number of case reports for an event by the number of prescriptions) can be used to compare one drug against another in a drug-against-drug analysis. This calculation will incorporate uncertainty in the numerator and, to a lesser extent, uncertainty in the denominator. Uncertainty in the numerator is afforded by differential reporting. At baseline, studies have estimated that the fraction of reports received by FDA often range between 1% to 10%, but the absolute percentage for any individual drug is unknown.[1] Notoriety of a drug-event combination (stimulated reporting), the reporting practices of different clinicians in disparate populations, the clinical severity of the event, different drug sponsors, and secular reporting trends may all affect reporting.[2] A consideration for calculation of reporting rates in this review would be uncertainty in assessment of exposure to the agents of interest. It is unknown if dispensed, retail prescriptions represent a reasonable assessment of exposure given extensive use of these agents in the outpatient clinic setting and long-acting exposure through parenteral, depot formulations.

In consideration for differential risk for the selected events among the popular atypical antipsychotics, drug-against-drug comparisons would be of interest. Such comparisons are most appropriate when there is a drug available to act as a comparator to the drug in question. When comparing two drugs they should be very similar with respect to: 1) the primary indication for

use, 2) initial marketing date (+/- 2-3 years), 3) route of administration (e.g., parenteral, oral, transdermal, inhalational), and 4) setting (inpatient versus ambulatory). Furthermore, drug-against-drug reporting rate comparisons are based on an assumption that reporting practices are similar for similar drug products over the observed reporting period. The 9-year interval between initial marketing for 3 agents in this review introduces the potential for a substantial reporting bias due to secular reporting trends. This would be among several issues that preclude application of a reporting rate analysis for this group of agents.

1.2 REGULATORY HISTORY

Table 1. FDA approved indications and initial FDA approval date

DRUG	FDA APPROVED INDICATIONS	INITIAL FDA APPROVAL DATE ADULT AND PEDIATRIC
Risperidone	-Schizophrenia in adults and adolescents aged 13 to 17 years -Alone, or in combination with lithium or valproate, for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults, and alone in children and adolescents aged 10-17 years -Irritability associated with Autistic Disorder in children and adolescents aged 5 to 16 years	December 29, 1993 (Adult) August 22, 2007 (Pediatric)
Olanzapine	-Acute and maintenance treatment of Schizophrenia in adults -Acute treatment of manic or mixed episodes associated with Bipolar I Disorder (monotherapy and in combination with lithium or valproate) and maintenance treatment of Bipolar I Disorder (monotherapy) in adults -Acute agitation associated with Schizophrenia and Bipolar I Mania in adults	September 30, 1996
Quetiapine	-Schizophrenia in adults -Depressive episodes associated with Bipolar Disorder -Acute manic episodes associated with Bipolar I Disorder as either monotherapy or adjunct therapy to lithium or divalproex. -Maintenance treatment of Bipolar I Disorder as adjunct therapy to lithium or divalproex -Depression -Acute Bipolar Mania -Maintenance treatment in Bipolar Disorder	September 26, 1997
Ziprasidone	-Schizophrenia in adults -Acute manic or mixed episodes associated with Bipolar I Disorder, with or without psychotic features -Acute Agitation in schizophrenic patients	February 5, 2001
Aripiprazole	-Schizophrenia in adults and adolescents aged 13 to 17 years -Manic or mixed episodes associated with Bipolar I Disorder as monotherapy or adjunctive to lithium or valproate in adults and pediatric patients aged 10 to 17 years -Adjunctive treatment of Major Depressive Disorder in adults -Treatment of adults with agitation associated with Schizophrenia or Bipolar I Disorder, manic or mixed episodes	November 15, 2002 (Adult) October 29, 2007 (Pediatric)

1.3 PRODUCT LABELING

Table 2. Currently approved product labeling

	Extrapyramidal symptoms	**Hyperprolactinemia**	**Metabolic effects**	**Precocious puberty**
Aripiprazole[3]	*Adverse Reactions*- Extrapyramidal disorder and extrapyramidal symptoms, and dystonia (class effect)	*Adverse Reactions*- Blood prolactin increased	*Warnings & Precautions*- Hyperglycemia & Diabetes mellitus *Adverse Reactions*- Hyperglycemia, Diabetes mellitus, diabetic ketoacidosis, and weight gain	Not currently labeled
Olanzapine[4]	*Adverse Reactions*- Extrapyramidal disorder and extrapyramidal symptoms, and dystonia (class effect)	*Warnings & Precautions*- Hyperprolactinemia *Adverse Reactions*- Elevated prolactin	*Warnings & Precautions*- Hyperglycemia (*"**The association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics."***) Weight Gain, Hyperlipidemia *Adverse Reactions*- Diabetic coma, diabetic ketoacidosis, weight gain *Patient Counseling Information*- Hyperglycemia, Weight Gain, and Hyperlipidemia	Not currently labeled
Quetiapine[5]	*Adverse Reactions*- Extrapyramidal disorder and extrapyramidal symptoms, and dystonia (class effect)	*Warnings & Precautions*- Hyperprolactinemia *Adverse Reactions*- Galactorrhea	*Warnings & Precautions*- Hyperglycemia & Diabetes mellitus, Hyperlipidemia, Weight gain *Adverse Reactions*- Hyperglycemia, hyperlipidemia, and weight gain *Patient Counseling Information*- Hyperglycemia & Diabetes mellitus, hyperlipidemia, and weight gain	Not currently labeled
Risperidone[6]	*Adverse Reactions*- Extrapyramidal disorder and extrapyramidal symptoms, and dystonia (class effect) *Use in specific populations-pediatrics*- Tardive dyskinesia	*Warnings & Precautions*- Hyperprolactinemia *Adverse Reactions*- Hyperprolactinemia *Use in specific populations-pediatrics*- Hyperprolactinemia	*Warnings & Precautions*- Hyperglycemia & Diabetes mellitus *Adverse Reactions*- hyperglycemia, diabetes mellitus aggravated, diabetic coma, diabetic ketoacidosis, and weight gain *Use in specific populations-pediatrics*- Weight gain	*Adverse Reactions*- precocious puberty
Ziprasidone[7]	*Adverse Reactions*- Extrapyramidal disorder and extrapyramidal symptoms, and dystonia (class effect)	*Precautions*- Hyperprolactinemia *Adverse Reactions*- Galactorrhea	*Warnings* – Hyperglycemia & Diabetes mellitus *Adverse Reactions*- Hyperglycemia, hyper/hypocholesterolemia, weight gain	Not currently labeled

