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

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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Product Name(s):	Seroquel (quetiapine fumarate), Seroquel XR (quetiapine fumarate, extended release)
Pediatric Labeling Approval Date:	April 30, 2013
Application Type/Number:	NDA #020639, 022047, 022172
Applicant/Sponsor:	AstraZeneca
OSE RCM #:	2015-1960

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act Pediatric Research Equity Act, the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for Seroquel and Seroquel XR (quetiapine fumarate) in pediatric patients. This review was triggered by the pediatric study of quetiapine for the indication of bipolar depression.

Quetiapine fumarate was first approved in 1997. Seroquel is indicated for the treatment of schizophrenia; bipolar I disorder manic episodes; and bipolar disorder, depressive episodes. Seroquel XR is indicated for the treatment of schizophrenia; bipolar I disorder, manic or mixed episodes; bipolar disorder, depressive episodes; and major depressive disorder, adjunctive therapy with antidepressants. The approved pediatric labeling is for schizophrenia in adolescents (13-17 years) and bipolar mania in children and adolescents (10-17 years).

The Food and Drug Administration Adverse Event Reporting System database was searched for all reports of adverse events received from August 1, 2011 through July 31, 2015. The Division of Pharmacovigilance (DPV) focused on the serious pediatric reports with unlabeled events.

DPV included 78 pediatric cases with serious, unlabeled events reported with quetiapine use in the case series. There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and there were no deaths directly associated with quetiapine. There were 16 fatal cases and 62 non-fatal cases from August 1, 2011 through July 31, 2015. More than half (n=9) of the fatal cases did not report a cause of death. The remaining 7 fatal cases that reported a cause of death were all due to multiple drug overdoses, except for 1 case that reported "cerebral death" in a 14-year-old female with a recent history of elevated valproate and alcohol blood levels. Almost half of the 62 non-fatal cases reported overdose, self-injurious behavior, suicidal ideation, or suicidal attempt. According to the Center for Disease Control and Prevention, suicide is the third leading cause of death for youths between the ages of 10 and 24 years. Poisoning is among the top three methods used in suicides of young people. A history of depression or other mental illness is among several risk factors that can put a young person at risk for suicide.

The drug utilization data showed that pediatric patients aged 0-17 years accounted for about 7% of total use during each 12-month period analyzed with approximately 168,000 patients during the 12-month period ending July 2012, increasing to about 184,000 patients during the 12-month period ending July 2015 in the outpatient retail pharmacy setting. A slight increase in the use of quetiapine in older pediatric patients aged 10 – 17 years was observed, whereas the use in younger pediatric patients aged 0-9 years showed minor fluctuations. Psychiatry specialists were the top prescribers of quetiapine, followed by nurse practitioner and family practice. Among pediatric patients aged 10-17 years, Affective Psychoses NEC/NOS was the only diagnosis *mentioned* in association with the use of quetiapine with reliable national estimates of use captured during the cumulative time analyzed.

Overall, there were no clear patterns or trends in drug utilization or in this case series to suggest a new pediatric safety signal associated with quetiapine. Additionally, there have been multiple OSE reviews on safety issues with quetiapine conducted since approval. Based on the data

summarized in this review, DPV recommends no labeling changes at this time. DPV will continue to monitor adverse events associated with the use of quetiapine.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Table 1.1. Formulations, Applications Numbers, and FDA Approval Dates for All Quetiapine Products[1]

Generic name	Formulation	Trade name	NDA	FDA Approval Date	Pediatric Indications	Sponsor
Quetiapine fumarate	Tablet, Oral	Seroquel®	020639	September 26, 1997	Schizophrenia (13-17 years old); Acute treatment of manic episodes associated with bipolar I disorder as monotherapy (10-17 years old)	AstraZeneca Pharms
	Tablet, Extended release, Oral	Seroquel XR®	022047; 022172	May 17, 2007; November 15, 2007		

Study D144AC00001 is an 8-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled study of efficacy and safety of quetiapine fumarate extended release (Seroquel XR) 150-300 mg/day in children and adolescents 10-17 years with bipolar depression. The multicenter trial was conducted in 42 centers in 7 countries, including US (29 centers), Colombia (3 centers), India (3 centers), Mexico (2 centers), Serbia (3 centers), South Africa (1 center), and Taiwan (1 center). A total of 262 subjects with a diagnosis of bipolar I or bipolar II disorder and depressed were enrolled into the study. Diagnosis was based on the DSM IV TR and confirmed by Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL). The two treatment groups had similar major demographic characteristics at baseline. Efficacy was not established in this study. Patients treated with Seroquel XR in this study exhibited metabolic changes (hyperglycemia, diabetes mellitus, serum lipid abnormalities, and weight gain), and increases in blood pressure and heart rate. These findings are similar to those from previous pediatric studies of quetiapine. The most commonly observed adverse reactions were dizziness 7%, diarrhea 5%, fatigue 5% and nausea 5%.[2]

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES [3,4]

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; AND SUICIDAL THOUGHTS AND BEHAVIORS *SEE FULL PRESCRIBING INFORMATION FOR COMPLETE BOXED WARNING.*

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. SEROQUEL is not approved for elderly patients with dementia-related psychosis (5.1)

Suicidal Thoughts and Behaviors

- Increased risk of suicidal thoughts and behavior in children, adolescents and young adults taking antidepressants (5.2)
- Monitor for worsening and emergence of suicidal thoughts and behaviors (5.2)

WARNINGS AND PRECAUTIONS

- *Cerebrovascular Adverse Reactions:* Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) has been seen in elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs (5.3)
- *Neuroleptic Malignant Syndrome (NMS):* Manage with immediate discontinuation and close monitoring (5.4)
- *Metabolic Changes:* Atypical antipsychotics have been associated with metabolic changes. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain (5.5)
  - Hyperglycemia and Diabetes Mellitus: Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes
  - Dyslipidemia: Undesirable alterations have been observed in patients treated with atypical antipsychotics. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically, during treatment
  - Weight Gain: Gain in body weight has been observed; clinical monitoring of weight is recommended
- *Tardive Dyskinesia:* Discontinue if clinically appropriate (5.6)
- *Hypotension:* Use with caution in patients with known cardiovascular or cerebrovascular disease (5.7)
- *Increased Blood Pressure in Children and Adolescents:* Monitor blood pressure at the beginning of, and periodically during treatment in children and adolescents (5.8)
- *Leukopenia, Neutropenia and Agranulocytosis:* Monitor complete blood count frequently during the first few months of treatment in patients with a pre-existing low white cell count or a history of leukopenia/neutropenia and discontinue SEROQUEL at the first sign of a decline in WBC in absence of other causative factors (5.9)
- *Cataracts:* Lens changes have been observed in patients during long-term quetiapine treatment. Lens examination is recommended when starting treatment and at 6-month intervals during chronic treatment (5.10)

- *QT Prolongation:* In clinical trials quetiapine was not associated with a persistent increase in QT intervals. However, the QT effect was not systematically evaluated in a thorough QT study. In post marketing experience, there were cases reported of QT prolongation in patients who overdosed on quetiapine [see Overdosage (10.1)], in patients with concomitant illness, and in patients taking medicines known to cause electrolyte imbalance or increase QT interval.

  The use of quetiapine should be avoided in combination with other drugs that are known to prolong QTc including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class III antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone).

  Quetiapine should also be avoided in circumstances that may increase the risk of occurrence of torsade de pointes and/or sudden death including (1) a history of cardiac arrhythmias such as bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval. Caution should also be exercised when quetiapine is prescribed in patients with increased risk of QT prolongation (e.g., cardiovascular disease, family history of QT prolongation, the elderly, congestive heart failure and heart hypertrophy).

  Caution should also be exercised when quetiapine is prescribed in patients with increased risk of QT prolongation (e.g., cardiovascular disease, family history of QT prolongation, the elderly, congestive heart failure and heart hypertrophy).

- *Hypothyroidism:* Children and Adolescents: Safety and effectiveness of SEROQUEL XR is supported In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of shifts for thyroid function values at any time for SEROQUEL treated patients and placebo-treated patients for elevated TSH was 2.9% (8/280) vs. 0.7% (1/138), respectively and for decreased total thyroxine was 2.8% (8/289) vs. 0% (0/145, respectively). Of the SEROQUEL treated patients with elevated TSH levels, 1 had simultaneous low free T4 level at end of treatment.

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5% and twice placebo):

Adults: somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, weight gain, lethargy, ALT increased, dyspepsia (6.1)

Children and Adolescents: somnolence, dizziness, fatigue, increased appetite, nausea, vomiting, dry mouth, tachycardia, weight increased (6.1)

DRUG INTERACTIONS

- *Concomitant use of strong CYP3A4 inhibitors:* Reduce quetiapine dose to one sixth when coadministered with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir) (2.5, 7.1, 12.3)
- *Concomitant use of strong CYP3A4 inducers:* Increase quetiapine dose up to 5 fold when used in combination with a chronic treatment (more than 7-14 days) of potent CYP3A4 inducers (e.g., phenytoin, rifampin, St. John's wort) (2.6, 7.1, 12.3)
- *Discontinuation of strong CYP3A4 inducers:* Reduce quetiapine dose by 5 fold within 7-14 days of discontinuation of CYP3A4 inducers (2.6, 7.1, 12.3)

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Limited human data. Based on animal data, may cause fetal harm. Quetiapine should be used only if the potential benefit justifies the potential risk **(8.1)**
- *Nursing Mothers:* Discontinue drug or nursing, taking into consideration importance of drug to mother's health (8.3)

PEDIATRIC USE

In general, the adverse reactions observed in children and adolescents during the clinical trials were similar to those in the adult population with few exceptions. Increases in systolic and diastolic blood pressure occurred in children and adolescents and did not occur in adults. Orthostatic hypotension occurred more frequently in adults (4-7%) compared to children and adolescents (< 1%) [see WARNINGS AND PRECAUTIONS (5.7) and ADVERSE REACTIONS (6.1)].

Schizophrenia

The efficacy and safety of SEROQUEL in the treatment of schizophrenia in adolescents aged 13 to 17 years were demonstrated in one 6-week, double-blind, placebo-controlled trial [see INDICATIONS AND USAGE (1.1), DOSAGE AND ADMINISTRATION (2.2), ADVERSE REACTIONS (6.1), and CLINICAL STUDIES (14.1)].

Safety and effectiveness of SEROQUEL in pediatric patients less than 13 years of age with schizophrenia have not been established.

Maintenance

The safety and effectiveness of SEROQUEL in the maintenance treatment of bipolar disorder has not been established in pediatric patients less than 18 years of age. The safety and effectiveness of SEROQUEL in the maintenance treatment of schizophrenia has not been established in any patient population, including pediatric patients.

