ANNEX 4

Psychiatric Adverse Events including Cumulative review of spontaneous reports of suicidal and self-injurious behaviour

1.0 Overview of Reports of Psychiatric Adverse Events associated with Atomoxetine

Up to the 22 September 2005 the MAH has received a total of 6,751 reports involving 10,988 psychiatric reactions. Of these reports 2,383 were from healthcare professionals (hcps).

The reactions where more than 50 reports have been received are provided in the table below. As can be seen from this table the most commonly reported reactions (all reports or hcps reports only) include insomnia, abnormal behaviour, aggression mood swings, irritability and agitation.

Reaction PT	Total No of reports	No of HCP reports	Non HCP reports
Insomnia	1159	250	909
Abnormal behaviour	989	263	726
Aggression	763	314	449
Mood swings	763	188	575
Irritability	599	185	414
Crying	491	105	386
Anxiety	449	164	285
Depression	393	140	253
Agitation	363	177	186
Anger	354	106	248
Nervousness	275	49	226
Middle insomnia	201	18	183
Sleep disorder	169	32	137
Suicidal ideation	143	104	39
Impulsive behaviour	134	27	107
Depressed mod	121	33	88
Mania	115	96	19
Emotional distress	112	27	85
Emotional disorder	111	23	88
Thinking abnormal	108	23	85
Nightmare	106	51	55
Initial insomnia	103	8	95
Restlessness	99	22	77
Confusional state	86	44	42
Apathy	84	23	61
Hallucinations	80	56	24
Personality change	70	18	52
Psychotic disorder	70	55	15
Libido decreased	68	25	43
Fear	67	11	56
Social avoidant behaviour	67	17	50
Excitability	61	10	51
AttentionDeficit/Hyperactivity disorder	57	17	40
Disorientation	55	22	33
Mood altered	55	22	33

Affect lability	54	15	39
Logorrhea	54	9	45
Early morning awakening	50	10	40
Panic attack	50	30	20

The total number of other reactions of interest are 10 reports of completed suicide (all hcps reports), 33 reports of suicide attempt (24 HCP reports), 7 reports of depression suicidal (3 hcp reports), 5 feelings of despair (2 hcp reports), 19 reports of homicidal ideation (9 hcp reports), 21 reports of intentional self-injury (11 hcp reports), 11 reports of self-injurious ideation (5 hcp reports) and 5 reports of self-injurious behaviour (1 hcp report).

The MAH has provided a cumulative review of all reports of suicidal and self-harm and all reports of acute overdose. These are considered in more detail below.

2.0 Cumulative review of spontaneous reports of suicidal and self-injurious behaviour

The MAH has submitted a cumulative review of all spontaneous reports of suicidal and self-injurious behaviour that they have received during the period of 26 November 2002 to 22 September 2005. The MAH's safety database (Clintrace) was searched for all spontaneous (serious and non-serious) reports that had been coded to one of the following MedDRA (version 8) preferred terms:

Accident, Accidental exposure, Accidental overdose, Accidental poisoning, Alcohol poisoning, Completed suicide, Death, Depression suicidal, Drug level above therapeutic, Drug level increased, Drug toxicity, Excoriation, Gas poisoning, Head banging, Injury, Injury asphyxiation, Intentional misuse, Intentional self-injury, Laceration, Morbid thoughts, Multiple drug overdose, Multiple drug overdose accidental, Overdose, Poisoning, Poisoning deliberate, Self injurious behaviour, Self mutilation, Self-injurious ideation, Sudden death, Suicidal ideation., Suicide attempt and Therapeutic agent toxicity.

This search identified 475 reports all of which underwent medical review. A total of 174 reports were excluded for one of the following reasons:

i) patient not prescribed atomoxetine or not routinely taking atomoxetine prior to the event;
ii) suicidal/self-injurious events occurred > 1 month after atomoxetine was discontinued;
iii) relevant events were considered accidental, non-suicidal, or non-intentional overdoses.
iv) overdose was due to a prescribing error, pharmacy error, or administering error from a caregiver were likewise excluded.

The remaining 301 reports were assigned according to the approach described by the Columbia group and adopted by the FDA to one of the following categories.

Code 1 -Completed suicide
Code 2 -Suicide attempt
Code 3 -Preparatory acts toward imminent suicidal behaviour

Code 4 -Suicidal ideation
Code 5 -Self-injurious behaviour, intent unknown
Code 6 -Not enough information, fatal
Code 7 -Self-injurious behaviour, no suicidal intent
Code 8 -Other: accident; psychiatric; medical
Code 9 -Not enough information, nonfatal

An additional category – Code 10 self-injurious ideation- includes the cases where no self-injurious behaviour occurred, but the patients were having thoughts of harming themselves.

Information on the categories to which these reports were assigned and the seriousness of these reports is provided in table 1.