2 METHODS AND MATERIALS

2.1 AERS SEARCH CRITERIA

The FDA Adverse Event Reporting System (AERS) database was searched for each of the five drugs in association with reports of extrapyramidal symptoms, hyperprolactinemia, metabolic effects, and precocious puberty using the following search strategies. Reports containing at least one of the MedDRA terms listed below were included in the overall report crude count for each category of adverse events.

2.1.1 Extrapyramidal symptoms (EPS)

- **Search dates**- Marketing through August 2009

- **Drug names**- aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone and all associated trade and verbatim names

- **MedDRA search terms**- Broad SMQ of Extrapyramidal syndrome, which includes the following Preferred Terms (PT)- abasia, akathisia, akinesia, athetosis, ballismus, blepharospasm, bradykinesia, buccoglossal syndrome, chorea, choreoathetosis, cogwheel rigidity, dopamine dysregulation syndrome, drooling, dyskinesia, dyskinesia neonatal, dyskinesia oesophageal, dysphonia, dystonia, emprosthotonus, extrapyramidal disorder, facial spasm, freezing phenomenon, gait disturbance, grimacing, hyperkinesia, hyperkinesia neonatal, hypertonia, hypertonia neonatal, hypokinesia, hypokinesia neonatal, laryngospasm, masked facies, meige's syndrome, micrographia, mobility decreased, motor dysfunction, movement disorder, muscle contractions involuntary, muscle rigidity, muscle spasms, muscle spasticity, muscle tightness, muscle twitching, musculoskeletal stiffness, oculogyric crisis, oesophageal spasm, on and off phenomenon, opisthotonus, oromandibular dystonia, parkinson's disease, parkinsonian crisis, parkinsonian gait, parkinsonian rest tremor, parkinsonism, bradyphrenia, pleurothotonus, postural reflex impairment, posture abnormal, posturing, protrusion tongue, psychomotor hyperactivity, rabbit syndrome, respiratory dyskinesia, restlessness, risus sardonicus, spasmodic dysphonia, tardive dyskinesia, tic, tongue spasm, torticollis, torticollis psychogenic, tremor, tremor neonatal, trismus, uvular spasm, and walking disability

- **Ages searched**- 0-17 years and All ages in two separate searches

- **Search criteria**- Domestic reports coded with the serious outcomes of death, disability, hospitalization, life-threatening, and required intervention

2.1.2 Hyperprolactinemia

- **Search dates-** Marketing through August 2009

- **Drug names-** aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone and all associated trade and verbatim names

- **MedDRA search terms-** Amenorrhea, blood prolactin increased, blood prolactin abnormal, breast discharge, delayed puberty, and hyperprolactinaemia

- **Ages searched-** 0-17 years and All ages in two separate searches

- **Search criteria-** Domestic reports coded with the serious outcomes of death, disability, hospitalization, life-threatening, and required intervention

2.1.3 Metabolic effects

- **Search dates-** Marketing through August 2009

- **Drug names-** aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone and all associated trade and verbatim names

- **MedDRA search terms**
  Preferred Terms (PT)- abnormal weight gain, blood cholesterol increased, blood glucose abnormal, blood glucose increased, blood insulin increased, blood pressure diastolic increased, blood pressure increased, blood pressure systolic increased, blood triglycerides increased, body mass index increased, C-reactive protein increased, central obesity, metabolic disorder, metabolic syndrome, dyslipidaemia, hepatic steatosis, high density lipoprotein decreased, hyperlipidaemia, hypertension, hypertriglyceridaemia, low density lipoprotein increased, obesity, overweight, and weight increased
  High Level Terms (HLT)- hyperglycaemic conditions NEC and diabetes mellitus (including subtypes)

- **Ages searched-** 0-17 years and All ages in two separate searches

- **Search criteria-** Domestic reports coded with the serious outcomes of death, disability, hospitalization, life-threatening, and required intervention

2.1.4 Precocious puberty

- **Search dates-** Marketing through August 2009

- **Drug names-** aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone and all associated trade and verbatim names

- **MedDRA search terms-** Early menarche, epiphyses premature fusion, incomplete precocious puberty, precocious puberty, pseudoprecocious puberty, and true precocious puberty

- **Ages searched-** 0-17 years and All ages in two separate searches

- **Search criteria-** Domestic reports coded with the serious outcomes of death, disability, hospitalization, life-threatening, and required intervention

2.2 DISPROPORTIONALITY ANALYSES

In an effort to address the consult request, this review includes disproportionality analyses and thus includes a comparison of the proportions the adverse events of interest appear for the selected agents within the context of all serious reports for each of the listed drugs. This type of analysis is analogous to a comparison of reporting rates that use drug utilization as a denominator.

