Appendix 16.
Cumulative Review of Spontaneous Case Reports of Mania, Psychotic Disorders, Hallucinations, and Agitation

Atomoxetine Hydrochloride

Cumulative Review of Spontaneous Case Reports of Mania, Psychotic Disorders, Hallucinations, and Agitation

26 November 2002 through 26 November 2007

1. Introduction

Atomoxetine was approved in the United States (US) on 26 November 2002 and in the United Kingdom (UK) on 26 May 2004. Following the reference member state (MHRA) review of the last 4 atomoxetine periodic safety update reports (PSUR 05 through PSUR 08) submitted by Eli Lilly and Company (Lilly), a cumulative review of all spontaneous adverse events involving psychiatric disorders (psychotic disorders, mania, agitation and hallucinations) in patients treated with atomoxetine was undertaken.

This document summarises all spontaneous case reports received by the market authorization holder (MAH), Lilly, between the reporting time periods of 26 November 2002 through 07 November 2007

2. Background

2.1. Mania, Psychotic Disorders, Hallucinations and Agitation

Definitions of mental diseases and mental disease symptoms can be found within the *Diagnostic and Statistical Manual of Mental Disorders*, Text Revision (DSM-IV-TR 2000). When possible, the DSM-IV-TR was used to develop definitions of mania, hypomania, agitation, hallucinations and psychotic disorders. Psychosis, agitation and hallucinations will be considered as symptoms rather than disease states. The focus of the assessment for these adverse events will be as symptoms.

Mania and Hypomania

Mania or a manic episode is defined as distinct period during which there is an abnormally and persistently elevated, expansive, or irritable mood. This period of abnormal mood must last at least 7 days or less if hospitalisation is required and treatment ensues. The manic mood disturbance (elevated and expansive mood) should be accompanied by at least 3 additional symptoms from a list that includes inflated self-esteem (grandiosity), decreased need for sleep, pressure of speech, flight of ideas, distractibility, increased involvement in goal directed activities or psychomotor agitation and excessive involvement in pleasurable activities with a high potential for painful consequences. The mixed manic episode (irritable rather than elevated and expansive) should be accompanied by at least 4 additional symptoms from the list of 7 additional symptoms presented with the manic mood disturbance (elevated and expansive mood) The disturbance should be sufficiently severe to cause marked impairment in social or occupational functioning or to require hospitalization; or it is characterised by the presence of psychotic features. The manic episode must not be due to the direct physiological effects of a drug of abuse, a medication, or other somatic treatments for depression or toxin exposure. Somatic treatments might include things such as electroconvulsive therapy. In addition, the manic episode must not be due to the direct physiological effects of a general medical condition such as multiple sclerosis or brain tumor.

Although elevated mood is considered the prototypical symptom, the predominant mood disturbance may be irritability, particularly when the wishes of the individual are thwarted. Lability of mood (alternating between euphoria and irritability) is frequently observed.

Hypomania or hypomanic episode is defined as a distinct period during which there is abnormally and persistently elevated, expansive, or irritable mood that will last at least 4-days. Hypomania and mania will have identical lists of symptoms required to meet a working definition (see manic episode symptom list). However, hypomania is differentiated from mania in that hypomania is not sufficiently severe to cause marked impairment in social or occupational functioning or to require hospitalisation. Some hypomanic episodes may evolve into full manic episodes.

Attention-deficit/hyperactivity disorder (ADHD) and a manic or hypomanic episode are both characterized by excessive activity. They are also both characterized by impulsive behaviour, poor judgment, and perhaps denial of problems. Attention-deficit/hyperactivity disorder may be differentiated from mania or hypomania by an earlier onset of symptoms. Attention-deficit/hyperactivity disorder symptoms are usually seen before age 7 years. In addition, ADHD differs from a manic episode in that a chronic nature is seen rather than episodic, it lacks a relatively clear onset and offset, and there is the absence of abnormally expansive or elevated mood or psychotic features.

Psychosis

The glossary of technical terms in the DSM-IV-TR provides a definition of psychosis.

The narrowest definition of psychosis would be restricted to delusions or prominent hallucinations, with the hallucinations occurring in the absence of insight into their pathological nature. A broader definition would also include other symptoms such as disorganised speech, grossly disorganised or catatonic behaviour, or gross impairment in reality testing.

Agitation

The glossary of technical terms in the DSM-IV-TR provides a definition of agitation. Agitation (psychomotor agitation) is considered to be excessive motor activity associated with a feeling of inner tension. The activity is usually nonproductive and repetitious and consists of such behaviour as pacing, fidgeting, wringing of the hands, pulling of clothes, and inability to sit still.

In addition, agitation may also be defined as excessive motor activity and inappropriate and/or purposeless verbal or motor activity. The agitated patient may display irritability that can rapidly escalate to threatening gestures and language. Agitation may also be characterised by combativeness, assaultiveness, poor impulse control, impaired judgment, decreased sleep, rapid fluctuation of symptoms over time and personal distress.

There is considerable overlap between agitation and ADHD or behaviours that can be associated with ADHD. The individual that suffers from ADHD may display restlessness, excessive talking, impulsivity, impaired judgment, aggressive behaviour, and abrupt mood changes.

Hallucinations

The DSM-IV-TR provides general definitions of hallucinations in the glossary of technical terms section. A hallucination is defined as a sensory perception that has the compelling sense of reality of a true perception but that occurs without external stimulation of the relevant sensory organ. Hallucinations should be distinguished from illusions, in which an actual external stimulus is misperceived or misinterpreted The person may or may not have insight into the fact that he or she is having a hallucination. The term hallucination is not ordinarily applied to the false perceptions that occur during dreaming, while falling asleep, or when awakening. Transient

hallucinatory experiences may occur in people without a mental disorder. Certain states in children may be mistaken for hallucinations including imaginary friends, auras associated with migraine headaches, images of loved ones who have died, some obsessive thoughts in obsessive compulsive disorder (OCD), flashbacks in post-traumatic stress disorder (PTSD), and other sensory phenomenon (for example, scary images from horror movies).

2.2. Epidemiology

In regards to mania, the mean age of a first manic episode is in the early 20s. Some cases of mania start in adolescence and others start after age 50 years. Manic episodes typically begin suddenly and may have a rapid escalation over several days. In 50% to 60% of manic episodes, a major depressive episode will immediately precede or follow.

Bipolar disorder is not an uncommon co-morbidity in a patient diagnosed with ADHD and some children with early onset bipolar disorder can be misdiagnosed as having ADHD due to symptom overlap. Similarly, many patients with early onset schizophrenia may have ADHD-like behaviour preceding the onset of frank psychosis including symptoms such as agitation, behaviour problems and difficulty learning in school.