Bipolar Mania

The efficacy and safety of SEROQUEL in the treatment of mania in children and adolescents ages 10 to 17 years with Bipolar I disorder was demonstrated in a 3-week, double-blind, placebo-controlled, multicenter trial [see INDICATIONS AND USAGE (1.2), DOSAGE AND ADMINISTRATION (2.3), ADVERSE REACTIONS (6.1), and CLINICAL STUDIES (14.2)].

Safety and effectiveness of SEROQUEL in pediatric patients less than 10 years of age with bipolar mania have not been established.

Bipolar Depression

Safety and effectiveness of SEROQUEL in pediatric patients less than 18 years of age with bipolar depression have not been established. A clinical trial with SEROQUEL XR was conducted in children and adolescents (10 to 17 years of age) with bipolar depression, efficacy was not established.
Some differences in the pharmacokinetics of quetiapine were noted between children/adolescents (10 to 17 years of age) and adults. When adjusted for weight, the AUC and Cmax of quetiapine were 41% and 39% lower, respectively, in children and adolescents compared to adults. The pharmacokinetics of the active metabolite, norquetiapine, were similar between children/adolescents and adults after adjusting for weight [see CLINICAL PHARMACOLOGY (12.3)].

---------- **OVERDOSAGE** ----------

- *Human Experience:* In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed experienced no adverse reactions or recovered fully from the reported reactions. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose [see WARNINGS AND PRECAUTIONS (5.11)]. One case, involving an

  marketing experience, there were cases reported of QT prolongation with overdose. There were also very rare reports of overdose of SEROQUEL alone resulting in death or coma.

1.3 PREVIOUS OSE POST-MARKETING SAFETY REVIEWS

There have been six previous post-marketing safety reviews involving quetiapine that specifically addressed safety concerns in pediatric patients. These reviews are detailed below.

- October 4, 2005. A class review of **galactorrhea** with atypical antipsychotic drugs in pediatric patients. The review supported further analysis of hyperprolactinemia and galactorrhea with atypical antipsychotics in order to update risperidone labeling to reflect the increased numbers of reports of hyperprolactinemia and galactorrhea associated with risperidone relative to other atypical antipsychotic drugs.[5]

- October 4, 2005. A class review of **pituitary tumors** with atypical antipsychotic drugs in pediatric patients. The review recommended further investigation, perhaps including reanalysis of the risperidone NDA, in order to update the risperidone label to include increased hyperprolactinemia compared to other atypical antipsychotic agents.[6]

- April 29, 2008. This review focused on **cases of death** in children 16 years old and younger. Quetiapine was associated with 25 death cases. This review concluded that the current safety profile in the labeling would not need revising to include any additional pediatric population specific adverse events.[7]

- May 7, 2009. A review of pediatric postmarketing data for quetiapine in patients aged 0-17 years of age since approval September 26, 1997. The focus of the review was **all pediatric cases of death, metabolic effects (blood triglycerides increased, diabetes mellitus, hyperglycemia, and weight increased), QT prolongation, and Torsade de**

pointes. The safety profile of the pediatric population is very similar compared to that of the adult population, and the adverse events occurred in much the same manner as well. No new safety signals emerged as part of this review.[8]

- October 14, 2009. As follow-up to a November 18, 2008 Pediatric Advisory Committee (PAC), DPV conducted a pediatric-focused safety review of **extrapyramidal symptoms, hyperprolactinemia, metabolic effects, and precocious puberty** of five atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone). 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. The disproportionality analyses presented in the review showed 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 were consistent with differences identified in a published analysis of clinical trials and in approved labeling for olanzapine. The review concluded that the quetiapine findings should be the subject for further review of data similar to the data reviews that have been used to analyze and label olanzapine.[9]

- December 1, 2011. A review of pediatric postmarketing data for quetiapine in children and adolescents 0-16 years of age from December 2, 2009 to July 31, 2011. The focus of the review was pediatric deaths and pediatric reports of serious, unlabeled adverse events with quetiapine fumarate. Overall, no new safety concerns in children and adolescents 0-16 years old treated with quetiapine were identified.[10]

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct these analyses. ***(See Appendix A for full database descriptions).***

2.1.1 *Determining Settings of Care*

The IMS Health IMS National Sales Perspectives™ database was used to determine the various retail and non-retail channels of distribution for quetiapine (Seroquel® and Seroquel XR®) in the United States. Approximately 77% of quetiapine bottles of tablets were sold to outpatient retail pharmacies (i.e. chain stores, independent pharmacies, and food stores), 19% to non-retail settings (i.e. clinics, long term care, non-federal hospitals, etc.), and 4% to mail-order/specialty pharmacies during 2014.[a] As a result of these distribution patterns, only US outpatient retail pharmacy utilization patterns were

[a] IMS Health National Sales Perspective (NSP), Years 2015, Extracted JAN2015

examined. Data from mail-order/specialty pharmacies and non-retail settings were not included in these analyses.

2.1.2 *Data Sources Used*

The IMS Health, Total Patient Tracker™ (TPT) database was used to obtain nationally estimated numbers of patients who received outpatient retail prescriptions for quetiapine in the U.S., stratified by patient age (0-9, 10-17, and 18 years and older), for four 12-month periods ending July 2015. The IMS Health, National Prescription Audit™ (NPA) database was used to obtain nationally estimated numbers of prescriptions dispensed for quetiapine from the U.S outpatient retail settings, stratified by prescriber specialty, from August 2011 through July 2015, cumulative.

Diagnoses associated with quetiapine use as reported by U.S. office-based physician surveys, stratified by patient age (0-9, 10-17, and 18 years and older), were obtained from Encuity Research, LLC., Treatment Answers™ with Pain Panel database for the same cumulative time period. Diagnoses were coded according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were obtained for the estimates.

2.2 RESULTS

2.2.1 *Patient Data for Quetiapine*

Table 2.2.1 shows the nationally estimated number of unique patients who received quetiapine prescriptions from outpatient retail pharmacies in the U.S., stratified by patient age (0-9, 10-17 and 18 years and older), for four 12-month periods ending in July 2015. Approximately 2.2 million total patients received quetiapine prescriptions during the 12-month period ending in July 2012, increasing gradually to approximately 2.8 million total patients during the 12-month period ending in July 2015. For each of the 12-month periods analyzed approximately 93% of the patients who received quetiapine prescriptions were adults aged 18 years and older. Pediatric patients aged 0-17 years accounted for approximately 7% of the total patients during each 12-month period analyzed, increasing from about 168,000 total patients during the 12-month period ending in July 2012 to about 184,000 total patients during the 12-month period ending in July 2015. Among pediatric patients aged 0-17 years, patients aged 10-17 years accounted for the majority of use with approximately 88-90% of the total estimated number of pediatric patients, while patients aged 0-9 years accounted for approximately 12-14% during each 12-month period analyzed.

Table 2.2.1: Nationally estimated number of patients with a prescription for quetiapine (Seroquel and Seroquel XR) from outpatient retail pharmacies in the U.S., stratified by patient age*, August 2011-July 2015

	Aug 2011 - Jul 2012		Aug 2012 - Jul 2013		Aug 2013 - Jul 2014		Aug 2014 - Jul 2015	
	Patients (N)	*Share %*	Patients (N)	*Share %*	Patients (N)	*Share %*	Patients (N)	*Share %*
Grand Total	2,205,421	*100%*	2,295,269	*100%*	2,486,461	*100%*	2,784,320	*100%*
0 - 17 years	168,318	*7.63%*	162,705	*7.09%*	174,213	*7.01%*	183,617	*6.59%*
0 - 9 years	23,084	*13.71%*	20,358	*12.51%*	20,617	*11.83%*	21,294	*11.60%*
10 - 17 years	148,485	*88.22%*	145,297	*89.30%*	156,406	*89.78%*	165,282	*90.01%*
18+ years	2,046,024	*92.77%*	2,140,944	*93.28%*	2,320,850	*93.34%*	2,591,031	*93.06%*

Source: IMS Health Total Patient Tracker (TPT), JUL2010-JUN 2015, Extracted JAN2016

Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-17 years include patients less than 18 years of age (17 years and 11 months). Patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories. For this reason, summing across patient age bands and time periods is not advisable and will result in overestimates of patient counts.

2.2.2 *Prescriber Specialty*

Table 2.2.2 below shows the nationally estimated number of quetiapine prescriptions dispensed from U.S. outpatient retail pharmacies, stratified by prescriber specialty, from August 2011 through July 2015, cumulative. Approximately 49 million prescriptions were dispensed from U.S. outpatient retail pharmacies during the examined time. Psychiatry was the top prescriber specialty accounting for 47% (23 million prescriptions) of the total prescriptions, followed by nurse practitioner with 14% (6.8 million prescriptions) and family practice with 12% (5.8 million prescriptions). Pediatrics accounted for less than 1% (300,000 prescriptions) of the total prescriptions dispensed.

Table 2.2.2: Nationally estimated number of prescriptions for quetiapine (Seroquel and Seroquel XR) from U.S. outpatient retail pharmacies, stratified by prescriber specialty, from August 2011 through July 2015, cumulative

	Total Rx	*Share %*
QUETIAPINE	**49,345,528**	***100%***
PSYCHIATRY	23,026,715	*46.66%*
NURSE PRACTITIONER	6,765,614	*13.71%*
FAMILY PRACTICE	5,758,825	*11.67%*
INTERNAL MEDICINE	4,280,726	*8.68%*
OSTEOPATHIC MEDICINE	3,120,841	*6.32%*
PHYSICIAN ASSISTANT	1,491,521	*3.02%*
NEUROLOGY	1,215,845	*2.46%*
SPECIALTY UNSPECIFIED	907,806	*1.84%*
GENERAL PRACTICE	300,520	*0.61%*
PEDIATRICS	300,175	*0.61%*
ALL OTHERS COMBINED	2,176,940	*4.41%*

Source: IMS Health National Prescription Audit (NPA), AUG2011-JUN2015, Extracted JAN2016

2.2.3 ***Diagnoses Associated with Use***

Table 2.2.3 shows the diagnoses associated with quetiapine use expressed as *drug use mentions*[b], stratified by patient age (0-9, 10-17, & 18+ years), as reported by office-based physician survey practices in the U.S., from August 2011 through July 2015, cumulative. Diagnoses were coded according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were obtained for the estimates. Approximately 90% of the *use mentions* for quetiapine were associated with adult patients aged 18 years and older, [point estimate: 17.6 million; 95% C.I. 16.9 million -18.3 million)], followed by pediatric patients aged 10-17 years accounting for approximately 3% [point estimate: 523,000; 95% C.I. 405,000-640,000] and pediatric patients aged 0-9 years accounting for less than 1% [point estimate: 45,000; 95% C.I. 11,000-80,000]. Of note, the estimates captured in pediatric patients aged 0-9 years were too low to be considered reliable national estimates of use. Among pediatric patients aged 10-17 years, the only diagnosis mentioned in association with the use of quetiapine with a reliable national estimate of use was "Affective Psychoses NEC/NOS" (ICD-9 code 296.9) with 21% of the total *use mentions* [point estimate: 111,000; (95% CI; 57,000 – 165,000)].

b The term *drug uses* refers to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit with a physician.