Reporting rates are typically based on case counts divided by dispensed prescriptions. Such comparisons require 1) very similar drug products (e.g., time on market, route of administration, spectrum of indication(s)) and 2) a belief that reporting practices are similar for similar drug products over the observed reporting period. Furthermore, standard reporting rate comparisons require an accurate estimate of drug exposure or utilization within the population. Since these conditions are difficult to satisfy, this consult will describe an analysis that is based on a comparison of the proportions for the event of interest (in this case as a composite endpoint) to all domestic serious adverse event reports for each of the drugs of concern irrespective of indication or setting of use. Such comparisons have been utilized in previous OSE consults.[8]

Given the limitations of such analyses, only a considerably large difference in the proportions between drugs and a selected adverse event (as defined) should be considered in order to support a hypothesis that a real difference could exist. No *a priori* threshold can be established for a "large difference" but a difference of 10-fold or higher should undoubtedly result in further review; a difference between 5-10 fold could also represent a valid signal threshold. Differences of < 3-fold could be consistent with normal variation within disparate, heterogeneous data and will not be considered as supporting a hypothesis of differential risk.

For the purposes of this review, proportional reporting rates (PRR) are based on crude (unreviewed) domestic report counts with a categorically serious outcome for any specified event based on the capture scheme outlined in section **2.1** for one agent divided by all domestic report counts with a categorically serious outcome for the agent. For any event based on a discrete *preferred term* or *preferred terms (X), calculation of a PRR for a selected drug (Y) is as follows:*

$$\textit{PRR for event X for drug Y} = \frac{\textit{crude domestic report counts of X for drug Y}}{\textit{total domestic report counts for drug Y}} \quad (\textit{x } 100\%)$$

For the purposes of this review, this calculation is restricted to the subset of domestic reports with a categorically serious outcome. PRRs are calculated cumulatively over time and for all ages and for the subset of pediatric reports, which list a patient age of ≤ 17 years.

3 RESULTS

3.1 AERS DATA

Summary report counts for the events of interest for the five atypical antipsychotics are presented in Table 3. Each event is described in further detail below (sections 3.2-3.5). As shown by these data, without restriction by age, the AERS database contains thousands of domestic reports describing extrapyramidal symptoms and metabolic effects reported in association with these agents. With interest in reports with age ≤ 17 years, the AERS database contains hundreds of reports describing extrapyramidal symptoms and metabolic effects reported in association with these agents. In contrast, domestic reporting for hyperprolactinemia and precocious puberty has been much lower, both for all ages and reports with age ≤ 17 years.

Table 3. Cumulative crude report counts* (domestic) for selected adverse events (as defined) reported in association with five atypical antipsychotics. AERS database, Marketing through August 2009.

	Extrapyramidal Symptoms		Hyperprolactinemia		Metabolic effects		Precocious puberty	
	0-17 yrs	All ages*	0-17yrs	All ages	0-17 yrs	All ages	0-17 yrs	All ages
Aripiprazole	122	467	1	2	28	197	0	0
Olanzapine	67	792	3	16	103	3228	0	0
Quetiapine	95	914	4	27	61	3079	0	0
Risperidone	139	1018	12	70	52	541	1	0
Ziprasidone	49	441	6	12	9	176	0	0

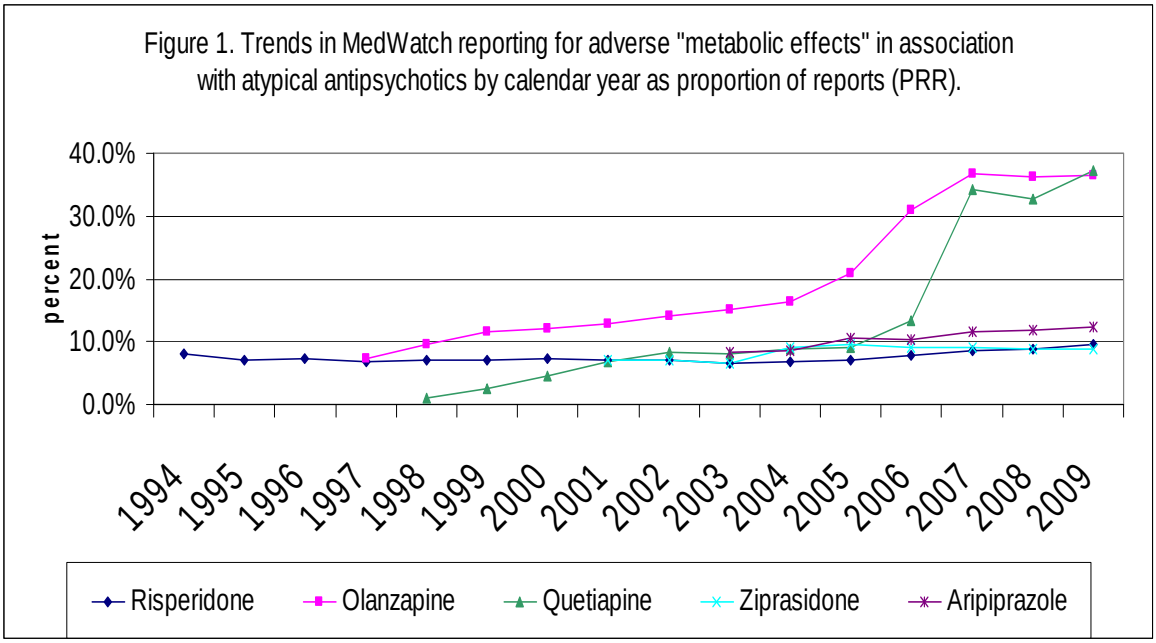
* These are crude counts, and as such, duplicated reports have not been reconciled; therefore, the numbers do not represent unique patient counts