2.3. Data from Clinical Trials

Data from placebo-controlled clinical trials with atomoxetine (data lock 01 March 2006) were reviewed for the psychiatric adverse events of interest in this report. In the Paediatric Acute Placebo-Controlled ADHD Analysis Group (1597 patients exposed to atomoxetine, 934 patients exposed to placebo) the events agitation (atomoxetine 0.4%, placebo 0.2%, p=.718), hallucination (atomoxetine 0.1%, placebo 0%, p=1.000) and hallucination, visual (atomoxetine 0.1%, placebo 0%, p=1.000) were all uncommonly reported. In the Paediatric Acute Placebo-Controlled ADHD Analysis Group the events mania, hypomania, psychosis, and psychotic disorder were not reported. In the Adult Acute Placebo-Controlled ADHD Analysis Group (540 patients exposed to atomoxetine, 402 patients exposed to placebo) the event agitation was commonly reported. In the Adult Acute Placebo-Controlled ADHD Analysis Group the events mania, hypomania, psychosis, psychotic disorder, and any events relating to hallucinations were not reported. Thus, in the clinical trials' databases for children, adolescents, and adults the psychiatric adverse events of interest to this report were not reported in atomoxetine-treated patients at frequencies that were statistically significantly greater than the frequencies observed in placebo-treated patients.

2.4. Global Atomoxetine Patient Exposure

In order to provide an estimate of patient exposure to atomoxetine, the MAH uses a methodology that combines multiple data sources to estimate a range of values, as well as a most likely estimate for the total number of exposed patients and patient

years of exposure. The sources of data include IMS prescription audit data, IMS National Disease and Therapeutic Index (NDTI) data, and internal bulk sales data

Based on these data, the cumulative number of patient exposures to atomoxetine since first approval on 26 November 2002 through 26 November 2007 (datalock for the current PSUR) is estimated to be 5,085,000 patients which represents 1,715,000 patient years

Therefore, the estimated atomoxetine patient exposure number through 07 November 2007 (datalock for this review) would be approximately 5 million.

3. Methodology

3.1. Global Patient Safety Adverse Event Data Source

The safety database utilised by Global Patient Safety (GPS) at Lilly is the Lilly Safety System (LSS). The LSS is a computerised safety database, implemented in 2005, but containing data from 1983, for the worldwide collection, storage and reporting of adverse events involving Lilly products. It includes serious and nonserious adverse events reported spontaneously from postmarketing experience (including literature and regulatory reports), postmarketing study adverse events described as "serious" and clinical trial adverse events described as "serious". The term "serious" refers to any adverse event that results in death, is life-threatening, is permanently or severely disabling, requires or prolongs inpatient hospitalisation, results in congenital anomaly or is significant for any other reason.

3.2. Global Patient Safety Database Search Criteria

The LSS safety database was searched for all spontaneous atomoxetine case reports through 07 November 2007. The datalock was about 20 days prior to the atomoxetine PSUR 09 datalock of 26 November 2007 to allow sufficient time to assess the topic prior to writing the full PSUR. The adverse event dictionary utilised by the MAH was the Medical Dictionary for Regulatory Activities (MedDRA). The version of the MedDRA dictionary in effect at the time of searching was Version 10.0. There were 4 clinical concepts involved in the overall searches. Those clinical areas were: 1) agitation; 2) mania; 3) psychotic disorders; and 4) hallucinations. The search strategy for agitation utilised the preferred term (PT) of *agitation* and restricted the search to serious case reports only, as agreed upon by the MHRA. To examine mania; there were 6 PTs utilised in the search and included *mania, hypomania, bipolar disorder, bipolar disorder I, bipolar disorder II* and *cyclothymic disorder*. The search for mania focused to the MedDRA dictionary High Level Group Term (HLGT) of *manic and bipolar mood disorders and disturbances* which involved the aforementioned 6 PTs. To examine psychotic disorders; the HLGT of *schizophrenia and other psychotic disorders* was explored and 31 PTs were utilised in the search strategy. Those 31 PTs were *transient psychosis, brief psychotic disorder with postpartum onset, brief psychotic disorder without marked stressors, brief psychotic disorder with marked stressors, alice in wonderland syndrome, delusional disorder erotomanic type, delusional disorder grandiose type, delusional disorder jealous type, delusional disorder mixed type, delusional disorder somatic type, delusional disorder unspecified type, delusional disorder persecutory type, acute psychosis, alcoholic psychosis, senile psychosis, shared psychotic disorder, reactive psychosis, epileptic psychosis, childhood psychosis, psychotic disorder, psychotic disorder due to general medical condition, hysterical psychosis, schizoaffective disorder, schizophreniform disorder, schizophrenia, schizophrenia simple, schizophrenia catatonic type, schizophrenia disorganized type, schizophrenia paranoid type, schizophrenia residual type* and *schizophrenia undifferentiated type*. To examine hallucinations, 4 MedDRA

PTs were utilised in the search and included *hallucination, hallucination auditory, hallucination visual* and *hallucination mixed*.

The search was designed to look at spontaneous case reports only. All reporter types were utilised in the analysis, including cases from consumers as well as health care professionals HCPs). Relatedness was not a criterion used to identify the cases, and therefore all reported events are analysed in the review.

In the overall analysis, an emphasis was placed upon serious case reports from HCPs. However based upon the regulatory request, both serious and nonserious cases were examined for the topics of hallucinations, psychotic disorders and mania. Because of the overlap between agitation and the hyperactive/impulsive symptoms of ADHD (and associated behaviours) only serious cases of agitation were examined.

3.2.1. Individual Case Report Analysis

All the cases from the search were spontaneous in nature.

Individual case reports were assessed along the following parameters in the report:

- Quality (completeness) of the report – The key parameters assessed were the information (or lack of) available for past medical history, concomitant medication, time to onset (TTO), indication for use, dose of atomoxetine, outcome details including dechallenge and rechallenge Increased importance was given to the outcome of the drug-event association when dechallenge and/or rechallenge information was provided by the reporter.
- Causality Assessment – Case reports were assessed for the presence of alternative aetiology or confounding/contributing factors to explain the event (presence of versus absence of confounding factors).

The reporters involved in atomoxetine cases are often consumers The medical information provided and importance of such for consumer reports compared to HCP reports must be carefully weighed when evaluating a drug-event association. Emphasis was placed upon HCP cases and serious reports.

3.2.2. Diagnostic Consideration of Identified Reports

The topics to be examined were quite broad and included psychotic disorders, mania, hallucinations and agitation. General working definitions for these topics were examined through the DSM-IV-TR information.