Table 2.2.3: Diagnoses associated with quetiapine (Seroquel and Seroquel XR) use as reported by an office-based physician surveys database in the U.S., stratified by patient age, from August 2011 through July 2015, cumulative

	August 2011 - July 2015		
	Uses (000)	*Share %*	95% C.I. (000)
Total	**19,529**	***100.0%***	**18,810 - 20,248**
0-9 years old	**45**	***0.2%***	**11 - 80**
3140 ATTENTION DEFICIT DIS	**13**	***27.7%***	**0.5 - 31**
2990 INFANTILE AUTISM	**10**	***21.1%***	**0.5 - 25**
2967 BIPOLAR AFFECTIVE NOS	**7**	***15.9%***	**0.5 - 21**
3110 DEPRESSIVE DISORDER NEC	**6**	***13.2%***	**0.5 - 19**
3138 OTH EMOTIONAL DIS CHILD	**5**	***11.6%***	**0.5 - 17**
2942 DEMENTIA UNSPECIFIED	**5**	***10.6%***	**0.5 - 16**
10-17 years old	**523**	***2.7%***	**405 - 640**
2969 AFFECT PSYCHOSES NEC/NOS	**111**	***21.2%***	**57 - 165**
2967 BIPOLAR AFFECTIVE NOS	**81**	***15.6%***	**35 - 128**
3140 ATTENTION DEFICIT DIS	**52**	***10.0%***	**15 - 90**
3000 ANXIETY STATES	**39**	***7.4%***	**7 - 71**
2990 INFANTILE AUTISM	**36**	***6.9%***	**5 - 67**
7805 SLEEP DISTURBANCES	**28**	***5.3%***	**1 - 55**
3098 OTHER ADJUST REACTION	**23**	***4.5%***	**0.5 - 48**
2999 EARLY CHLD PSYCHOSIS NOS	**20**	***3.8%***	**0.5 - 42**
3138 OTH EMOTIONAL DIS CHILD	**19**	***3.7%***	**0.5 - 42**
2957 SCHIZOAFFECTIVE TYPE	**14**	***2.7%***	**0.5 - 34**
All Others Combined	**99**	***18.9%***	**48 - 150**
18+ years	**17,611**	***90.2%***	**16,929 - 18,294**
UNSPECIFIED	**1,350**	***6.9%***	**1,161 - 1,539**

Source: Encuity Treatment Answers with Pain™, JUL2010-JUN2015, Extracted JAN2016
NEC: Not elsewhere classified, NOS: Not otherwise specified.

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 *FDA Adverse Event Reporting System (FAERS) Search Strategy*

DPV searched the FAERS database with the strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy	
Date of Search	September 2, 2015
Time Period of Search	August 1, 2011* - July 31, 2015
Search Type	Quick Query
Product Name(s)	Product Active Ingredient: Quetiapine; Quetiapine fumarate
Search Parameters	All ages, all outcomes, worldwide

* The cut-off date for the December 2011 DPV pediatric review was July 31, 2011.

3.1.2 *Inclusion Criteria*

DPV included cases that reported:

- Patients between 0 and under 17 years old who received quetiapine and experienced
  - Fatal outcomes, OR
  - Serious, *unlabeled* adverse events

All FAERS reports retrieved were analyzed and reviewed. The reports that met the inclusion criteria above were included in the case series.

3.2 RESULTS

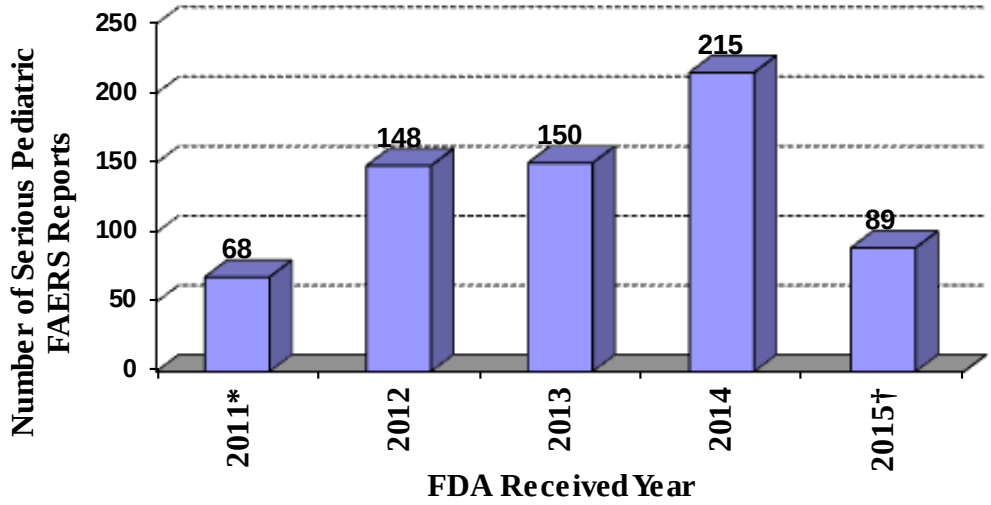
3.2.1 *Total number of FAERS reports by Age*

Table 3.2.1 Total Adult and pediatric FAERS reports* **from August 1, 2011† to July 31, 2015 with Quetiapine fumarate**

	All reports (US)	**Serious‡ (US)**	**Death (US)**
Adults (≥ 17 years)	19,495 (13,325)	12,419 (6,289)	3,103 (2,408)
Pediatrics (0 - <17 years)	838 (403)	670 (236) §	77 (42)

** May include duplicates and transplacental exposures, and have not been assessed for causality*
†Date from last AERS search in DPV pediatric review of quetiapine fumarate dated December 2011
‡For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.
§See Figure 3.2.2

Figure 3.2.1 Serious Pediatric Reports for Quetiapine fumarate, by year of FDA receipt from August 1, 2011 – July 31, 2015 (n=670)



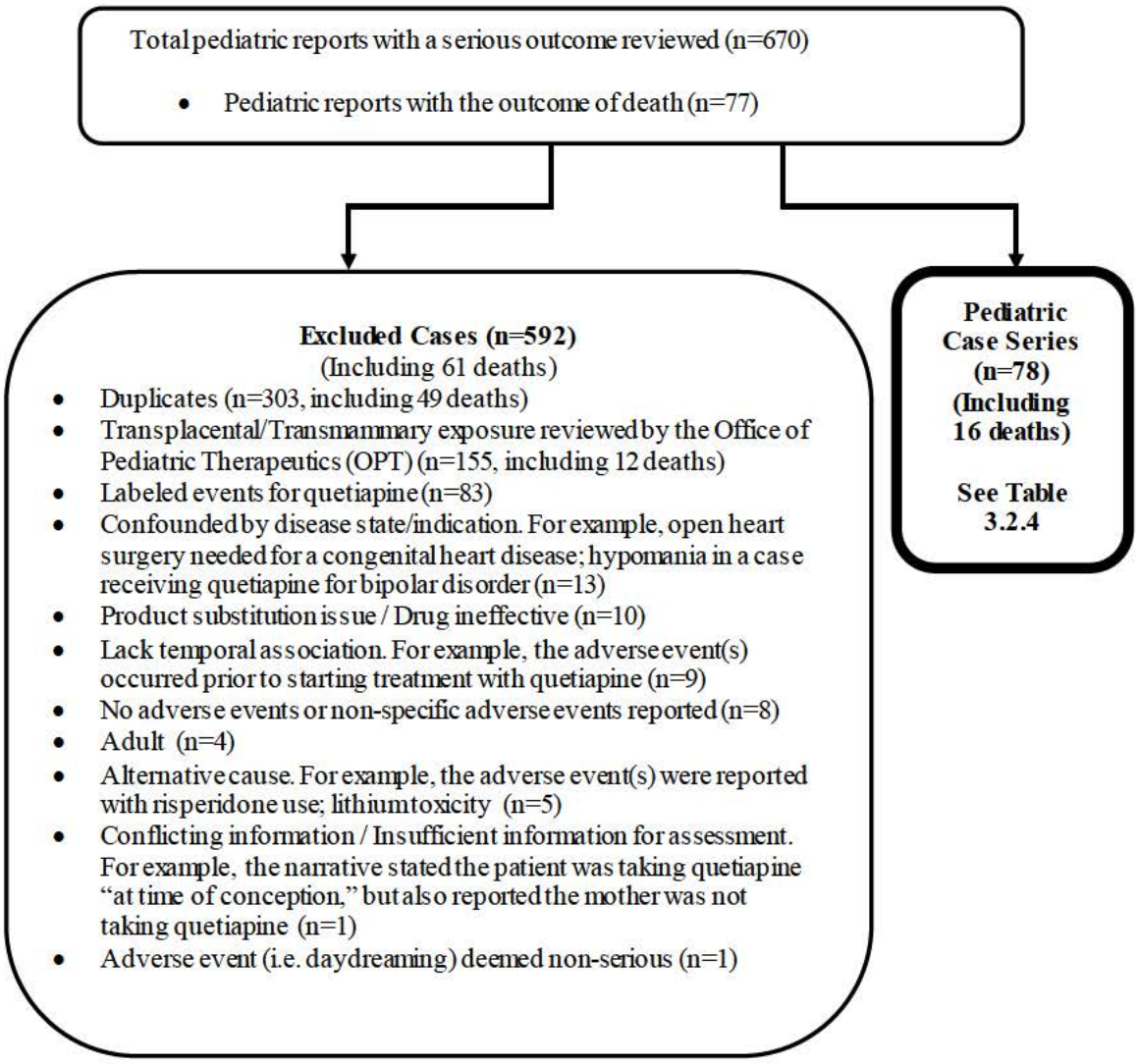
**The 2011 value represents reports received from August 1, 2011 through December 31, 2011.*

†The 2015 value represents reports received from January 1, 2015 through July 31, 2015.