3.2 METABOLIC EFFECTS

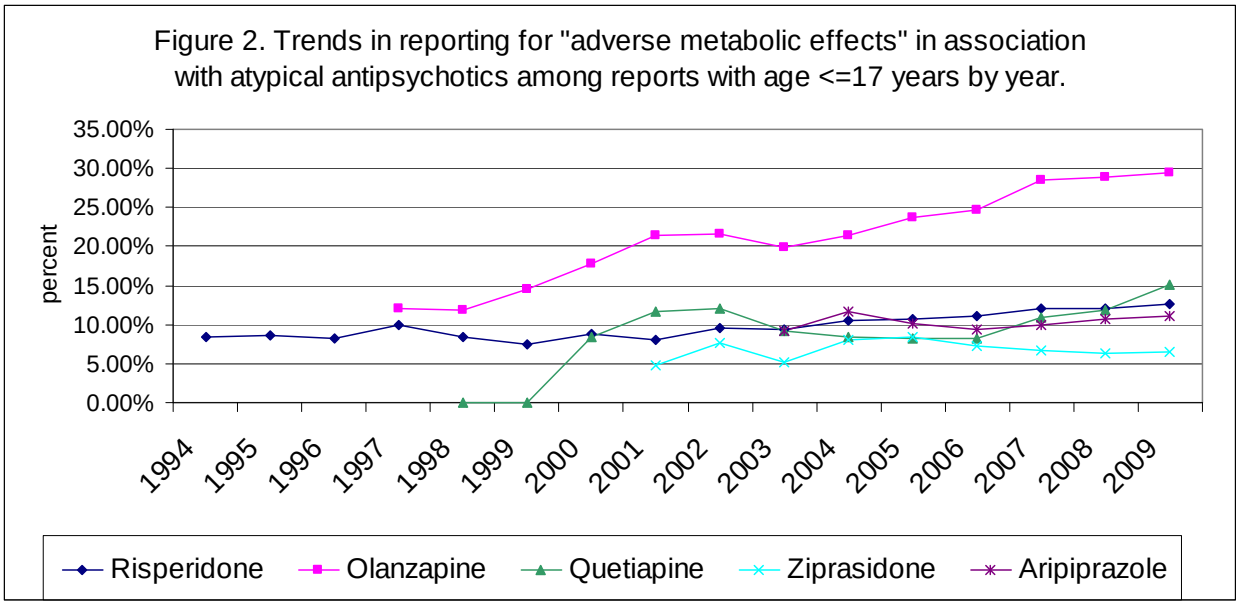
Report counts were obtained from the AERS database as outlined above in section **2.1.3** in August 2009 and imputed into EXCEL for calculations and graphing. Report counts for all ages are included in the Appendix as Table A1. As of August 2009, approximately one-third of all domestic, categorically serious adverse event reports for olanzapine and quetiapine included a serious adverse metabolic effect in comparison to only approximately 10% for the remaining three atypical antipsychotics.

Trends in PRRs as defined for **metabolic effects** and for **all reports** are shown graphically in Figure 1. These data indicate that, as a proportion of all reports, reporting for metabolic effects has been generally higher in association with olanzapine in comparison to the other four agents. This difference is notable during early marketing but then increases in 2006. A similar trend is seen with quetiapine, although the PRRs are generally similar to other agents until 2007, when it

increases rapidly to the level of olanzapine. A number of lawsuits against olanzapine and quetiapine involving metabolic effects can partly explain the spike in reporting during this period due to the many adverse event reports submitted from the law firms involved in the lawsuits.

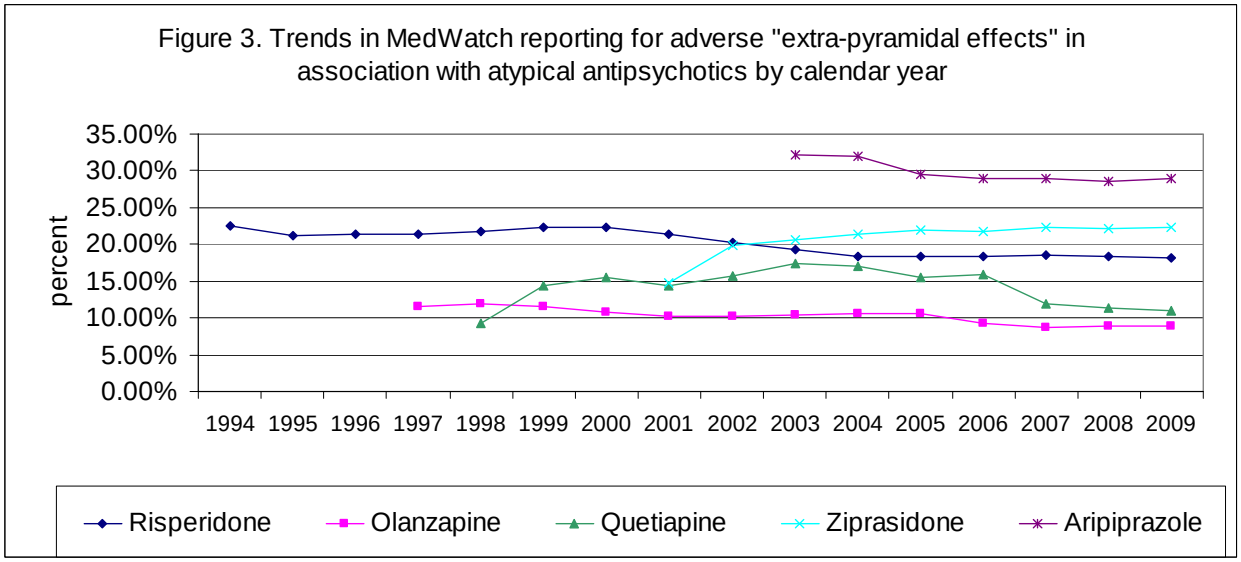


Trends in PRR as defined for **metabolic effects** for the subset of domestic, categorically serious reports with **age listed as ≤ 17 years** are shown graphically in Figure 2; report counts are included in the Appendix as Table A2. As before, with a PRR of ~30% olanzapine stands apart with a higher PRR each year compared with other agents . In contrast to the all reports / all ages analysis, quetiapine does not appear to stand apart from comparators in this age-stratified analysis, although it does have the highest PRR of the remaining four agents.