3.2.3. Etiologic Consideration of Identified Reports

Reports were reviewed for risk factors and confounding factors regarding mania, psychotic disorders, hallucinations and agitation. Careful attention was paid to co-morbidities such as bipolar disorder and schizophrenia. The disease state being treated with atomoxetine may be a significant factor in some of the adverse events found with the search strategy Careful attention was paid to the case discussion surrounding the control of ADHD signs and symptoms. Significant life stressors,

family history of various mental disorders, substance abuse, and physical illness were considered possible confounding factors, as these increase the risk for mania, psychosis, and agitation. Confounding factors will be briefly discussed. Cases with an apparent absence of confounding factors will be discussed if found.

Those cases that did not contain sufficient information to assess etiologic factors (lack of information) were considered to be indeterminate. The remaining cases were categorised into those with the presence of confounding factors and those with the absence of confounding factors

4. Results

4.1. Summary of Clinical Evaluation and Report Categorisation

A search of the GPS atomoxetine database utilising the terms previously listed for agitation, mania, hallucinations and psychotic disorders identified 533 spontaneous case reports. The search strategy was divided into 4 general topics. Among these 533 reports were 4 literature cases, 18 regulatory authority cases and 511 general spontaneous cases from the clinical setting.

There were 17 MedDRA PTs utilised in the search that returned case reports and are listed in Table 1 together with the corresponding number of occurrences.

Table1. Events by Preferred Term for the 4 topics of Mania, Psychotic Disorders, Hallucinations and Agitation

MedDRA Preferred Term	Number of Events	Number of Serious Events
Mania search:		
Mania	157	25
Hypomania	24	6
Bipolar disorder	21	4
Bipolar disorder I	6	0
Subtotal	**208**	**35**
Hallucinations search:		
Hallucination	108	14
Hallucination, auditory	83	17
Hallucination, visual	45	4
Hallucination, mixed	6	2
Subtotal	**242**	**37**
Agitation search:		
Agitation	38	20
Subtotal	**38**	**20**
Psychotic disorders search:		
Delusional disorder, unspecified type	2	1
Delusional disorder, persecutory type	8	1
Acute psychosis	3	2
Psychotic disorder	102	32
Schizoaffective disorder	1	1
Schizophreniform disorder	1	0
Schizophrenia, disorganized type	1	0
Schizophrenia	3	0
Schizophrenia, paranoid type	2	1
Subtotal	**123**	**38**
Total Events	**611 events**	**130 events**

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities

There were 611 adverse events found with the search strategy representing the 533 cases reports. Among the 611 adverse events, 130 adverse events from the search

strategy were categorised as serious. Within the 533 cases there were 137 reports classified as serious.

The 533 cases were categorised as serious in 137 reports and nonserious in 396 reports.

Among the 533 case reports, the reporter was a HCP in 401 cases and a consumer in 132 cases (24.8%).

Among the 137 serious cases, the reporter was a HCP in 112 cases (81.8%) and a consumer in 25 cases (18.2%).

Among the 396 nonserious cases, the reporter was a HCP in 289cases (73%) and a consumer in 107 cases (27%).

4.2. Patient demographics (Gender, Age)

Table 2. **Age and Gender Distribution for Mania, Psychotic Disorders, Hallucinations and Agitation Case Reports (Serious and Nonserious cases)**

Age Category	Male	Female	Unknown gender	Total
0 to 5 years	13	3	0	16
6 to 12 years	180	54	21	255
13 to 17 years	81	21	6	108
18 to 64 years	46	41	0	87
≥65 years	1	0	0	1
Unknown age	39	25	2	66
Total	**360**	**144**	**29**	**533**

Overall, the gender was provided for 504 cases and 71% of the patients were male. The ages were provided in 467 of 533 cases and 363 (77.8%) of those patients with an age provided were between 6- and 17-years-old.

The age range for the cases displayed in Table 2 was 3- to 67-years-old. The mean age for all cases (serious combined with nonserious) was 14.7-years-old.

Table 3. **Age and Gender Distribution for Mania, Psychotic Disorders, Hallucinations and Agitation Case Reports (Serious Cases Only)**

Age Category	Male	Female	Unknown gender	Total
0 to 5 years	3	0	0	3
6 to 12 years	49	13	2	64
13 to 17 years	23	9	1	33
18 to 64 years	15	10	0	25
≥65 years	0	0	0	0
Unknown age	7	4	1	12
Total	**97**	**36**	**4**	**137**

The gender distribution for the serious case reports with stated gender was 73% male and 27% female. Approximately 88% of the serious case reports provided a patient age. For the 125 cases with a stated age, 78% had a patient between the ages of 6- and 17-years-old. The age range for the serious case reports was 5- to 43-years-old. The mean age was 14.3-years-old for the serious case reports.

4.3. Overview of Atomoxetine Serious Case Reports Regarding Co-Morbidities, Clinically Significant Factors and Dechallenge/Rechallenge Information

Attention-deficit/hyperactivity disorder that is poorly controlled as a disease state may be associated with signs and symptoms representing psychiatric issues. The actual terminology utilised by a reporter may not lend itself to an obvious MedDRA PT choice. For example, a symptom description that is coded to hallucination may at times involve an external stimulus that is misinterpreted by a paediatric patient and is an illusion rather than a hallucination. Therefore, some case reports coded to PTs such as mania, psychotic disorders, hallucination and agitation may not be such when a case narrative is explored.

Because the atomoxetine indication for use was ADHD in the vast majority of case reports, the aforementioned challenge presented itself.

However, all 137 serious case reports were examined closely for co-morbid conditions and confounding factors. These cases will be discussed in the sections that follow.

There were 44 serious cases (38 serious psychotic disorder adverse events) that involved PTs from the psychotic disorder search, 22 serious cases (20 serious agitation adverse events) that involved agitation, 45 serious cases (35 serious mania adverse events) that involved PTs from the mania search and 52 serious cases (43 serious hallucination adverse events) that involved PTs from the hallucinations search. The case IDs and general information are displayed in the following tables. When a case ID does not mention the coded PT is it was coded to *psychotic disorder*.