3.2.2 *Selection of Serious Pediatric Cases in FAERS*

We identified 670 pediatric reports with a serious outcome (See Table 3.2.1). See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Sections 3.3 and 3.4.**

Figure 3.2.2 Selection of Serious Pediatric Cases with Quetiapine fumarate



3.2.3 *Characteristics of Pediatric Case Series*

Appendix C lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 3.2.4 Characteristics of Pediatric Case Series with Quetiapine fumarate (N=78)			
Age	1 month - <2 years	2	
	2- < 6 years	3	
	6- <12 years	11	
	12- < 17 years	62	
Sex	Male	42	
	Female	36	
Country	United States	43	
	Foreign	35	
Reported reason for use	Bipolar disorder		14
	Depression		9
	Behavior disorder		4
	Schizophrenia/Schizophrenia, paranoid/Psychosis		3
	Suicide attempt/Suicide		3
	Affective disorder		2
	Attention Deficit/Hyperactivity Disorder (ADHD)		2
	Post-Traumatic Stress Disorder (PTSD)		2
	Accidental exposure		1
	Adjustment disorder with mixed anxiety and depressed mood		1
	Aggression		1
	Agitation, Delirium		1
	Anxiety state		1
	Asperger's Disorder		1
	Autistic Spectrum Disorder (ASD)		1
	Hallucinations, mixed		1
	Impulsive behavior		1
	Insomnia		1
	Mood disorder, Not Otherwise Specified (NOS)		1
	Obsessive Compulsive Disorder (OCD)		1
	Oppositional Defiant Disorder (ODD)		1
	Schizotypal personality disorder		1
	Unknown		25
Serious Outcome*	Death	16	
	Life-threatening	16	
	Hospitalized	29	
	Disability	3	
	Other serious	25	

***** Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may have more than one outcome.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=16)

A total of 16 cases in this case series reported death as an outcome. The fatal cases included children and adolescents 4 to 16 years old, with a median age of 14 years old. The reported total daily dose of quetiapine ingested were 50 mg, 200 mg, 500 mg, 900 mg, and 16,000 mg (n=5). Seven of the 16 fatal cases reported an autopsy was performed, and 8 of the 16 fatal cases reported a proposed cause of death or cause of death determined by autopsy. The majority of the fatal cases reported the cause of death as multi-drug exposure or as unknown. Half of the 16 fatal cases were from literature sources, including 7 cases reported by the American Association of Poison Control Centers' National Poison Data System (AAPCC NPDS). All but 3 fatal cases reported ingestion of multiple drugs concomitantly. The multiple drug overdose cases reported ingesting 3 to 10 drugs or substances, including quetiapine. The 3 fatal cases of apparent monotherapy with quetiapine are summarized below. See Appendix D for full narratives for all fatal cases.

FAERS Case # 8884159, USA, 2012: AAPCC NPDS reported a 15-year-old female presented to the emergency room (ER) "claiming to have ingested 2 quetiapine tablets of unknown strength." Her past medical history (PMH) and her concomitant medications, if any, were not reported. Her initial heart rate (HR) was 150 beats per minute (BPM), but decreased to 115 BPM during her ER stay. She was transferred to an inpatient psychiatry unit for observation, and then she returned to the ER within six hours with fixed and dilated pupils and seizing. No electrocardiogram (ECG) was obtained, and cardiopulmonary resuscitation (CPR) was initiated but was unsuccessful. Blood concentrations, if any obtained, were not reported. The cause of death was not reported and it is unknown whether an autopsy was performed.

FAERS Case # 8959911, USA, 2012: A 15-year-old male received quetiapine 900 mg daily that was started on an unspecified date for bipolar disorder. His PMH or concomitant medications, if any, were not reported. The "expert witnesses did not believe that the patient had NMS (Neuroleptic malignant syndrome)." He was reportedly in sepsis and died on an unspecified date. The cause of the death was not reported and it is unknown whether an autopsy was performed.

FAERS Case # 9913353, USA, 2014: AAPCC NPDS reported a 14-year-old female who "died of unknown reason defined as reason for the exposure cannot be determined or no ingestion of quetiapine as primary toxic substance. The relative contribution of fatality was assessed as probably responsible in the opinion of the CRT the Clinical Case Evidence suggests that the substances caused the death, but some reasonable doubt remained." Her PMH; concomitant medications, if any; quetiapine dose, frequency, therapy dates, and indication; cause of death; and whether an autopsy was performed were not reported.

Reviewer's comment: The cause of death in all three apparent monotherapy quetiapine cases was not reported and, therefore, it is unknown whether the deaths could be attributed to quetiapine. The amount of quetiapine consumed alone in the first case is unlikely to have caused her demise; the highest strength available for quetiapine is a 400 mg tablet and the recommended maximum daily dose is 800 mg. In the second case, the expert apparently ruled out NMS, and the sepsis possibly contributed to his death; however, there is insufficient

clinical information for causality assessment. In the last case, there is doubt whether the patient had consumed quetiapine, and there was missing critical clinical information; thus, a causality assessment was not possible.

One of the remaining 13 fatal cases that involved multiple drug ingestions ranked quetiapine as the number one cause of death, among 9 other drugs consumed (FAERS Case #8292727), but no additional clinical information was provided. Another case reported 80 to 90 tablets of quetiapine were consumed by the patient, but he may have also drank alcohol and used heroin or cocaine on the same night (FAERS Case #8964524). The third case reported clonidine as the cause of death (FAERS Case #8111608). The fourth case reported "cerebral death" as the cause of death in a 14-year-old female with a recent history of elevated valproate and alcohol blood levels (FAERS Case #10874222). All remaining 9 fatal cases either attributed the deaths to the results of a combination of the drugs ingested or did not provide the cause of death.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=62)

A total of 62 non-fatal pediatric cases reporting serious and unlabeled adverse events were included in this case series. These non-fatal cases are summarized below by system organ class. The unlabeled adverse events are underlined.

3.4.1 *Psychiatric Disorders (n=35)*

3.4.1.1 Psychiatric Disorders - Suicidal thoughts and behaviors (n=28)

Twenty-eight of the psychiatric disorders cases reported an overdose, self-injurious behavior, suicidal ideation, or suicidal attempt. The median age was 15 years old, ranging from 7 to 16 years old among an equal number of females and males. The reported reasons for use of quetiapine were depression or depressed mood (n=9), bipolar disorder (n=6), PTSD (n=2), suicide attempt (n=2), unspecified (n=5), and one each of affective disorder, Asperger's disorder, ASD, and schizotypal personality disorder.

Although "suicidal thoughts and behaviors" are included in the boxed warning in the quetiapine labeling specifically for "children, adolescents and young adults taking antidepressants," 13 of the 28 cases were taking quetiapine for an indication other than depression or bipolar disorder, or did not report an indication. Of note, there is a substantially increased risk of suicide and suicidal ideation and behavior with all of the psychiatric disorders for which quetiapine is indicated. Five of these 13 cases reported the events resolved when quetiapine was discontinued; however, all 5 cases reported taking an overdose of quetiapine, ranging from approximately 3 g to 24 g of quetiapine ingested. It was unclear in 2 of these 5 cases whether the patients were receiving quetiapine on a routine basis; the reasons for use reported were "suicide attempt" for one case and unspecified for the other case. The remaining 3patients with overdoses reported were receiving quetiapine for PTSD in 2 cases, and schizotypal personality disorder in the last case. Additionally, these 3 patients who overdosed were taking at least one concomitant medication, including clonazepam, escitalopram, levomepromazine (an antipsychotic used outside of the US), or lorazepam.

Seven of the remaining 8 cases did not report on the outcome of the events or the action taken with quetiapine. The last case was a 7-year-old male with a history of "sensory disorder," tic disorder, and hospitalization due to unspecified medicinal side effects on an unspecified date. His medications included aripiprazole, guanfacine, and haloperidol decanoate (unspecified dose, frequency, therapy dates) for ASD, and quetiapine 25 mg every evening for ASD and ADHD. An unspecified time after starting quetiapine, he developed "tics" described as "his neck would go back and lock up," he had tremors, "his eyes would close and would not open," and "dystonic muscle movements." He was treated with diphenhydramine in the ER. After 1 year and 5 months of starting quetiapine, he became more irritable, aggressive, and impulsive, had increased appetite especially before bedtime, was "oversensitive to stimuli," and "talking louder than usual." He told his teacher that he "just wanted to die." His mother discontinued quetiapine, but the outcome of suicidal ideation and "his eyes would close and would not open," were not reported, and "oversensitive to stimuli," and "talking louder than usual" were ongoing at the time of the report.

Reviewer's comment: The description of the "tics" in the last case could be consistent with oculogyric crisis, a well-known type of dystonia known to occur with antipsychotic treatment. However, the outcome of the event was not reported; thus, causality assessment was not possible.

3.4.1.2 Psychiatric Disorders - Others (n=7)

The remaining 7 cases of psychiatric disorders reported drug abuse (n=2), tic (n=2), and one case each of mental damage, mood swings, and OCD. Three of these 7 cases reported the events resolved when quetiapine was discontinued; two of which also reported the events recurred when quetiapine was reintroduced. These 3 cases are briefly summarized below. The last 4 cases did not report the action taken with quetiapine or the outcome of the events.

- **FAERS Case # 10188839, China, 2014:** Chen, et al. reported a 16-year-old male who developed a tic, described as "blinked his eyes," when quetiapine was titrated to 150 mg daily for bipolar disorder. The tic worsened to "recurrent episodes of tightening of his eyes, nose, and the corner of his mouth increased in frequency, ultimately occurring thousands of times per day" when quetiapine was increased to 600 mg daily. Therefore, the quetiapine dose was decreased. Two weeks after decreasing the quetiapine dose to 50 mg daily, his tic symptoms resolved, but he was still "hyperactive." The quetiapine dose was titrated to 600 mg daily again, and within two weeks, his manic symptoms resolved but the tic symptoms returned. His tic symptoms resolved when haloperidol 4 mg daily was started and quetiapine 600 mg daily was continued.

- **FAERS Case # 10197388, USA, 2014:** A 13-year-old male experienced "mental damage" when quetiapine was "reintroduced." Although the reporter noted that the "event abated after use stopped or dose reduced" and "event reappeared after

reintroduction" with quetiapine (checked boxes on MedWatch form), no additional clinical information was provided in the narrative.

- **FAERS Case #9882531, France, 2014:** An 11-year-old male experienced OCD symptoms approximately one month after starting quetiapine 300 mg daily and valproate sodium 600 mg daily "as anti-impulsive aim." His OCD symptoms, described as "repetitive storage of his affairs, disassembly of furniture and standing position on one foot," improved when the quetiapine dose was decreased to 200 mg daily. His relevant history included depressive episode with multiple therapeutic failures, extrapyramidal disorder with risperidone, "thrombopathy" with fluoxetine, and institutionalized for "hetero aggressive major behavioral disorder." He also has a catatonic component, "incessant howling," and pervasive developmental disorder (PDD) with stereotypes.