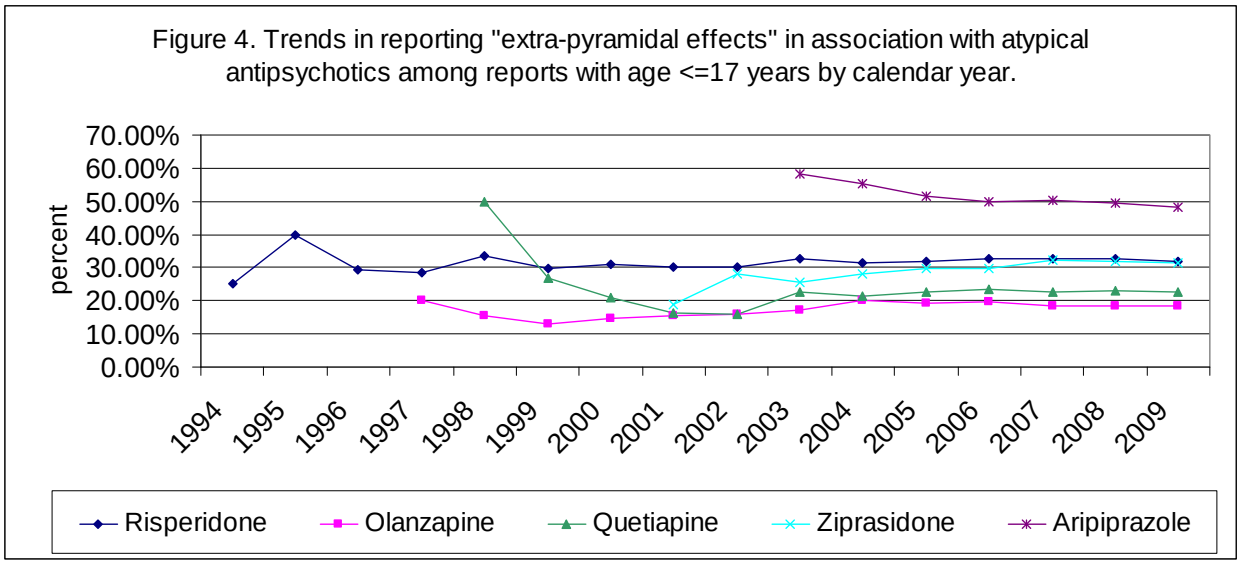


3.3 EXTRAPYRAMIDAL SYMPTOMS

Report counts were obtained from the AERS database as outlined above in section **2.1.1** in August 2009 and imputed into EXCEL for calculations and graphing. Report counts for all ages are included in the Appendix as Table A3. Trends in PRR as defined for **extrapyramidal effects** and for all reports are shown graphically in Figure 3. In contrast to the preceding analysis for metabolic effects, no one agent appears to stand out from the others with regards to a cumulatively rising PRR, although the PRR difference between the agent with the highest PRR (aripiprazole (~30%)) and the agent with the lowest PRR (olanzapine (~10%)) is notable.



Trends in PRRs as defined for extrapyramidal effects for the subset of domestic, categorically serious reports with age listed as ≤ 17 years are shown graphically in Figure 4; report counts are included in the Appendix as Table A4 . As before, aripiprazole stands apart with a higher PRR each year than comparators (~50% versus ~10%-20% through Aug 2009).



Because of the number and heterogeneity of the terms included in this search for events consistent with extrapyramidal symptoms, the top 10 discrete *preferred terms* to appear for each agent that appear in reports within reports captured using the extrapyramidal symptoms SMQ listed in Table A5 (ages ≥18) and Table A6 (ages ≤17) in the Appendix.

3.4 HYPERPROLACTINEMIA

Report counts were obtained from the AERS database as outlined above in section **2.1.2** in August 2009. Domestic, categorically serious report counts were small for hyperprolactinemia in association with the selected atypical antipsychotics in comparison to report counts for adverse metabolic and extrapyramidal effects. Total report counts are shown below, in Table 4. The report counts are not large enough to undertake a cumulative, disproportionality analysis. Instead, only a PRR from available aggregate data for each drug is calculated (Table 4). As shown in Table 4, the calculated PRR for risperidone is higher than that for the other agents but risperidone does not appear to stand out in the comparison. The observed PRR for aripiprazole is based on only two reports and should be considered unstable.

Table 4. Proportional reports rates (PRRs) for hyperprolactinemia (as defined) in association with atypical antipsychotics and supporting data. Crude counts obtained from the AERS database from Marketing through August 2009					
Drug	**Risperidone**	**Olanzapine**	**Quetiapine**	**Ziprasidone**	**Aripiprazole**
	n	n	n	n	n
Reports of hyperprolactinemia	70	16	27	12	2
All serious reports	5,595	8,863	8,270	1,981	1,614
PRR (%)	1.3	0.2	0.3	0.6	0.1
Report count for age ≤ 17 years	12	3	4	6	1

Table 4 also includes absolute report counts for the subset of reports with age listed as ≤ 17 years. These small counts preclude any further analyses except for case review.

3.5 PRECOCIOUS PUBERTY

Report counts were obtained from the AERS database as outlined above in section **2.1.4** in August 2009 and included in Table 3. As shown in Table 3, the capture scheme recovered only one domestic, categorically serious report (associated with risperidone) from the AERS database.