4.3.1. Psychotic Disorder Serious Cases

Table 4. Co-Morbid Conditions or Confounding Factors in Serious Cases with Psychotic Disorder Search Strategy as Adverse Events

Case IDs (n=44)	Co-morbid conditions or Confounding factors
	Acute overdose of atomoxetine and acetaminophen
	Anoxic brain injury history - also coded to *mania*
	Postpartum depression history and acute infection treated with macrolide antibiotics
	Tourette's syndrome and mental retardation
	Postpartum depression and acute infection treated with macrolide antibiotics – also coded to *hypomania*
	Obsessive compulsive disorder, depression and failure to thrive – also coded to *hallucination*
	Asperger's syndrome and oppositional defiant disorder – also coded to *mania*
	Mental retardation and sleep deprivation
	Mental retardation and exacerbation of depression
	Alcohol and marijuana abuse – also coded to *hallucination, auditory*
	Anger management problems and active urinary tract infection
	Anxiety history and strong family history of bipolar disorder
	Depression history and anger management problems
	Depression and mood swing history
	Learning disorder and depression history
	Significant social stressors at time of symptoms (change in schools, aunt diagnosed with cancer, father moved out of house and abruptly stopped methylphenidate after 3 years use)
	Long psychiatric history including suicidal ideation – also coded to *hallucination, auditory*
	Generalized anxiety disorder and panic attacks – also coded to *bipolar disorder*
	Acute atomoxetine overdose (up to 640 mg) leading to psychiatric symptoms
	Major depression history and family history of bipolar disorder - also coded to *mania* and *agitation*
	Family history of psychosis and manic attacks - also coded to *mania* and *hallucination*
	Bipolar disorder history

(continued)

Table 4. **Co-Morbid Conditions or Confounding Factors in Serious Cases with Psychotic Disorder Search Strategy as Adverse Events (Concluded)**

Case IDs (n=44)	Co-morbid conditions or Confounding factors
	Depression, panic attacks and family history of bipolar disorders
	Family history of depression and visual hallucinations – also coded to *hypomania*
	History of psychosis and psychotic behavior
	History of paranoid schizophrenia along with ADHD – also coded to *hallucination visual, hallucination auditory* and *schizophrenia paranoid type*
	Probable history of dissociative disorder prior to atomoxetine therapy
	History of irritability problems
	Anxiety, social aggression anger against others, including mother. Family history of mental disease. Started on neuroleptic medication.
	Family history of schizophrenia and schizoaffective disorder. Patient diagnosed with bipolar disorder – also coded to *bipolar disorder* and *hallucinations mixed*
	Family history of emotional problems - patient set fire to room
No apparent co-morbid conditions or confounders	
Unknown medical history (n=12)	
Cases from Table 4 in other tables	

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; n = number of cases.

There were 44 serious cases among the 137 serious reports that contained a PT from the psychotic disorders search; although, in some cases, the event which met serious criteria was not the psychiatric disorder PT.

All 44 cases are displayed in Table 4 above.

There were 12 cases among these 44 reports that did not provide sufficient medical history to assess for confounding factors.

There was a single notable case of psychosis among the 44 reports that was without apparent confounding factors. The case is discussed as follows

Case was reported from a consumer and provided a statement that mentioned a negative psychiatric history. However, medical and family history were not reported. The patient was a eceiving 40 mg daily of atomoxetine in the treatment of ADHD. Amphetamine/dextroamphetamine therapy had been active and was continued after the start of atomoxetine but underwent a dose reduction. Upon an increase of atomoxetine to 60 mg daily, the patient began to exhibit mood swings, insomnia, psychosis (paranoid behaviour) and irritability. The patient was hospitalised, and atomoxetine was discontinued. A drug screen was negative. The patient made a full recovery

Dechallenge/rechallenge information was explored for these 44 psychotic disorder adverse event cases. In 2 cases atomoxetine was continued and in another 11 cases the disposition of atomoxetine could not be determined. Therefore, in 31 cases atomoxetine was discontinued. Upon assessing the outcome of atomoxetine dechallenge in these 31 cases, it was determined that a positive dechallenge took place in 13 cases, a negative dechallenge occurred in 6 cases and in 12 cases the outcome of dechallenge could not be determined

There was 1 case that involved an atomoxetine rechallenge among these 44 serious cases. However, the rechallenge information addressed auditory hallucinations rather than the psychotic disorder

4.3.2. Agitation Serious Cases

Table 5. Co-Morbid Conditions or Confounding Factors in Serious Cases with Agitation as an Adverse Event

Case IDs (n=22)	Co-morbid conditions or Confounding factors
	Aggressive and violent behavior history, recent school stressors and problems
	History of social behavior deemed hyperkinetic
	Autistic with severe learning disorder
	Neuroleptic therapy (aripiprazole) considered suspect drug. Positive dechallenge to aripiprazole
	Asperger's syndrome and "high" anxiety patient
	Long standing history of impulsivity and aggression
	Autistic disorder and sleep deprivation
	Autistic spectrum disorder with sleep difficulties
	Learning disability and conduct disorder – **also coded to *mania***
	Development of urticarial rash in 9-year-old male
	Autistic disorder
	Tourette's syndrome and pervasive developmental disorder
	Major depressive disease and family history of bipolar disorder – **also coded to *mania* and *psychotic disorder***
	Allergy to dyes – reaction to dye in atomoxetine capsule?
	Bipolar disorder history
	Seizure activity leading to status epilepticus
	Cerebral palsy. Development of hallucinations leading to agitation – **also coded to *hallucination***
	History of psychotic depression and post traumatic stress disorder. Acute changes and in ICU at time of agitation and hallucinations – **also coded to *hallucination visual* and *hallucination auditory***
	Development delayed patient
	Schizoaffective bipolar disorder history along with mental retardation and daily hallucinations – **also coded to *hallucination***

(continued)

Table 5. Co-Morbid Conditions or Confounding Factors in Serious Cases with Agitation as an Adverse Event (Concluded)

Case IDs (n=22)	Co-morbid conditions or Confounding factors
No apparent co-morbid conditions or confounders	
Unknown medical history (n=1)	
Cases from Table 5 in other tables	

Abbreviations: ICU = intensive care unit; n = number

There were 22 serious cases that involved agitation as an adverse event. Twenty case reports contained a serious adverse event of agitation. Two of the cases have a nonserious adverse event of agitation. All 22 case reports are displayed in Table 5 above.

The case that follows was considered to be without significant confounders. All of the other case reports either lack a medical history or provided a medical history that contained co-morbid conditions or other factors that would confound the aetiology of the agitation.

Case did not have any apparent confounding factors or co-morbidites of significance. The patient was taking montelukast as a concomitant drug. The patient was considered to have no known significant medical history. The patient reportedly experienced severe agitation and psychotic mania with auditory hallucinations Auditory hallucinations were not considered as an adverse event and were classified as homicidal ideation due to their theme Atomoxetine was discontinued and therapy was started with lithium, valproic acid and risperidone.

Dechallenge/rechallenge information was explored for these 22 agitation adverse event cases. In 3 cases atomoxetine was continued and in 1 case the disposition of atomoxetine could not be determined. Therefore, in 18 cases atomoxetine was discontinued. Upon assessing the outcome of atomoxetine dechallenge in these 18 cases it was determined that a positive dechallenge took place in 10 cases, a negative dechallenge occurred in 2 cases and in 6 cases the outcome of dechallenge could not be determined.