Reviewer's comment: The tic symptoms resolved in the first case after starting haloperidol and continued high-dose quetiapine. Additionally, events are probably consistent with extrapyramidal symptoms and possibly tardive dyskinesia, both labeled events for quetiapine. The second case did not provide any clinical information to describe the course of events. It is unclear whether the third case was experiencing a worsening of his underlying disorder of PDD with stereotypes or if he is exhibiting a new onset of OCD. Nevertheless, his symptoms improved when the quetiapine dose was reduced.

3.4.2 *Eye Disorders (n=7)*

The eye disorders cases included 3 females and 4 males with a median age of 15 years old, ranging from 10 months to 16 years old. The total daily dose of quetiapine received was 50 mg, ranging from 25 mg to 100 mg (n=5). The reported events were papilledema (n=2), "vision loss" (n=2), and one case each of astigmatism, miosis, extraocular muscle disorder.

3.4.2.1 Eye Disorders - Papilledema (n=2)

The first case was a 10-year-old female who was initially receiving quetiapine XR 300 mg daily for OCD, but due to "learning difficulties," her quetiapine dose was decreased to 100 mg daily. Since then, she experienced unspecified edema, muscle stiffness, tiredness, and weight gain. She also experienced "eyeground swelling" and "optic nerve congested" 22 months after starting quetiapine XR for OCD. There were no findings on the magnetic resonance imaging (MRI). Quetiapine was continued and all events were ongoing at the time of the report. The second case was a 12-year-old female who received fluoxetine 20 mg daily and quetiapine 100 mg daily for unspecified indications. One month after she started both medications, she developed unspecified edema. Ten months after she started both medications, she developed papilledema, described as "prominent optic disc, swelling behind the eye and optic nerve stasis." On an unspecified date, she was hospitalized due to the events. Both medications were continued, but the outcome of the events was not reported.

Reviewer's comment: A causality assessment was not possible in the first case because she did not change her treatment regimen and the events were ongoing at the time of the

report. The patient in the second case was also taking fluoxetine, which is labeled for optic neuritis.

3.4.2.2 Eye Disorders - Vision loss (n=2)

Both cases of vision loss were in 16-year-old males. The first case received quetiapine 50 mg daily for depression and sleep difficulties. He complained of constant headaches since the first dose of quetiapine. Thirteen days after starting quetiapine, or 3 days after a dose increase with quetiapine (dose not reported), he experienced bilateral visual loss for 2 minutes. His vision gradually returned over 30 seconds. There were no findings on MRI. The quetiapine dose was reduced, and the loss of vision resolved. The second case received quetiapine 12.5 mg twice daily for bipolar disorder, as well as aripiprazole and fluoxetine for unspecified indications. On an unspecified date, he experienced "vision loss," which was ongoing at the time of the report; however, the action taken with quetiapine was not reported.

3.4.2.3 Eye Disorders - Others (n=3)

One of the remaining 3 cases was an accidental ingestion of quetiapine 50 mg and an unspecified antidepressant 25 mg tablet by a 10-month-old male. He experienced vomiting, somnolence, miosis, and "unrest." He was treated with gastric lavage, but the outcome of the events was not reported. Another case was a 15-year-old male who received quetiapine 400 mg (unspecified frequency) for "physical aggression and argumentative behavior" when he was diagnosed with cataract and astigmatism. His concomitant medications were mixed amphetamines for ADHD, escitalopram for depression, trazodone for sleep, and levosalbutamol for asthma. Quetiapine was discontinued but the outcome of the events was not reported. Of note, cataracts is a labeled event in the Warnings and Precaution section of the labeling for quetiapine. The last case was a 16-year-old female who received quetiapine 75 mg (unspecified frequency) for insomnia. Her PMH and concomitant medications, if any, were not reported. During an eye exam at school, her eyes were found to track abnormally, described as "no activity in the medial rectus OS when crossing eye," or "left eye was not tracking with the right side." She was seen by an ophthalmologist, discontinued quetiapine, but the outcome of the event was not reported.

Reviewer's comment: The first case of vision loss may be related to the headaches that started after initiating quetiapine. The remaining 4 cases of eye disorders did not report the outcome of the events in 3 cases, and the action taken with quetiapine in the last case. Thus, these cases were not assessable.

3.4.3 ***Gastrointestinal (GI) and Hepatic Disorders (n=6)***

The GI and hepatic disorders cases included 5 males and 1 female with a median age of 12 years old, ranging from 8 months to 15 years old. Four cases reported the total daily doses of quetiapine, and they were 150 mg, 300 mg, 475 mg, and 800 mg. The events reported were one each of gastroesophageal reflux disorder (GERD), GI bleed, hepatic enzyme increased, hepatic steatosis, paralytic ileus, and viral gastroenteritis.

3.4.3.1 GI (n=4)

The first GI case was a 10-year-old male who experienced a GI bleed and was hospitalized 22 days after starting quetiapine XR 800 mg daily for defiance disorder; the reporting physician believed the GI bleed was due to his underlying GERD and continued treatment with quetiapine. The outcome of the event was not reported. The second case was a 5-year-old male with a history of autism who received quetiapine 25 mg (unspecified frequency) for bipolar disorder, as well as risperidone (unspecified dose, therapy dates, and indication). Within 6 months of starting quetiapine, he experienced GERD, insulin dependent diabetes, and diabetic ketoacidosis. Quetiapine was discontinued but the outcome of events was not reported. The third case was a 14-year-old male who received quetiapine 475 mg daily for manic depression, behavior problems, and "possibly autism." Three years and 4 months after starting quetiapine, he had viral gastroenteritis with vomiting, possible dehydration, and seizure. He was seen in the ER, but was not admitted. Four months later, he experienced another seizure for which he received unspecified treatment in the ER and discharged 6 hours later. Treatment with quetiapine continued, but the outcome of events was not reported. The last case was reported by Kim, et al. of a 14-year-old male who developed paralytic ileus from worsening underlying constipation at an unspecified time. His medications were quetiapine 300 mg daily and risperidone 6 mg daily for schizophrenia. As treatment for paralytic ileus, all oral medications were discontinued. Two days later, he received intramuscular injections of haloperidol and lorazepam for symptom control, and developed NMS, which resolved with treatment. The outcome of paralytic ileus was not reported.

3.4.3.2 Hepatic (n=2)

The first hepatic case was reported by Jacobson, et al. of an 8-month-old Asian female who experienced elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) with fluphenazine, which was discontinued and the event resolved. One week after she started quetiapine, she also experienced elevated AST and ALT, which decreased when quetiapine was discontinued. The second case was a 15-year-old male who was incarcerated in a juvenile detention center. He received quetiapine 150 mg every evening for auditory and visual hallucinations, as well as fluoxetine (unspecified dose, therapy dates, and indication). Six months after starting quetiapine, he gained weight from BMI[c] of 29 kg/m^2 to BMI of 36 kg/m^2, developed hypercholesterolemia, and fatty liver disease (GGT[d] 83 U/L, alkaline phosphatase[e] 208 U/L, ALT[f] 72 U/L, AST[g] 46 U/L). Of note, he has a strong family history of diabetes, hypercholesterolemia, and early cardiovascular death in his father and paternal grandfather. Treatment with quetiapine was discontinued, and he was counseled on lifestyle modifications, but the outcome of the events was not reported.

[c] Body Mass Indexreference rage 18.5-24.9 kg/m^2
[d] Gamma-glutamyl transferase reference range 0-60 U/L
[e] Alkaline phosphatase reference range 30-110 U/L
[f] Alanine transaminase reference range 0-55 U/L
[g] Aspartate transaminase reference range 0-45 U/L

Reviewer's comment: Transaminase elevations is a labeled event for quetiapine in the Adverse Reactions section, but in the adult population only. However, we have only one pediatric case in the context of the high drug utilization for quetiapine in the past 4 years. Additionally, the AST and ALT levels in this case were not reported; therefore, we are unable to determine the severity of this event. The second case of fatty liver disease is likely due to his metabolic syndrome that may have been caused by quetiapine, as well as his "strong" family history for diabetes, hypercholesterolemia, and early cardiovascular death.

3.4.4 *Pulmonary/Respiratory/Vascular Disorders (n=4)*

The pulmonary, respiratory, or vascular disorders cases included 3 females and 1 male with a median age of 14 years old, ranging from 10 to 16 years old. The total daily doses of quetiapine were reported in 3 of the cases: 100 mg daily; "0.5 mg/kg" every morning and "1 mg/kg" every evening; and 200 mg three times daily then overdose with 1200 mg. The reported events were pulmonary hypertension, pleural effusion, central sleep apnea (CSA), and pulmonary embolism (PE).

The first case is a 15-year-old female with an unspecified medical history who received fluoxetine and quetiapine 100 mg daily for an unspecified duration. On an unspecified date, she developed pulmonary hypertension and was hospitalized. Quetiapine was discontinued and restarted at a lower dose, but the outcome of the event was not reported. The case of CSA in a 10-year-old male was confounded by 7 concomitant medications, including methadone and lorazepam. The case of PE in a 16-year-old female was confounded by 13 concomitant medications, including enoxaparin for an unspecified indication, as well as misuse of quetiapine at a dose of 1200 mg. The outcome of the events and the action taken with quetiapine for the CSA or PE cases were not reported. The last case was a 12-year-old female who received lithium 8.5 mg/kg every morning and 5.7 mg/kg every night, and quetiapine 0.5 mg/kg every morning, and 1 mg/kg every night for bipolar disorder (her weight was not reported). Approximately 3 to 4 years after starting lithium and quetiapine, she developed vomiting, cough, and congestion, followed by facial swelling and slurred speech two days later. She presented to the ED one week later with worsening symptoms. Upon examination, she had generalized edema with moist mucous membranes, tongue fasciculation, moderate tremor in the upper extremities, and 3+ patellar reflexes with 1 beat of inducible clonus. Chest x-ray revealed small bilateral pleural effusions, EKG showed prolonged QT interval, and she was admitted for lithium toxicity with acute kidney injury. As treatment, she received hemodialysis, unspecified steroids, and discontinued all "antipsychotic medications." Her lithium level decreased from 4.6 mmol/L to less than 1.0 mmol/L after 6 days of hemodialysis. Approximately 5 months later, she made a full recovery.