4 DISCUSSION

With interest in the adverse metabolic effects associated with exposure to one of the five atypical antipsychotics included in this review and without concern for patient age, all five product labels include a text within **Warnings and Precautions** for hyperglycemia and diabetes mellitus. Notably, current labeling for olanzapine (Zyprexa) states that this product "appears" [text as it appears in the label for Zyprexa] to confer increased risk over other atypical antipsychotics. Although such labeling is typically based on robust scientific evidence, it is beyond the scope of this review to assess the data reviewed by CDER to advance differential labeling for this event amongst this class of agents. As shown in data presented herein (Fig 1), olanzapine appears to differentiate itself from other atypical antipsychotics in reporting for metabolic effects, although the difference is marked only in later years. This finding has also been reported in previous reviews of clinical studies[9,10], observational studies[11,12], and published datamining analyses of the AERS database.[13,14] Thus, the marked increase in reporting for olanzapine could have been a result of labeling ("stimulated reporting") and not present prior to differential labeling. Notably, the review[9] by Haddad a review on the risk for a 7% increase in body weight as shown in clinical trials. These data, compiled in Table 5, might suggest that the risk is distributed in a continuum across these agents – a finding that is reflected in the approved labeling for olanzapine.

Table 5. Percentage of patients with clinically significant weight gain (>7%) in short-term (3-8 weeks) placebo-controlled trials in schizophrenia. [Adapted from Haddad[9] and based on data from US labels.]		
	Active arm	Placebo arm
	%	%
Olanzapine	29	4
Quetiapine	23	6
Risperidone	18	9
Ziprasidone	10	4
Aripiprazole	8	4

The disproportionality analyses presented herein also show increased reporting for metabolic effects in association with quetiapine (Seroquel) (Fig 1) following a rapid increase in reports with this outcome in calendar year 2007. This rapid rise after the initial lag from the beginning of marketing may reflect stimulated reporting, but the reason for the reporting is unknown. This finding has also been reported in previous, published datamining analyses of the AERS database.[13,14] The review article by Haddad (see figure) suggests that quetiapine follows olanzapine in apparent risk for significant weight gain, which could be broadly interpreted as metabolic effects.

At this time, approved labeling for the five atypical antipsychotics included in this review does not offer information for adverse metabolic effects **for patients aged < 17 yrs** apart from that offered in the **Warnings and Precautions.** As shown previously in the disproportionality analysis conducted without restriction by age, reporting for olanzapine has been higher than the other selected atypical antipsychotics in the disproportionality analysis conducted on the subset of reports listing age ≤ 17 yrs (Fig 2). In contrast, reporting for quetiapine was generally similar to the other atypical antipsychotics. No analysis of spontaneous reporting data with stratification by age was recovered from the published medical literature. Importantly, a recent observational study[15] by Hammerman et al reported that children treated with any antipsychotic (including the five atypical antipsychotics included in this review) were much more likely to experience an adverse metabolic effect than adults and the likelihood was directly correlated with age. The likelihood decreased from an OR of 8.9 (95% CI 7.0 to 11.3) for individuals aged 0-24 years to an OR of 1.3 (95% CI 1.2 to 1.4) for individuals aged 55-64 years. Results from this study are reproduced in Table 6. Although observational studies have limitations, such as biases that result from confounding and generalizability, this provocative hypothesis should nonetheless be subject to some further evaluation by the Agency.

Table 6. Summary data elements adapted from the study[15] by Hammerman et al on diabetes in association with antipsychotic exposure with stratification by age.					
Age	**0-24**	**25-44**	**45-54**	**55-64**	**>=65**
Antipsychotic Recipients frequency (%)	71 / 7,456 1.0%	896 / 22,096 4.1%	1,449 / 13,944 10.4%	1,641 / 10,274 16.0%	5,141 / 28,984 17.7%
No receipt of antipsychotic frequency (%)	1,687 / 1,565,463 0.1%	8,966 / 891,996 1.0%	23,623 / 416,099 5.7%	38,855 / 305,867 12.7%	88,144 / 469,087 18.8%
OR*	8.9 (7.0-11.3)	4.2 (3.8-4.5)	1.9 (1.8-2.1)	1.3 (1.2-1.4)	0.9 (0.9-1.0)

With interest in the adverse extrapyramidal effects associated with exposure to one of the five atypical antipsychotics included in this review not stratified by age, all five product labels include shared ("class") labeling within the Adverse Reactions section regarding dystonia. None of the five atypical antipsychotics included in the review are currently identified with differential labeling. As seen in Figure 5, the disproportionality analysis conducted for this review resulted in varied reporting for the five selected agents, with reporting from about 10% (olanzapine and quetiapine) to about 30% (aripiprazole [Abilify]). In contrast, a review article[9] published in 2007 based on clinical trials suggests that high dose risperidone (Risperdal) might confer the highest risk for adverse extrapyramidal effects. Of note, the lower PRRs observed for both olanzapine and quetiapine in this analysis could be a result of stimulated reporting of adverse metabolic effects for these agents, which in part may be due to notoriety (including lawsuits) surrounding adverse metabolic effects associated with both olanzapine and quetiapine. In this regard, increased reporting for one drug increases the size of the denominator for that drug and thus "dilutes" observed PRRs for other outcomes. A disproportionality analysis for adverse extrapyramidal effects associated with exposure to one of the five atypical antipsychotics included in this review stratified by reports of age ≤ 17 yrs closely resembles the results for the unstratified analysis.

There is substantial diversity in approved labeling for hyperprolactinemia among the five atypical antipsychotics included in this review. Hyperprolactinemia appears under **Warnings and Precautions** for olanzapine, quetiapine, and risperidone. Of the five agents included in this review, this event – and only this event - is singled out in approved labeling as a unique risk for **pediatric patients with the risperidone label**. Hyperprolactinemia appears within the Adverse Reactions section of labeling for aripiprazole and ziprasidone (Geodon). Due to small report counts, only a terminal (all data) PRR was calculated for this event (Table 5). These data indicate that absolute reporting of hyperprolactinemia has been highest for risperidone (70 reports), followed by quetiapine (27 reports), and then olanzapine (16 reports). These 3 agents are also the three oldest agents among the five included in this review. In a comparison of the calculated PRRs, risperidone also has the highest PRR (1.3%) in contrast to PRRs of 0.3% for quetiapine and 0.2% for olanzapine. The apparent risk for prolactinemia in association with

risperidone was also highlighted in the review of trials by Haddad et al.[9] Report counts for the subset of reports with age ≤ 17 are not large enough to offer robust PRRs.