There were 2 cases from the agitation cases with rechallenge of atomoxetine. In case atomoxetine underwent a positive rechallenge. This case is discussed in **section 4.7 (Dechallenge / Rechallenge)**. In case the results of the rechallenge cannot be determined.

4.3.3. Mania/Hypomania Serious Cases

Table 6. **Co-Morbid Conditions or Confounding Factors in Serious Cases Identified with Mania Search Strategy as Adverse Events**

Case IDs (n=45)	Co-morbid conditions or Confounding factors
	History of bipolar disorder and treated with lithium
	Anxiety and diagnosed with bipolar I disorder
	Autistic spectrum disorder and epilepsy
	Oppositional defiant disorder and depression
	Mania history and history suggestive of bipolar I disorder – manic episodes while on antidepressants
	Law school student with stress
	Poorly controlled ADHD, depression and strong family history of bipolar disorder
	History of manic episodes and olanzapine therapy
	History of bipolar disorder treated with lithium and sertraline
	History of bipolar disorder and seizure disorder treated with valproic acid and clonidine
	History of bipolar disorder. Developed symptoms of bipolar disorder after stopping atomoxetine.
	History of bipolar disorder and had aggravation of symptoms. Atomoxetine continued.
	Sleep disorder history and diagnosis of bipolar disorder
	Drug screen found marijuana and cocaine in system, Family history of bipolar disorder.
	Family history (both parents) of bipolar disorder
	History of bipolar disorder, conflict with spouse and boss at work
	Learning disability patient with confrontational behavior - also coded to *agitation*
	Fetal alcohol syndrome and history of bipolar disorder – also coded to *bipolar disorder*
	History of mania, anxiety and seizure disorder. Diagnosed with childhood bipolar disorder

(continued)

Table 6. Co- Morbid Conditions or Confounding Factors in Serious Cases Identified with Mania Search Strategy as Adverse Events (Continued)

Case IDs (n=45)	Co-morbid conditions or Confounding factors
	History of bipolar disorder and positive urinalysis for phencyclidine - also coded to *hallucination*
	Family history of mental disease and significant social stressors
	Anoxic brain injury history - also coded to *acute psychosis*
	Post partum depression and acute infection treated with macrolide antibiotics – also coded to *psychotic disorder*
	Asperger's syndrome and oppositional defiant disorder – also coded to *psychotic disorder*
	Generalized anxiety disorder and panic attacks – also coded to *psychotic disorder*
	Major depression history and family history of bipolar disorder - also coded to *psychotic disorder* and *agitation*
	Family history of depression and visual hallucinations – also coded to *psychotic disorder*
	Family history of psychosis and manic attacks - also coded to *psychotic disorder* and *hallucination*
	Family history of schizophrenia and schizoaffective disorder. Patient diagnosed with bipolar disorder – also coded to *schizoaffective disorder* and *hallucinations mixed*
	Bipolar disorder, substance abuse (alcoholic), and borderline personality disorder
	Depression and significant school stressors
	Family history of depression and patient diagnosed with bipolar disorder
	Disturbance in social interaction and anger management issues

(continued)

Table 6. Co- Morbid Conditions or Confounding Factors in Serious Cases Identified with Mania Search Strategy as Adverse Events (Concluded)

Case IDs (n=45)	Co-morbid conditions or Confounding factors
No apparent co-morbid conditions or confounders	
Unknown medical history (n= 10)	
Cases from Table 6 in other tables	

Abbreviations: ADHD = attention-deficit/hyperactivity

There were 45 serious cases that contained a PT from the mania search Some of the mania PTs were considered nonserious adverse events. All 45 serious case reports are displayed in Table 6 above. There were 10 case reports that did not provide a past medical history. Many of the case reports contain significant past medical history or had a patient undergoing an acute change that was important in the development of mania or hypomania.

There were 2 cases considered to be without apparent confounding factors The cases are discussed in the section that follows.

Case was a literature case that concerned an with a history of treatment with amphetamines The patient had been diagnosed with ADHD 2 years prior to starting atomoxetine Symptoms without medication included inattention, distractibility, excessive talking, restlessness and impulsivity. Concomitant medications were not provided. Two weeks after the start of atomoxetine, the patient displayed elevated and expansive mood, irritability, pressured speech along with psychomotor agitation consistent with a manic episode. Atomoxetine was discontinued, and the patient's behaviour improved over 7 days. Upon follow-up 1 year later, the patient was not taking any medications and was behaving in school.

Case has been mentioned in Table 5 and discussed within **Section 4.3.2. (agitation reports).**

Dechallenge/rechallenge information was explored for these 45 mania adverse event cases. In 7 cases atomoxetine was continued and in 6 cases the disposition of atomoxetine could not be determined. Therefore, in 32 cases atomoxetine was discontinued. Upon assessing the outcome of atomoxetine dechallenge in these 32 cases it was determined that a positive dechallenge took place in 12 cases, a negative dechallenge occurred in 8 cases and in 12 cases the outcome of dechallenge could not be determined.

There were not any cases among the adverse events of mania that involved a rechallenge for atomoxetine.

4.3.4. Hallucination Serious Cases

Table 7. Co-Morbid Conditions or Confounding Factors in Serious Cases with Hallucination Search Strategy as Adverse Events

Case IDs (n=52)	Co-morbid conditions or Confounding factors
	History of panic attacks. Patient had brief auditory hallucinations with panic attack
	Off atomoxetine at time of auditory hallucinations. Considered possible withdrawal symptom.
	Depression, mood lability history, oppositional defiant disorder, victim of abuse
	Family history of schizophrenia
	Depression and anxiety disorder. Hallucinations followed a syncopal episode.
	Learning disability and history of deprivation and trauma.
	Blood pressure fluctuations with elevated readings
	Suicidal ideation with behavioral disorder
	History of delusions and hallucinations
	Off atomoxetine at time of symptoms. Had loss of consciousness and considered changes as possible discontinuation syndrome
	History of mood swings and altered perceptions while on amphetamine
	Significant life stressors. 9 year-old with parents going through divorce
	Explosive emotional episode history, depression and bipolar disorder medical history
	Sleep and distractibility problems
	Life stressors including recent death of grandmother
	Bipolar disorder history with poor symptom control. History of auditory hallucinations
	Substance abuse history and depression
	Seizure disorder, developmental delay and history of depression
	Active infection treated with cefadroxil and pseudoephedrine and poorly controlled ADHD
	History of bipolar disorder and positive urinalysis for phencyclidine - also coded to *mania*
	Family history of psychosis and manic attacks - also coded to *psychotic disorder* and *mania*

(continued)