Table 3.4.4 Labeling status for Seroquel and Seroquel XR[3,4]

Event(s)	***Warnings & Precautions***	***Adverse Reactions***	***Drug Interactions***
Sedation/ Somnolence	*Seroquel and Seroquel XR*	*Seroquel and Seroquel XR*	*Seroquel and Seroquel XR*
Dyspnea		*Seroquel and Seroquel XR*	

3.4.5 *Nervous System Disorders (n=3)*

The nervous system disorders cases included 3 females aged 14-, 15-, and 16 years old. Two of the 3 cases reported loss of consciousness (described as "passed out"), and the last case reported dementia. None of the cases reported the quetiapine dose, but one case reported a 15-year-old female who "passed out" because the unspecified quetiapine dose was "so high." None of the cases required hospitalization. All 3 cases did not report on the action taken with quetiapine or the outcome of events.

3.4.6 *Musculoskeletal Disorders (n=2)*

The first case was a 15-year-old female who experienced excessive sedation, "could not move," muscle spasm due to a medication error with quetiapine. The pharmacist had incorrectly dispensed quetiapine XR 300 mg for a refill (correct dosage was not reported), and the patient experienced these adverse events following the first incorrect dose. Quetiapine XR was discontinued, and the event of "could not move" and muscle spasm resolved. The second case was a 15-year-old male who experienced incontinence, muscular weakness, paresthesia, and visual impairment while receiving quetiapine 25 mg daily and sertraline 50 mg daily for an unspecified indication. The action taken with both medications was not reported, but the events were reported as "improving" at the time of the report.

Reviewer's comment: Although the clinical details were not clear (i.e. the actual dose of quetiapine that should have been dispensed), the event was due to a medication error. The second case did not report the action taken with quetiapine, and thus, is not assessable. Of note, musculoskeletal stiffness and paresthesia are both labeled events under the Adverse Reactions section of the quetiapine labeling.

3.4.7 *Miscellaneous Disorders (n=5)*

The remaining 4 cases reported one case each of alopecia, aplastic anemia, hematocolpos, thyroid nodules/ovarian cysts, and ventricular tachycardia. The first case was reported by Yazici and Perçinel of a 16-year-old female who received sertraline 75 mg daily and quetiapine 50 mg daily for depression. Seven weeks after starting sertraline and 3 weeks after starting quetiapine, she experienced "intense hair loss." A battery of tests was performed to rule out possible medical causes and all were within normal limits. The dermatology clinic did not identify dermatological diseases that would contribute to alopecia. The patient did not have a history of alopecia. Treatment with quetiapine discontinued, sertraline continued, and no other therapy for alopecia given. After one month, she had no complaints of hair loss.

The second case was a 12-year-old male with a family history of arterial hypertension who received quetiapine XR for ADHD. His quetiapine dose was titrated from 50 mg daily to 200 mg daily over about 1.5 months. His ECG showed "ventricular tachycardia (125 min-1)" when he started taking 200 mg daily. "ECG showed sinus rhythm, 56/min, steeply type, in total without age relevant finding." He recovered from the event on the same day, and quetiapine was discontinued 9 days later. The last 3 cases reported continued treatment with quetiapine; one case (13-year-old female) reported the hematocolpos resolved, the second case (16-year-old female) reported the thyroid nodules/ovarian cysts

persisted, and the last case (16-year-old female) did not report the outcome of aplastic anemia.

Reviewer's comment: While the alopecia case appears compelling by ruling out other medical causes of alopecia in this patient; however, in the context of the drug utilization of quetiapine in the past 4 years, we are unable to draw any conclusions from these singular cases for these events.

4 DISCUSSION

DPV included 78 pediatric cases with serious, unlabeled events reported with quetiapine use in the case series. There were no new pediatric safety signals identified, no apparent increased severity or frequency of any labeled adverse events, and there were no deaths directly associated with quetiapine. There were 16 fatal cases and 62 non-fatal cases from August 1, 2011 through July 31, 2015. More than half (n=9) of the fatal cases did not report a cause of death. The remaining 7 fatal cases that reported a cause of death were all due to multiple drug overdoses, except for 1 case that reported "cerebral death" in a 14-year-old female with a recent history of elevated valproate and alcohol blood levels. Furthermore, only 4 of these 7 cases reported an autopsy was performed.

Almost half of the 62 non-fatal cases (n=28) reported overdose, self-injurious behavior, suicidal ideation, or suicidal attempt. Of note, quetiapine carries a boxed warning for "suicidal thoughts and behaviors" specifically for children, adolescents and young adults using quetiapine as antidepressant therapy. Although 13 of these 28 cases reported a reason for use for quetiapine other than depression or bipolar disorder, unfortunately, cases of suicidality occur in children and adolescents, especially cases with a history of mental illness. In general, there is a significantly increased risk of suicide and suicidal behavior in patients with these conditions, very commonly involving intentional drug overdoses. According to the Center for Disease Control and Prevention, suicide is the second leading cause of death for youths between 10-24 years in 2012. Poisoning is among the top three methods used in suicides of young people.[11] Among students in grades 9-12 in the US during 2013, 8% of the students attempted suicide one or more times in the previous 12 months, and 2.7% of the students made a suicide attempt that resulted in an injury, poisoning, or an overdose that required medical attention.[12] A history of depression or other mental illness is among several risk factors that can put a young person at risk for suicide.[13] See Appendix E for the complete table of suicide injury deaths and rates per 100,000 for all ages from 0 to 24 years old.[14] The remaining 7 psychiatric disorders cases reported 5 events (e.g. drug abuse, tic, mental damage, mood swings, OCD) that either did not provide sufficient clinical information for causality assessment, or the events described were not definitively attributed to quetiapine use.

Of the remaining 34 cases that reported events across 14 system organ classes, there were no clear patterns or trends for a new safety signal. Twenty-four of the 34 cases did not provide sufficient information for causality assessment (e.g. action taken with quetiapine or outcome of the event). Four of the remaining 10 cases continued quetiapine and the event resolved or was improving. It is difficult to draw any conclusions from the last 6 cases, especially in the context of the drug utilization in the last 4 years.

The drug utilization data provided in this review showed that the majority of pediatric use of quetiapine was in older pediatric patients aged 10 – 17 years, which is consistent with the present FAERS case series with a majority of the cases aged 12 - <17 years (n=62). Based on data from an office-based physician surveys database, we observed a number of diagnoses associated with the use of quetiapine; however, the majority of *use mentions* were too small to provide reliable national estimates of use. "Affective Psychoses NEC/NOS" (ICD-9 code 296.9) was the only diagnosis mentioned in association with quetiapine use with reliable national estimates captured in pediatric patients aged 10 - 17 years.

5 CONCLUSION

Overall, there were no clear patterns of reported adverse events in the cases or trends in drug utilization to suggest a new safety signal associated with quetiapine in pediatric patients. Additionally, there have been multiple OSE reviews addressing safety issues with quetiapine in the pediatric population conducted since approval.

6 RECOMMENDATIONS

Based on the data summarized in this review, DPV recommends no labeling changes at this time. DPV will continue to monitor adverse events associated with the use of quetiapine.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

The findings from this review should be interpreted in the context of the known limitations of the databases used. Based on the IMS Health, IMS National Sales Perspectives™ database, we estimated that about 77% of all quetiapine bottles were distributed to outpatient retail pharmacy settings in the United States. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution.

IMS, Vector One®: Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. Of note, if trends over time or between products are imputed, caution should be exercised. Furthermore, statistical analysis may be necessary to determine any statistically significant changes over time or between products.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

IMS, National Prescription Audit

The National Prescription Audit (NPATM) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA™ receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 86% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and

include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions.

Data are also collected from approximately 40 - 70% (varies by class and geography) of mail service pharmacies and approximately 45-55% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

Encuity Research, LLC., TreatmentAnswers™

Encuity Research, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs 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, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH QUETIAPINE (N=78)

FAERS Case #	Version #	Manufacturer Control #
8063657	2	US-ASTRAZENECA-2011SE43795
8064644	1	US-JNJFOC-20110710330
8111608	1	US-B.I. PHARMACEUTICALS,INC./RIDGEFIELD-2007-DE-00851GD
8111755	1	US-ASTRAZENECA-2011SE50053
8147992	1	US-ASTRAZENECA-2010SE40203
8150736	1	US-ASTRAZENECA-2009UW09920
8151590	1	US-ASTRAZENECA-2011SE35937
8152829	1	US-ASTRAZENECA-2011SE54946
8182655	1	(blank)
8184435	2	US-ASTRAZENECA-2011SE60614
8239520	2	CA-ASTRAZENECA-2011SE67286
8242002	3	CA-ASTRAZENECA-2011SE67387
8291279	4	PHHY2011US108222
8292727	3	PHHY2011US108066
8331527	1	CA-ASTRAZENECA-2012SE01160
8331601	1	US-ASTRAZENECA-2011SE60351
8387345	1	US-COVIDIEN/TYCO HEALTHCARE/MALLINCKRODT-T201200139
8387630	1	US-ASTRAZENECA-2012SE05216
8464801	1	(blank)
8466562	1	US-ASTRAZENECA-2012SE17185
8479081	1	AT-ASTRAZENECA-2012SE19554
8536098	3	AT-ASTRAZENECA-2012SE26968
8602993	2	PHHY2012JO048284
8605404	1	US-ASTRAZENECA-2012SE37411
8643194	1	MX-ASTRAZENECA-2012SE42026
8673922	2	US-WATSON-2012-11992
8690556	1	US-ASTRAZENECA-2012SE28015
8749396	1	2012MA009095
8884159	1	US-ROXANE LABORATORIES, INC.-2012-RO-02289RO
8886830	1	US-ASTRAZENECA-2012SE81916
8956216	2	GXKR2012DE003765
8959911	2	US-ASTRAZENECA-2012SE92115
8964524	1	CA-ASTRAZENECA-2003UW10892
8966801	2	DE-ASTRAZENECA-2012SE91916
8980324	1	IT-JNJFOC-20121206632
9004631	2	DE-ASTRAZENECA-2013SE00040
9167453	1	1611009
9202265	2	US-ASTRAZENECA-2013SE19296
9291055	1	US-ASTRAZENECA-2013SE32424
9293976	1	PHEH2012US009107
9397911	3	AUR-APL-2013-05726
9398961	1	ES-ASTRAZENECA-2013SE51721
9531390	1	2013-00597
9570934	1	US-ASTRAZENECA-2013SE71729
9689503	1	CA-ASTRAZENECA-2013SE82129