Only one report of precocious puberty (for risperidone) as defined was identified in this review. This could be a function of a restriction to categorically serious reports or restriction to domestic reports. This adverse event appears only in the risperidone label under **Adverse Reactions**.

5 CONCLUSIONS

A hypothesis-generating datamining exercise was conducted for four adverse events of interest with five selected atypical antipsychotics with specific interest in the subset of the population ≤ 17 years of age. Except for the event of hyperprolactinemia, which appears as a risk within the pediatric subpopulation, risk for the remaining three adverse events that specifically addresses the pediatric population does not appear in approved labeling in the four other agents. With interest in adverse metabolic effects, the disproportionality analysis presented herein is consistent with an interpretation that the frequency of adverse metabolic effects could be higher with treatment with olanzapine in comparison to other atypical antipsychotics. This is the position offered in approved labeling. The disproportionality analysis also suggested that the frequency of adverse metabolic effects may be higher with treatment with olanzapine and quetiapine in comparison to other atypical antipsychotics although a lag between initiation of marketing of quetiapine and the rise of PRR in 2007 cannot be accounted for. These findings by themselves are hypothesis-generating may not reflect agent specific differences in risk. The findings are consistent with differences identified in an analysis of clinical trials of some atypical antipsychotic drugs. This possibility was also reported in the published literature[13,14] and should be the subject for further review of data similar to that used to differentiate olanzapine for metabolic effects.

With interest in adverse metabolic effects of atypical antipsychotics in the pediatric population, a published report based on administrative claims data suggest that the risk for adverse metabolic effects is substantially higher in children than in adults.[15] This provocative hypothesis is also worthy for further study with robust, clinical data.

Disproportionality analyses for extrapyramidal effects showed wide dispersion of PRRs: no single agent appears to stand out either for all reports or for the subset of reports with age ≤17 years.

Absolute report counts for the adverse events of hyperprolactinemia and precocious puberty were much smaller than report counts obtained for metabolic effects and extrapyramidal symptoms, especially for reports with age ≤ 17 years. Hyperprolactinemia is a labeled event for all five products included in this review, but precocious puberty is labeled only for risperidone. To this last point, the only report of precocious puberty recovered in this review was in association with risperidone. The search criteria used in this review could have limited recovery of additional reports, in association with both risperidone and the remaining atypical antipsychotics. A further hands-on analysis of all reports would be necessary in order to identify and describe potential cases of precocious puberty reported in association with these five agents.

6 RECOMMENDATIONS

This review identifies a study from the medical literature that reports a direct association between adverse metabolic effects of treatment with atypical antipsychotics and younger age groups. Although observational studies have limitations, this hypothesis should nonetheless be subject to some further evaluation by the Agency. If substantiated by well-designed clinical trial data, this finding would be important information for product labeling.

The disproportionality analyses presented herein show increased reporting for metabolic effects in association with olanzapine and quetiapine, hypothesis-generating findings, which by themselves may not reflect true agent-specific differences in risk. These findings are consistent with differences identified in a published analysis of clinical trials and in approved labeling for olanzapine . The quetiapine finding should be the subject for further review of data similar to that have been used to analyze and label olanzapine.

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8 APPENDIX

Table A1. PRR supporting data: cumulative domestic crude report counts for "metabolic effects" (as defined) and total / all reports coded with serious outcomes by year for selected atypical antipsychotics.

Crude data are from the AERS database from Marketing through August 2009.

	Risperidone		Olanzapine		Quetiapine		Ziprasidone		Aripiprazole	
Year	Met effects	Total serious	Met effects	Total serious	Met effects	Total serious	Met effects	Total serious	Met effects	Total serious
1994	35	432								
1995	60	859								
1996	85	1185								
1997	93	1349	40	546						
1998	120	1693	110	1147	1	98				
1999	139	1999	188	1642	5	202				
2000	166	2311	270	2229	14	314				
2001	189	2675	376	2924	36	534	16	224		
2002	216	3104	484	3451	74	896	33	464		
2003	237	3574	600	3998	109	1344	50	754	22	264
2004	277	4077	764	4638	150	1715	93	1019	46	533
2005	310	4360	1142	5479	200	2221	125	1305	84	801
2006	379	4791	2153	6935	496	3746	138	1526	98	942
2007	435	5019	2943	8021	1970	5761	152	1693	132	1152
2008	468	5338	3053	8422	2231	6801	163	1851	160	1347
2009	541	5595	3228	8863	3079	8270	176	1981	197	1614

Table A2. PRR supporting data: cumulative domestic crude report counts for "metabolic effects" (as defined) and total / all reports coded with serious outcomes by year for selected atypical antipsychotics for the subset of reports with a reported age ≤ 17 years.

Crude data are from the AERS database from Marketing through August 2009.

	Risperidone		Olanzapine		Quetiapine		Ziprasidone		Aripiprazole	
Year	Met effects	Total serious	Met effects	Total serious	Met effects	Total serious	Met effects	Total serious	Met effects	Total serious
1994	1	12								
1995	3	35								
1996	5	61								
1997	7	70	3	25						
1998	8	96	6	51	0	6				
1999	9	121	10	69	0	15				
2000	14	158	17	96	2	24				
2001	15	185	29	135	5	43	1	21		
2002	21	220	35	162	9	75	3	39		
2003	23	245	39	196	11	120	3	59	5	55
2004	29	276	48	225	12	141	6	75	12	103
2005	32	300	62	262	14	172	8	94	15	149
2006	38	342	70	283	23	279	8	111	16	172
2007	44	365	90	315	36	332	8	118	20	201
2008	47	393	95	330	44	369	8	125	23	216
2009	53	419	101	343	63	417	9	137	28	253

Table A3. PRR supporting data: cumulative domestic crude report counts for "extrapyramidal effects" (as defined) and total / all reports coded with serious outcomes by year for selected atypical antipsychotics.