Table 7. Co-Morbid Conditions or Confounding Factors in Serious Cases with Hallucination Search Strategy as Adverse Events (Continued)

Case IDs (n=52)	Co-morbid conditions or Confounding factors
	Cerebral palsy and development hallucinations leading to agitation. – also coded to *agitation*
	History of psychotic depression and post traumatic stress disorder. Acute changes and in ICU at time of agitation and hallucinations – also coded to *agitation*
	Schizoaffective bipolar disorder history along with mental retardation and daily hallucinations – also coded to *agitation*
	Obsessive compulsive disorder, depression and failure to thrive – also coded to *psychotic disorder*
	Alcohol and marijuana abuse - also coded to *psychotic disorder*
	Long psychiatric history including suicidal ideation - also coded to *psychotic disorder*
	History of paranoid schizophrenia along with ADHD - also coded to *psychotic disorder*
	Family history of schizophrenia and schizoaffective disorder. Patient diagnosed with bipolar disorder - also coded to *schizoaffective disorder* and *bipolar disorder*
	Asperger's syndrome, depression, "horrible" mood swings and acute ingestion of 1150 mg trazodone
	Development of seizure activity
	Acute ingestion of atomoxetine (overdose symptoms included hallucinations)
	Acute ingestion of 400 mg atomoxetine leading to symptoms including hallucinations
	Amphetamine therapy suspected and possible drug interaction
	Bipolar disorder and auditory hallucination history

(continued)

Table 7. Co-Morbid Conditions or Confounding Factors in Serious Cases with Hallucination Search Strategy as Adverse Events (Concluded)

Case IDs (n=51)	Co-morbid conditions or Confounding factors
	History of auditory hallucinations
	Autistic spectrum disorder, epilepsy and sleep disturbances
No apparent co-morbid conditions or confounders	
Unknown medical history (n=14)	
Cases from Table 7 in other tables	

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ICU = intensive care unit; n = number of cases

There were 52 serious reports that contained a PT from the hallucinations search strategy. All 52 serious cases are displayed in Table 7 above. Nine of the 52 serious cases contain an adverse event from the hallucinations search that was non-serious.

The majority of serious case reports in Table 7 contained significant co-morbid conditions or had confounding factors in the medical history or lacked sufficient information to assess. There were 14 cases that did not provide a medical history.

There was a single case that was without apparent confounding factors. The case is as follows: Case that was considered as not having any medical history that was significant. The patient was not taking any concomitant drugs. After receiving atomoxetine daily for approximately 40 days, the patient experienced auditory hallucinations. Following a psychological assessment, it was determined to stop atomoxetine and the auditory hallucinations resolved.

Dechallenge/rechallenge information was explored for these 52 hallucination adverse event cases. In 6 cases atomoxetine was continued and in 10 cases the disposition of atomoxetine could not be determined. Therefore, in 36 cases atomoxetine was discontinued. Upon assessing the outcome of atomoxetine dechallenge in these 36 cases it was determined that a positive dechallenge took place in 12 cases, a negative dechallenge occurred in 10 cases and in 14 cases the outcome of dechallenge could not be determined.

There was 1 case among the adverse events of hallucination (auditory hallucinations) that involved the rechallenge of atomoxetine. The patient underwent a positive rechallenge to atomoxetine in regards to auditory hallucinations.

4.4. Diagnostic Criteria Assessment – Serious Cases

All 137 serious case reports were examined for the signs and symptoms discussed in the background section of the current report. All 137 serious case reports were spontaneous in nature and many reports did not provide sufficient information regarding the patient situation(s) to thoroughly subject the signs and symptoms to the definitions.

Upon reading the full case narratives for the 137 serious case reports it was very difficult to determine the validity of the MedDRA PT coding based on the limited information within many of the spontaneous reports. Most of the serious cases of agitation, mania, psychosis, and hallucinations had significant co-morbidities or confounding factors for the events of interest.

A significant number of the cases may represent a patient with mood swings associated with the atomoxetine ADHD indication for use or associated with an aspect of an already present co-morbidity.

4.5. Etiologic Criteria Assessment – Serious Cases

The 137 serious case reports were evaluated for confounding factors. Table 4, Table 5, Table 6 and Table 7 have divided the case reports into psychotic disorders, agitation, mania and hallucinations respectively. There were a number of case reports

with multiple adverse events from the searches. In those situations, the case will be displayed in multiple tables based upon the adverse events.

4.6. Nonserious Case Assessments

There were 396 nonserious case reports found with the search methodology. These cases were examined and assessed for dechallenge and rechallenge information along with the actual descriptions of the coded adverse events.

4.6.1. Psychotic Disorders Nonserious Cases

There were 74 nonserious case reports that involved a PT from the psychotic disorders search strategy.

The 74 case reports were closely examined for dechallenge/rechallenge information

In 11 nonserious case reports (15%), atomoxetine was continued and the adverse events were managed. In 46 nonserious case reports, atomoxetine was discontinued while in 17 patients the atomoxetine disposition could not be determined. Among the 46 nonserious cases with dechallenge of atomoxetine, 21 displayed a positive dechallenge, 5 showed a negative dechallenge and in 20 patients the results of dechallenge could not be determined. In doing the assessments, the dechallenge information was strictly applied to the psychotic disorder psychiatric adverse event and not to other adverse events. When the dechallenge information only involved outcomes on non-psychiatric events, the dechallenge outcome was categorised as undetermined.

There were 2 cases among the 74 nonserious psychotic disorder reports that discussed rechallenge. In both cases atomoxetine underwent a negative rechallenge regarding the psychotic disorder adverse event. In Case [redacted] who reportedly experienced psychotic behaviours and atomoxetine was discontinued. The result of dechallenge is not discussed. However, atomoxetine was rechallenged without psychotic disorder symptoms. The other case [redacted] that became psychotic and, atomoxetine was discontinued. Atomoxetine had been administered at 60 mg daily when symptoms developed. Atomoxetine underwent a negative rechallenge and was being administered at 40 mg daily.

4.6.2. Agitation Nonserious Cases

There were 16 nonserious case reports that involved agitation as a PT within the 533 cases analysed. These agitation cases were found by searching for all nonserious case reports that involved mania, psychotic disorders and hallucination. The basic search strategy for agitation only looked for serious adverse events, but nonserious agitation events were present in cases found with the other 3 searches.
Dechallenge/rechallenge information for these 16 nonserious agitation case reports only provided a small subset of all nonserious agitation adverse events within the atomoxetine safety database. Therefore, these 16 cases were not assessed for dechallenge/rechallenge information.

The 16 nonserious agitation case reports were examined for general information in regards to actual adverse event description The case information within this review suggests that signs and symptoms associated with ADHD may explain a significant number of these agitation adverse events.