FAERS Case #	Version #	Manufacturer Control #
9720067	1	JP-ASTRAZENECA-2013SE87081
9739098	1	US-DRREDDYS-USA/USA/13/0036144
9882531	1	FR-ASTRAZENECA-2014SE07170
9913353	1	AUR-APL-2014-01273
9958355	3	IT-ASTRAZENECA-2014SE14625
10188839	1	CN-ROXANE LABORATORIES, INC.-2014-RO-00779RO
10197388	1	(blank)
10206366	2	CH-ASTRAZENECA-2014SE36743
10235187	1	FR-ASTRAZENECA-2014SE40893
10294934	1	US-ASTRAZENECA-2014SE48429
10354542	1	US-ASTRAZENECA-2014SE54123
10356242	1	US-ASTRAZENECA-2014SE54858
10472930	1	US-ASTRAZENECA-2014SE69733
10493858	1	JP-ASTRAZENECA-2014SE73700
10633429	1	2014SA161948
10652711	1	CH-ASTRAZENECA-2014SE95105
10652736	1	US-APOTEX-2014AP006146
10654708	1	NO-TEVA-529004ISR
10684515	2	IT-ACCORD-027822
10686911	1	KR-LUPIN PHARMACEUTICALS INC.-2014-01896
10757970	1	TR-ROXANE LABORATORIES, INC.-2015-RO-00156RO
10790165	1	FR-ASTRAZENECA-2015SE13074
10802660	1	US-APOTEX-2015AP006541
10812229	1	US-ASTRAZENECA-2015SE14182
10833514	1	ZA-ASTRAZENECA-2015SE16051
10874222	1	FR-ABBVIE-15P-056-1353278-00
10978001	1	US-ASTRAZENECA-2015SE30616
11033740	1	US-ASTRAZENECA-2015SE33778
11087551	1	AU-WATSON-2015-08928
11098991	2	FR-ASTRAZENECA-2015SE41999
11190944	2	AT-ASTRAZENECA-2015SE57434
11247920	2	AU-AUROBINDO-AUR-APL-2015-05637
11317068	1	FR-ASTRAZENECA-2015SE71915

8.4 APPENDIX D. FATAL CASE NARRATIVES

FAERS Case #	Country	FDA Received Year	Age (years)/ Sex	Quetiapine Total Daily Dose; Therapy Dates; Indication(s)	Past/Concurrent Medical History	Concomitant Medications	Autopsy Performed	Cause of Death	Literature Case Report
APPARENT MONOTHERAPY WITH QUETIAPINE									
8884159	USA	2012	15/F	2 tablets of unspecified strength; Not reported; Not reported	Not reported	Not reported, unknown if any	Unknown	Unknown	Yes; AAPCC NPDS
AAPCC NPDS reported a 15-year-old female presented to the ED "claiming to have ingested 2 quetiapine tablets of unknown strength. Her initial heart rate was 150 beats/min, but decreased to 115 beats/min during her ED stay. She was transferred to an inpatient psychiatry unit. No electrocardiogram (ECG) was obtained. She was observed for ~ 6 hours. She was returned to the ED within six hours with fixed and dilated pupils and seizing. Cardiopulmonary resuscitation (CPR) was unsuccessful. The poison center was informed about the case at this time." Blood concentrations, if any, were not reported. Literature reference: Lai MW, *et al*. 2005 Annual Report of the American Association of Poison Control Centers' National Poisoning and Exposure Database. Clinical Toxicology. 2006;44:803-932.									
8959911	USA	2012	15/M	900 mg QD; Not reported; Bipolar disorder	Not reported	Not reported, unknown if any	Unknown	Unknown	No
A 15-year-old male received quetiapine 900 mg daily started on an unknown date for bipolar disorder. The "expert witnesses did not believe that the patient had NMS (Neuroleptic malignant syndrome)." He was reportedly in sepsis and died on an unspecified date.									
9913353	USA	2014	14/F	Not reported; Not reported; Not reported	Not reported	Not reported, unknown if any	Unknown	Unknown	Yes; AAPCC NPDS
AAPCC NPDS reported a 14-year-old female who "died of unknown reason defined as reason for the exposure cannot be determined or no ingestion of quetiapine as primary toxic substance. The relative contribution of fatality was assessed as probably responsible in the opinion of the CRT the Clinical Case Evidence suggests that the substances caused the death, but some reasonable doubt remained." Literature reference: James B. Mowry, Daniel A. Spyker, Louis R. Cantilena, J. Elise Bailey and Marsha Ford. 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report. Clinical Toxicology. 2013;51:949-1229.									

FAERS Case #	Country	FDA Received Year	Age (years)/ Sex	Quetiapine Total Daily Dose; Therapy Dates; Indication(s)	Past/Concurrent Medical History	Concomitant Medications	Autopsy Performed	Cause of Death	Literature Case Report
MULTIPLE DRUG INGESTION									
8064644	USA	2011	8/M	Not reported; Not reported; Not reported	Not reported	Acetaminophen; Cyclobenzaprine; Hydrocodone	Yes	Suffocation and intoxication with multiple medications	No
An 8 year-old-male was abducted and intoxicated with cyclobenzaprine, acetaminophen, quetiapine, and hydrocodone on an unspecified date in July 2011. On (b) (6), he experienced multiple drug intoxication. He was suffocated and died on the same day. An autopsy was performed on (b) (6), and the chief medical examiner said that the cause of death was not just suffocation, but also 'intoxication by the combined effects of cyclobenzaprine, quetiapine, hydrocodone, and acetaminophen."									
8111608	USA	2011	4/F	200 mg/day; Not reported; ADHD and bipolar disorder	Not reported	"Children's Tylenol Plus Cough & Runny Nose"; clonidine 0.35 mg/day; divalproex semisodium 750 mg/day	Yes	Drug overdose from a mix of medications; "… amount of clonidine alone would have been fatal."	No; News report
A news anchor reported on a 4-year-old female who allegedly overdosed on psychotropic drugs and died on (b) (6). Her psychiatrist diagnosed her with bipolar and ADHD, and began prescribing medications before she turned 3-years-old. The State Police investigator reported that the psychiatrist prescribed 3 medications for the girl: divalproex semisodium 750 mg daily, quetiapine 200 mg daily, and clonidine 0.35 mg daily for ADHD and bipolar disorder. The night before her death, her mother gave the patient "Children's Tylenol Plus Cough & Runny Nose," because she thought the patient had "a little bit of a cold." The mother also gave the patient "half a clonidine" before the patient went to bed. "According to the medical examiner, her heart and lungs were damaged, and this was due to prolonged abuse of these prescription drugs, rather than one incident." The medical examiner ruled the death as a "drug overdose from a mix of medications. And that the amount of clonidine alone would have been fatal."									
8242002	Canada	2011	9/M	Extended-release 25 mg BID; 2007; Not reported	Not reported	atomoxetine; clonidine; fluticasone; haloperidol; methylphenidate; mometasone; olanzapine; salbutamol; sertraline	Unknown	Unknown	No
A 9-year-old male received quetiapine 50 mg, methylphenidate 40 mg daily, sertraline 20 mg daily, atomoxetine 40 "micrograms," clonidine 50 "micrograms" daily, fluticasone propionate 250 mcg, haloperidol 2 mg daily, mometasone furoate 50 mcg daily, olanzapine 2.5 mg twice a daily, and salbutamol 100 mcg, which were started on an unknown date									

FAERS Case #	Country	FDA Received Year	Age (years)/ Sex	Quetiapine Total Daily Dose; Therapy Dates; Indication(s)	Past/Concurrent Medical History	Concomitant Medications	Autopsy Performed	Cause of Death	Literature Case Report
for unknown indication. He experienced "dizziness, dyspnea, dysstasia, eye movement disorder, gastric dilatation, gastrointestinal sounds abnormal, and weight increased." The action taken with suspect drugs and the outcome of the events were not reported.									
8291279	USA	2011	16/F	Not reported; Not reported; Not reported	Not reported	amlodipine; amphetamine/ dextroamphetamine; bupropion; lamotrigine; metoprolol; salicylate	Unknown	Unknown	Yes; AAPCC NPDS
AAPCC NPDS reported a 16-year-old female received metoprolol, bupropion, amlodipine, amphetamine/dextroamphetamine, quetiapine, lamotrigine, and salicylate, at an unknown dose for unspecified indications. She was reportedly on "acute exposure to metoprolol." On an unknown date she died due to suicide. At autopsy, drug levels in the blood were obtained for bupropion 3.8 mg/L and threobupropion 11 mg/L; drug levels in the liver were bupropion 2 mg/kg and threobupropion 68 mg/kg. Salicylate levels obtained "1.5 h (pe)" and "4.5 h (pe)" were 48.2 mg/dL and 32 mg/dL, respectively. Reference ranges for the drug levels were not reported. Literature reference: Alvin C. Bronstein et al. 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS)" 27th Annual Report. Clinical Toxicology. 2010;48:979-1178.									
8292727	USA	2011	10/M	Not reported; Not reported; Not reported	Not reported	alprazolam; atomoxetine; clonazepam; lorazepam; loratadine; methylphenidate; omeprazole; risperidone; valproic acid	Unknown	"acute exposure"	Yes; AAPCC NPDS
AAPCC NPDS reported a 10-year-old male received methylphenidate at an unspecified dose for an unknown indication. On an unknown date, the patient died. "The author used a tool called cause rank to judge two or more substances in contribution to fatality. According to this, the drugs quetiapine (cause rank: 1), risperidone (cause rank: 2), clonazepam (cause rank: 3), lorazepam((cause rank: 4), alprazolam (cause rank: 5), valproic acid (cause rank: 6), atomoxetine (cause rank: 7), methylphenidate (cause rank: 7), loratadine (cause rank: 9) and omeprazole (cause rank: 10) were suspected. The reason for death was given as 'other malicious'. The event was reported as 'death due to acute exposure'. The causality for the suspect drugs was noted as undoubtedly responsible for death." Literature reference: Bronstein AC, *et al*. 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS)" 27th Annual Report. Clinical Toxicology. 2010;48:979-1178.									