Crude data are from the AERS database from Marketing through August 2009.

	Risperidone		Olanzapine		Quetiapine		Ziprasidone		Aripiprazole	
Year	ExtraP reports	Total serious	ExtraP reports	Total serious	ExtraP reports	Total serious	ExtraP reports	Total serious	ExtraP reports	Total serious
1994	97	432								
1995	182	859								
1996	254	1185								
1997	289	1349	63	546						
1998	367	1693	137	1147	9	98				
1999	446	1999	190	1642	29	202				
2000	514	2311	239	2229	49	314				
2001	570	2675	299	2924	77	534	33	224		
2002	631	3104	354	3451	141	896	92	464		
2003	688	3574	419	3998	235	1344	155	754	85	264
2004	752	4077	495	4638	292	1715	218	1019	170	533
2005	799	4360	576	5479	344	2221	286	1305	237	801
2006	883	4791	647	6935	595	3746	332	1526	272	942
2007	935	5019	702	8021	692	5761	378	1693	334	1152
2008	981	5338	749	8422	774	6801	411	1851	386	1347
2009	1018	5595	792	8863	914	8270	441	1981	467	1614

Table A4. PRR supporting data: cumulative domestic crude report counts for "extrapyramidal effects" (as defined) and total / all reports coded with serious outcomes by year for selected atypical antipsychotics for the subset of reports with a reported age ≤ 17 years.

Crude data are from the AERS database from Marketing through August 2009.

	Risperidone		Olanzapine		Quetiapine		Ziprasidone		Aripiprazole	
Year	ExtraP reports	Total serious	ExtraP reports	Total serious	ExtraP reports	Total serious	ExtraP reports	Total serious	ExtraP reports	Total serious
1994	3	12								
1995	14	35								
1996	18	61								
1997	20	70	5	25						
1998	32	96	8	51	3	6				
1999	36	121	9	69	4	15				
2000	49	158	14	96	5	24				
2001	56	185	21	135	7	43	4	21		
2002	66	220	26	162	12	75	11	39		
2003	80	245	34	196	27	120	15	59	32	55
2004	87	276	45	225	30	141	21	75	57	103
2005	96	300	51	262	39	172	28	94	77	149
2006	112	342	56	283	65	279	33	111	86	172
2007	119	365	58	315	75	332	38	118	101	201
2008	129	393	61	330	85	369	40	125	107	216
2009	133	419	63	343	94	417	43	137	122	253

Table A5. Frequency distribution (limited to top 10) of preferred terms listed in reports for adult patients (≥ 18 years) and captured with the Extrapyramidal Symptoms (EPS) SMQ					
	ARIPIPRAZOLE	**OLANZAPINE**	**QUETIAPINE**	**RISPERIDONE**	**ZIPRASIDONE**
1	Tremor	Tremor	Tardive Dyskinesia	Tremor	Tremor
2	Dystonia	Gait Disturbance	Tremor	Neuroleptic Malignant Syndrome	Dystonia
3	Tardive Dyskinesia	Muscle Rigidity	Diabetes Mellitus	Extrapyramidal Disorder	Tardive Dyskinesia
4	Muscle Rigidity	Pyrexia	Gait Disturbance	Muscle Rigidity	Extrapyramidal Disorder
5	Musculoskeletal Stiffness	Neuroleptic Malignant Syn	Dyskinesia	Gait Disturbance	Neuroleptic Malignant Syndrome
6	Dyskinesia	Weight Increased	Confusional State	Pyrexia	Agitation
7	Extrapyramidal Disorder	Confusional State	Extrapyramidal Disorder	Hypertonia	Dyskinesia
8	Gait Disturbance	Extrapyramidal Disorder	Weight Increased	Tardive Dyskinesia	Akathisia
9	Akathisia	Increase Creatine Phosphokinase	Muscle Spasms	Confusional State	Dyspnoea
10	Pyrexia	Tardive Dyskinesia	Dizziness	Increase Creatine Phosphokinase	Gait Disturbance

SMQ- Standardized MedDRA Query- groupings of terms from one or more MedDRA System Organ Classes (SOCs) that relate to a defined medical condition or area of interest

Table A6. Frequency distribution (limited to top 10) of preferred terms listed in reports for patients (≤ 17 years) and captured with the Extrapyramidal Symptoms (EPS) SMQ					
	ARIPIPRAZOLE	**OLANZAPINE**	**QUETIAPINE**	**RISPERIDONE**	**ZIPRASIDONE**
1	Dystonia	Aggression	Tardive Dyskinesia	Dyskinesia	Dystonia
2	Tremor	Tremor	Dyskinesia	Dystonia	Tremor
3	Extrapyramidal Disorder	Abnormal Behaviour	Dystonia	Tardive Dyskinesia	Extrapyramidal Disorder
4	Musculoskeletal Stiffness	Weight Increased	Extrapyramidal Disorder	Tremor	Dyskinesia
5	Dyskinesia	Dystonia	Aggression	Aggression	Agitation
6	Muscle Rigidity	Suicidal Ideation	Tremor	Extrapyramidal Disorder	Convulsion
7	Drooling	Dyskinesia	Abnormal Behaviour	Condition Aggravated	Vomiting
8	Muscle Spasms	Vomiting	Agitation	Drug Interaction	Hallucination
9	Agitation	Agitation	Convulsion	Speech Disorder	Insomnia
10	Lethargy	Extrapyramidal Disorder	Akathisia	Drooling	Neuroleptic Malignant Syndrome

SMQ- Standardized MedDRA Query- groupings of terms from one or more MedDRA System Organ Classes (SOCs) that relate to a defined medical condition or area of interest

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10/14/2009

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MARK I AVIGAN
10/14/2009