4.6.3. Mania/ Hypomania Nonserious Cases

There were 127 nonserious case reports that involved a PT from the mania search strategy.

The 127 case reports were closely examined for dechallenge/rechallenge information.

In 26 nonserious case reports (20%), atomoxetine was continued, and the adverse events were managed. In 70 nonserious case reports, atomoxetine was discontinued while in 31 patients the atomoxetine disposition could not be determined Among the 70 nonserious cases with dechallenge of atomoxetine, 32 displayed a positive dechallenge, 3 showed a negative dechallenge and in 35 patients the results of dechallenge could not be determined In doing the assessments, the dechallenge information was strictly applied to the mania/hypomania psychiatric adverse event and not to other adverse events. When the dechallenge information only involved outcomes on non-psychiatric events, the dechallenge outcome was categorised as undetermined.

There were 5 cases among the 127 nonserious mania reports that discussed an aspect of rechallenge. Three of those 5 cases involved a modified rechallenge, 1 case had a negative rechallenge and 1 case had rechallenge without providing the outcome.

Three cases came from the same reporter and involved an increase in atomoxetine dosing. All 3 cases involved a paediatric patient reportedly developing a manic episode after starting atomoxetine. In each case, the atomoxetine dose was increased (modified rechallenge), and the mania subsided.

Another case that reportedly developed mania. Atomoxetine underwent a positive dechallenge that included the addition of a mood stabilizer. At some time (undetermined interval) later, atomoxetine was rechallenged without mania symptoms (negative rechallenge).

The final case had an atomoxetine rechallenge and the outcome was not provided other than stating atomoxetine was continued.

4.6.4. Hallucination Nonserious Cases

There were 175 nonserious case reports that involved a PT from the hallucination search strategy. The primary PTs used in these 175 cases were *hallucination* (108 adverse events), *hallucination auditory* (83 adverse events) and *hallucination visual* (45 adverse events).

The 175 case reports were closely examined for dechallenge/rechallenge information.

Cumulatively, the 137 serious psychiatric adverse event reports were reviewed for dechallenge/rechallenge information. In 15 serious case reports, atomoxetine was continued, and the adverse events were managed. In 97 serious case reports, atomoxetine was discontinued while in 25 patients the atomoxetine disposition could not be determined. Among the 97 serious cases with dechallenge of atomoxetine, 31 displayed a positive dechallenge, 19 showed a negative dechallenge and in 47 patients the results of dechallenge could not be determined. In doing the assessments, the dechallenge information was strictly applied to the psychiatric adverse events and not to any non-psychiatric adverse events. When the dechallenge information only involved outcomes on non-psychiatric events, the dechallenge outcome was categorised as undetermined

There were 4 cases of atomoxetine rechallenge among the 137 serious case reports. There were 2 serious cases with a positive rechallenge to atomoxetine and 2 serious cases without an outcome on rechallenge.

Case with an unknown medical history and concomitant drug history. The patient reportedly developed auditory hallucinations after 24 to 48 hours of an increase of atomoxetine 25 mg daily from an undetermined period of time on atomoxetine 18 mg daily. The patient was hospitalised, atomoxetine was discontinued and the hallucinations subsided. Atomoxetine 10 mg daily was rechallenged, and the auditory hallucinations returned. All psychological evaluations while hospitalised were within normal limits.

The other case of positive rechallenge concerned a with a medical history that included autism and a severe learning disorder that reportedly developed agitation, aggression and overactivity while on atomoxetine. Atomoxetine underwent a positive dechallenge over the course of 48 hours. Atomoxetine 20 mg daily had been administered for 1 day only when the symptoms were reported. A rechallenge of atomoxetine was reported as positive. No information was available on the rechallenge symptoms.

The information obtained from the assessment of dechallenge and rechallenge results for the serious case reports raises some questions regarding the influence of atomoxetine on psychiatric adverse events but does not provide any compelling information regarding the causality of the psychiatric adverse events of interest. Among the 50 serious cases with dechallenge information, a significant number (19 cases) provided information regarding a negative dechallenge with 31 suggesting a positive dechallenge.

There were 396 nonserious case reports in the overall assessment. However, upon evaluating dechallenge/rechallenge information for all psychiatric adverse events it was discovered that a significant number of the 396 nonserious case reports contained PTs from more than 1 of the reviewed topics.

There were 175 nonserious case reports involving hallucinations, 127 nonserious case reports involving mania/hypomania, 16 nonserious case reports involving agitation and 74 nonserious case reports involving psychotic disorders. When a case report contained more than 1 psychiatric adverse event from the searches, information was

In 56 nonserious case reports (32%), atomoxetine was continued and the adverse events were managed. In 89 nonserious case reports, atomoxetine was discontinued while in 30 patients the atomoxetine disposition could not be determined. Among the 89 nonserious cases with dechallenge of atomoxetine, 48 displayed a positive dechallenge, 10 showed a negative dechallenge and in 31 patients the results of dechallenge could not be determined. In doing the assessments, the dechallenge information was strictly applied to the hallucination psychiatric adverse event and not to other adverse events. When the dechallenge information only involved outcomes on non-psychiatric events, the dechallenge outcome was categorised as undetermined.

There were 3 cases of atomoxetine rechallenge among the 175 nonserious case reports. There were 2 nonserious cases with a positive rechallenge to atomoxetine and 1 case of a negative rechallenge to atomoxetine.

Case with a medical history not provided other than past methylphenidate therapy. The patient was currently not receiving any concomitant drugs. The patient had received atomoxetine 40 mg daily for about 20 days and experienced "seeing strange men watching her" during the night. The case information was coded to *hallucination visual*. Atomoxetine was discontinued, and the reported visual hallucinations abated. Atomoxetine was restarted, and the patient's description of seeing things returned. However, atomoxetine therapy was continued and diagnostic tests were planned regarding an electroencephalogram (EEG).

The second case of a positive rechallenge involved with an unknown medical history that reported hallucinations. The reported hallucinations were not described by the mother. Atomoxetine 40 mg daily was the only drug being taken by the patient. Atomoxetine underwent a positive dechallenge (mother stopped the drug) followed by a positive rechallenge in regards to the hallucinations. Atomoxetine than underwent a second positive dechallenge. The case information was initially provided by the mother of the patient with physician followup.

Case with an unknown medical history receiving concomitant methylphenidate that reportedly experienced hallucinations. The hallucinations were not described. Atomoxetine was discontinued and later rechallenged without further development of hallucinations. The case information suggests the hallucinations may have been disease state symptoms or associated with methylphenidate and somewhat controlled with atomoxetine.

There were no other cases of atomoxetine rechallenge.