FAERS Case #	Country	FDA Received Year	Age (years)/ Sex	Quetiapine Total Daily Dose; Therapy Dates; Indication(s)	Past/Concurrent Medical History	Concomitant Medications	Autopsy Performed	Cause of Death	Literature Case Report
8387345	USA	2012	13/F	Not reported; Not reported; Not reported	Not reported	fluoxetine; lorazepam; olanzapine; oxcarbazepine; temazepam; trazodone; zolpidem	Yes	"prehospital cardiac and/or respiratory arrest"	Yes; AAPCC NPDS
AAPCC NPDS reported a 13-year-old female "died following a prehospital cardiac and/or respiratory arrest after acute ingestion of fluoxetine, temazepam, olanzapine, zolpidem, lorazepam, oxcarbazepine, quetiapine and trazodone. Drug levels in whole blood at autopsy included: olanzapine 0.46 mg/L, zolpidem 58 ng/mL and trazodone 3.3 mg/L." Literature reference: Bronstein AC, *et al*. 2010 Annual report of the American Association of Poison Control Centers National Poison Data System (NPDS):28th Annual Report. Clin Toxicol, 2011, 49, 910-941.									
8749396	USA	2012	14/M		"in and out of institutions" over the past four years, ADD, oppositional defiant personality, physical and verbal aggression, self-harm, and domestic abuse; rule-out diagnoses included borderline personality, developmental delay, bipolar, and learning problems	acetaminophen with codeine; aripiprazole; clonidine; diphenhydramine; lisdexamfetamine; meloxicam; penicillin; sertraline; valproic acid	Yes	Unknown	Yes; AAPCC NPDS
AAPCC NPDS reported a 14-year-old male received quetiapine, sertraline, valproic acid, clonidine, aripiprazole, diphenhydramine, meloxicam, penicillin, lisdexamfetamine, and acetaminophen with codeine (as needed basis). He was seen in the ED for complaints of tooth/jaw pain. He was diagnosed with abscess and was prescribed acetaminophen with codeine. Then he was seen by an oral surgeon in clinic, but the oral surgeon did not find an abscess. He was given penicillin with a plan to remove his wisdom teeth. Two days following the ED visit, he had "question of fever, headache and jaw pain. The patient's behavior was described as 'hanging out' and chatting with people. That evening, the patient went to bed and was snoring. The patient had never been diagnosed with OSA, and the extent of the snoring was unknown. The patient was found unresponsive and apneic in bed the following morning about 0600 and was declared dead at 0654." Acetaminophen with codeine given on the following times:									

FAERS Case #	Country	FDA Received Year	Age (years)/ Sex	Quetiapine Total Daily Dose; Therapy Dates; Indication(s)	Past/Concurrent Medical History	Concomitant Medications	Autopsy Performed	Cause of Death	Literature Case Report
"Day of emergency department visit: 1218 1 day after emergency department visit: 0700, 0900, 1135 2 days after emergency department visit: 0900, 1423" "Autopsy Findings:* Height: 70 inches, Weight: 250 pounds* Hand injuries healing; didn't look infected; cultures negative for viruses. • Positive cultures of staph and strep in blood and lungs; normal flora., No tooth abscess; 1 cm ulcer adjacent to molar without puss. • Laryngeal inlet small. (+) pulmonary edema and hepatosplenomegaly.¿ Slight cushingoid appearance. • Neuropathology: Megacephaly; abnormal gyri; ischemia in watershed areas; megaloencephalopathic syndrome. Tryptase level 12.9 ng/mL • Femoral blood: Amphetamine: 93 ng/mL, Morphine: 11.8 ng/mL, Codeine: 117 ng/mL, Valproic acid: 19.6 mcg/mL Sertraline: 274 ng/mL Nor-sertraline: 526 ng/mL Diphenhydramine: 138 ng/mL Aripiprazole: 190 ng/mL, Quetiapine: 190 ng/mL Antibiotic "Negative" as reported out, but PCN not listed on comprehensive from AIT laboratories. No acetaminophen reported in post-mortem blood. • Urine: Amphetamine: 4629 ng/mL Morphine: 5069 ng/mL Codeine: >10,000 ng/mL Hydrocodone: 57 ng/mL • Vitreous: Electrolytes normal post-mortem pattern" Literature reference: Bronstein AC, *et al*. 2010 Annual report of the American Association of Poison Control Centers National Poison Data System (NPDS):28th Annual Report. Clin Toxicol, 2011, 49, 910-941.									
8964524	Canada	2012	15/M	16 g; Once; Schizophrenia and bipolar disorder	Not reported	alcohol; cocaine; heroine; lithium; valproate semisodium; zopiclone	Yes	Unknown	No
A 15-year-old male received quetiapine for schizophrenia and bipolar disorder starting on an unknown date. His concomitant medications included lithium, valproate semisodium, and zopiclone. "It was reported that the police arrested him after he committed an illegal act. While in the jail cell his mother noticed something was seriously wrong with him and insisted that he be taken to the hospital. The patient was taken to the hospital and they tried to resuscitate him for many hours." He took 80 to 90 tablets (approximately 16 grams) of quetiapine to commit suicide from which he experienced irregular heartbeat, convulsed, and died. The police reported that they interviewed kids on the street who were with the patient the night of the overdose and they stated that he took alcohol, heroin and/or cocaine the same night. A preliminary autopsy and toxicity screening was done, but the results were not reported.									
9397911	Australia	2013	15/M	Not reported; Not reported; Not reported	Not reported	morphine; oxycodone	Unknown	"Combination of drugs was likely to have resulted in death."	No

FAERS Case #	Country	FDA Received Year	Age (years)/ Sex	Quetiapine Total Daily Dose; Therapy Dates; Indication(s)	Past/Concurrent Medical History	Concomitant Medications	Autopsy Performed	Cause of Death	Literature Case Report
A 15-year-old male of unspecified ethnicity received quetiapine, morphine, and oxycodone, all with unknown dosages and indications, starting on an unspecified date. He had taken "a number of morphine, oxycodone and quetiapine tablets," and experienced "toxicity to various agents, overdose and drug interaction." The reporter determined that the "combination of drugs was likely to have resulted in death."									
9531390	USA	2013	15/M	Not reported; Not reported; Not reported	Not reported	acetaminophen with codeine; venlafaxine extended-release	Yes	Unknown	Yes; AAPCC NPDS
AAPCC NPDS reported a 15-year-old male who committed suicide by consuming quetiapine XR, venlafaxine, and acetaminophen/codeine of unspecified route, dose, form, frequency, and indication. He died on an unknown date. At autopsy, his blood concentrations were quetiapine 2.1 mg/L, venlafaxine 16.5 mg/L, codeine 0.79 mg/L, and acetaminophen 59.6 mg/L. The gastric concentrations found in stomach contents were quetiapine 48222.8 mg/kg and venlafaxine 12213.7 mg/kg. Reference ranges were not provided for the blood or gastric concentrations. Literature reference: Bronstein AC, Spyker DA, Cantilena LR Jr, Rumack BH, Dart RC. 2011 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th Annual Report. Clinical Toxicology. 2012;50:911-1164.									
10633429	USA	2014	14/M	Not reported; Not reported; Suicide	Not reported	acetaminophen; diphenhydramine; fluvoxamine	Unknown	Multi-drug overdose	Yes
Vieweg et al. reported a 14 years old male patient who died due to intentional overdose with diphenhydramine, acetaminophen, quetiapine, and fluvoxamine to commit suicide. An unspecified time later, she died due to diphenhydramine, acetaminophen, quetiapine, and fluvoxamine overdose. No autopsy information was provided Literature reference: Vieweg WVR, Linker JA, Anum EA, Turf E, Pandurangi AK, Sood B, et al. Child and Adolescent Suicides in Virginia: 1987 to 2003. Journal Of Child And Adolescent Psychopharmacology 2005; 15(4):655-63.									
10874222	France	2015	14/M	500 mg QD; Not reported; Not reported	bipolar disorder, liver cirrhosis due to both alcoholism and hepatitis C, epilepsy due to alcoholic weaning, cannabis and tobacco use	valproate sodium 1 g daily, furosemide 125 mg daily, zopiclone 7.5 mg daily, pantoprazole, ledipasvir/ sofosbuvir 82 mg daily, tadalafil 40 mg daily, spironolactone 75 mg daily, and nicotinamide 1 g	Unknown	"Central neurological failure with state of cerebral death"	No

FAERS Case #	Country	FDA Received Year	Age (years)/ Sex	Quetiapine Total Daily Dose; Therapy Dates; Indication(s)	Past/Concurrent Medical History	Concomitant Medications	Autopsy Performed	Cause of Death	Literature Case Report
						daily			
A 14-year-old female received quetiapine 500 mg daily along with 8 other medications for unknown indications starting on unspecified dates. An unspecified time after initiation of these medications, she experienced several epileptic seizures with confusion, aphasia, agitation, and disorientation. On an unspecified date, dose of valproate sodium was increased to 500 mg twice a day, and on the same day, the valproate blood level was 113 mg/L. Around the same time, both "MNR" and biological work-up were unremarkable including liver function tests and renal function. She was treated with clobazam. The same day, the valproate blood level was 59 mg/L and alcohol blood level was 0.04 g/L. A couple days later, she was hospitalized, and an EEG showed "diffuse slow waves due to vigilance disorders." In the following 7 days, no epileptic seizures were reported. She died on an unspecified date, and the cause of death was reported as "central neurological failure with state of cerebral death."									
11247920	Australia	2015	15/M	Not reported; Not reported; Not reported	Not reported	Alcohol; morphine; oxycodone	Yes	"combination of drugs"	Yes
Pilgrim, *et al* conducted a study that identified two patients who died following abuse of quetiapine; one patient had also abused oxycodone and morphine [dosages not stated]. "A 15-year-old boy had been consuming alcohol for approximately 3 hours before he consumed some of his mother's medication. A few hours later, he went to sleep. He was found dead the next morning, having taken a number of tablets of quetiapine, morphine and oxycodone. Toxicological analysis found the following drug concentrations in his leg blood: quetiapine 0.2 mg/L, oxycodone 0.2 mg/L and morphine 0.02 mg/L. The coroner suggested that the combination of drugs likely resulted in death." Author comment: "There were a small number of cases where quetiapine contributed to a death where it had not apparently been prescribed. . . Toxicological analysis showed alcohol in leg blood at 0.08 g/100mL, quetiapine 0.2 mg/L, oxycodone 0.2 mg/L and morphine 0.02 mg/L. The coroner suggested that although the levels of each individual drug were not excessive, the combination was likely to have resulted in death." Literature reference: Pilgrim JL, et al. The toxicology and comorbidities of fatal cases involving quetiapine. Forensic Science, Medicine, and Pathology 9: 170-176, No. 2, Jun 2013.									

8.5 Appendix E Suicide Injury Deaths and Rates per 100,000 for Ages 0-24 years old, 2014

2014, United States
Suicide Injury Deaths and Rates per 100,000
All Races, Both Sexes, Ages 0 to 24[15]
ICD-10 Codes: X60-X84, Y87.0,*U03

Age Group	Number of Deaths	Population	Crude Rate
00-04	0*	19,876,883	0.00*
05-09	3*	20,519,566	0.01*
10-14	425	20,671,506	2.06
15-19	1,834	21,067,647	8.71
20-24	3,245	22,912,174	14.16

* Rates based on 20 or fewer deaths may be unstable. Use with caution.
Produced by: National Center for Injury Prevention and Control, CDC
Data Source: NCHS Vital Statistics System for numbers of deaths. Bureau of Census for population estimates.

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/s/

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Drug use data cleared by data vendors

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