4.7. Overview of Dechallenge/Rechallenge Information

The atomoxetine dechallenge/ information was carefully examined to address the psychosis, agitation, mania, and hallucinations adverse events. Following the tables for psychotic disorder (Table 4), agitation (Table 5), mania (Table 6) and hallucinations (Table 7) can be found dechallenge/rechallenge information regarding the 4 general psychiatric serious adverse event categories.

explored regarding dechallenge/rechallenge for each psychiatric event, and the case was counted more than once. When the nonserious cases of hallucinations, mania/hypomania, and psychotic disorders were reviewed for rechallenge cases, there were 10 cases that reported atomoxetine rechallenge. In the 2 nonserious cases of psychotic disorder adverse events that reported rechallenge, both were considered negative. In the 5 nonserious cases of mania/hypomania adverse events that reported rechallenge, 1 case did not report an outcome and 4 of the rechallenges were negative. In the 3 cases of hallucinations adverse events that reported rechallenge, 1 case did not report an outcome and 2 cases reported positive rechallenge.

5. Discussion and Analysis of Results

There were 533 spontaneous reports with MedDRA coding suggestive of mania, agitation, psychotic disorders and hallucinations in the GPS database (LSS). The 533 spontaneous reports were further subdivided into 137 serious case reports and 396 non-serious case reports. All of the searches were cumulative and examined serious and nonserious adverse events with the exception of searching for the PT of *agitation*. The search for agitation looked for serious agitation adverse events and nonserious adverse events of agitation contained in a serious case. It was agreed with MHRA to only review serious cases of agitation because of symptom overlap between ADHD and agitation.

There were not any cases with a fatal outcome among the 137 serious case reports.

The 137 serious case reports were assessed in regards to confounding factors and numerous co-morbidities were present. Most of the serious cases of agitation, mania, psychosis, and hallucinations had significant co-morbidities or confounding factors for the events of interest. There were 4 unique serious case reports identified with the apparent absence of confounding factors. There was 1 case of psychosis reported by a consumer that lacked apparent confounding factors although no medical or family history was provided. Although case documentation provides a good description of apparent psychosis, attributing this case to atomoxetine is difficult without physician confirmation. For the serious case of agitation apparently without confounding factors (although no family history is reported), it appears that the agitation was part of an apparent manic or hypomanic episode. In most of the other cases of agitation, it seems that there are other likely explanations for the agitation (based upon review of co-morbidities and confounding factors) or that these cases represented poorly controlled ADHD or other behaviour problems commonly associated with ADHD. There is 1 case of mania reported by a child psychiatrist that lack apparent co-morbidity or confounding factors. Although this case could represent an early onset bipolar disorder instead of ADHD, the reporter did not think any of the patient's ADHD symptoms would suggest mania. There is 1 case of hallucinations that is apparently not confounded although a family history is unknown. Although the patient's hallucinations resolved after atomoxetine dechallenge, other details of a psychological assessment performed are not available to more precisely determine causality.

Dechallenge and rechallenge information was assessed for all 533 atomoxetine reports with special emphasis upon the 137 serious case reports. Although traditionally cases with positive dechallenge are thought to provide evidence for a causal association, positive dechallenge in the case of events that maybe be episodic is of uncertain value. Agitation, hallucinations, psychosis, and mania can be episodic, and spontaneous remissions are possible in each of these events. There were 4 rechallenge cases found within the 137 serious cases that included 2 positive rechallenges and 2 cases without information on the outcome of rechallenge. One of the serious cases with positive rechallenge reported recurrence of agitation, and the other case reported recurrence of hallucinations.

Dechallenge and rechallenge information for the 396 nonserious case reports is not displayed cumulatively due to the analysis process. A significant number of the nonserious cases contained PTs from more than 1 of the 4 areas for review. There were 10 cases that reported rechallenge information, including 2 cases where hallucination events recurred after atomoxetine was rechallenged.

6. Conclusion

The Company Core Data Sheet (CCDS) contains the adverse events of mood swings, aggression, hostility and suicidal ideation in regards to psychiatric symptoms associated with atomoxetine treatment. The adverse events of agitation, mania, hypomania, psychotic disorders and any associated hallucinations are all considered unlisted.

The estimated patient exposure through 07 November 2007 (datalock of this review) is 5 million. There were 611 adverse events (serious and nonserious combined) found with the cumulative search strategy. The most frequently observed adverse events included 157 adverse events coded to the PT of *mania*, 108 adverse events coded to the PT of *hallucination* and 102 adverse events coded to the PT of *psychotic disorder*. In addition, the adverse event of agitation was searched looking for serious adverse events only or an agitation adverse event contained within a case from the other 3 searches (mania, psychotic disorder, hallucination). There were 38 adverse events of agitation. All of the adverse events utilised for the searches would be considered very rarely reported.

Assessment of the cases retrieved by the search of spontaneous was difficult because multiple comorbidities and confounders were found in the vast majority of cases, or the lack of pertinent details in other cases. Comorbidities and confounders relevant to agitation, mania, psychosis, and hallucinations in this review included family or personal history of psychotic illnesses and bipolar disorder, other psychiatric disorders, use of other psychotropic medications, significant stressors, medication overdoses, illicit substance use, acute physical illnesses, neurological and developmental disorders, and history of aggression or a disruptive behaviour disorder like conduct disorder or oppositional defiant disorder (relevant to agitation) Symptom overlap between ADHD and mania events and agitation events also make case evaluation difficult. There are very few unconfounded cases for each of these events of interest within the serious case reports. A significant number of the nonserious case reports did not provide an adequate history for assessment of confounders. Based upon the information available it appears unlikely that atomoxetine is causally related to the majority of these events.

Attention-deficit/hyperactivity disorder as a disease state presents patients with significant symptoms and co-morbidities that provide confounding factors and competing aetiology in the development of psychiatric and nervous system adverse events. The patient population would appear to be more significant in the aetiology of these psychiatric adverse events than would atomoxetine treatment.

Lilly currently believes that there is not enough evidence from clinical trial data and analysis of spontaneously reported events to warrant addition of events involving agitation or mania/hypomania to atomoxetine labeling. While placebo controlled clinical trials of atomoxetine in children and adolescents had reports of hallucinations, these events were uncommon and the descriptions of these events were vague. Likewise, there have been spontaneous reports of psychotic symptoms and hallucinations associated with atomoxetine use in children, adolescents, and adults,

but causality is difficult to assess in many cases. Also, there is uncertainty as to whether some of the events represent true hallucinations or psychotic events due to vague descriptions and the possibility that the events reported might represent other phenomena. Nevertheless, Lilly will consider adding language regarding psychotic symptoms including hallucinations to the CCDS.