Table 1 Diagnostic Categorization and Seriousness of Case Reports

Code	Diagnostic Category	Fatal	Serious	Non-Serious	Total
1	Completed suicide	13	0	0	13
2	Suicide attempt	0	32	8	40
3	Preparatory acts toward imminent suicidal behaviour	0	3	2	5
4	Suicidal ideation	0	30	113	143
5	Self-injurious behaviour, intent unknown	0	13	21	34
6	Not enough information, fatal	4	0	0	4
7	Self-injurious behaviour, no suicidal intent	0	4	6	10
8	Other: accidental; psychiatric; medical	0	1	6	7
9	Not enough information, nonfatal	0	0	40	40
10	Self-injurious ideation	0	1	4	5
Total Case Reports		**17**	**84**	**200**	**301**

Patient age distribution in these cases ranged from 5 to 69 years. Of the 240 cases where age was known, the average patient age was 17.8 years, and the median age was 14 years. All the reports categorised as completed suicide occurred in adolescents aged 13-17 years (n=4) or adults (n=9). The same is true for the majority of reports (78%; 31 out of 40 reports) categorised as suicide attempts. The majority of reports of suicidal ideation (69%; 99 out of 143 reports) and self-injurious behaviour (79%; 27 out of 34 reports) occurred in children aged 12 years or below and adolescents. Information on the number of reports for each category broken down by age group can be found in Appendix A.

Of the 301 reports, a total of 191 were in males (63%), 93 in females (31%) and in 17 reports the gender was unspecified (6%). The ratio of male to female was higher in

paediatric and adolescent patients with a ratio of three to one, compared with adult patients at a ratio of almost one to one.

Where the information was provided, the atomoxetine daily therapeutic doses ranged from 10 mg to 180 mg daily, with an average dose of 51.3 mg daily, and the median dose of 40 mg daily. The time to onset of the events ranged from 1 day to more than 1 year. The time to onset in 45 cases was reported within 2 weeks after the start of atomoxetine treatment, 56 cases within 2 months, and in 50 cases from more than 2 months to more than 1 year. There were 8 cases where the events occurred after the first dose of atomoxetine.

In 13 of the reports there was a fatal outcome – these reports will be considered in more detail in the discussion of the completed suicide category. In the remaining reports (n=237), in approximately one half of the cases the patients has recovered at the time of reporting.

Completed suicide (Code 1)
A total of 13 reports were placed in this category. All are hcp reports and a summary for the information for each case is provided in the table below. In three of these cases (USA040979428, USA041079929 and USA050188413) it is questionable whether these were suicides.

As previously described all these cases occurred in either adolescents (n=4) or adults (n=9). In 10 of the 13 cases there was a pre-existing or history of a psychiatric disorder, such as depression (in 7 cases), prior suicidal ideation or attempts (6 cases) or other psychiatric disorders (5 cases). In two further reports information on medical history was not provided. This leaves one report which specified that the patient did not have a prior history of depression. The case narratives for these reports can be found at Appendix B.

Table 2 Code 1 – Completed Suicide (N=13)

Case ID	Age/ Sex	Daily dose	Time-to-onset	Brief descriptor of event	Risk or Confounding Factors	Cause of Death
	39/M	40 mg	1 week	Patient first received atomoxetine while still hospitalised. On the first weekend of vacation at home committed suicide. According to the reporter "it was obvious that the suicide was planned"	History of depression, suicide ideation, schizotypal personality disorders. Concomitant olanzapine, escitalopram and diazepam	Overdosed unspecified medications
	17/M	80 mg	>4 months	After having been on treatment for 4 months patient had a disagreement with his parents and left home. The next day was found dead in a park faced down. It was reported his death appeared to be suicide. Elevated blood atomoxetine level found on autopsy.	History of suicide attempts, overdose of zoldipem 6 months prior to death. Had a disagreement with his parents prior to his death. Taking paroxetine, zoldipem, lamotrigine and quetiapine.	Unknown. Possible overdose including atomoxetine
	42/M	120 mg	~ 1 month	Approximately a month after atomoxetine initiation, patient took an overdose of atomoxetine and escitalopram in a suicide attempt and died.	History of depression. Taking escitalopram.	Overdosed atomoxetine and escitalopram.
	13/M	60 mg	~ 1month	Patient was tolerating atomoxetine well, was coming out of shell and becoming more involved. About one month after atomoxetine initiation patients went into back yard and hung himself.	Unknown history. Four-year methylphenidate treatment stopped when atomoxetine started.	Hung himself
	35/F	60 mg	Unknown	The patient was prescribed atomoxetine for unspecified indication and duration. Found dead in her apartment, an empty pill bottle and syringe found nearby. A note of intent was also found.	History of bipolar disorder, psychosis, previous suicide attempts, and possible schizophrenia. Multiple psychiatric concomitant medications.	Overdosed multiple medications, including atomoxetine.
	35/M	60 mg	Unknown	On atomoxetine for ADHD for unknown duration then took an intentional overdose of atomoxetine and hydrocodone/acetaminophen -found dead the next day	Previous suicide attempts	Overdosed atomoxetine and hydrocodone.
	17/M	20 or 40 mg	Unknown	On atomoxetine for unknown indication and duration. Committed suicide by hanging. It is noted that he had no emotional stressors at time of event.	History of depression. Taking escitalopram.	Hung himself

	18/M	10 mg for 5 days.	2-3 days after Atx stopped	Experienced drug induced psychosis with suicidal intent 3 months prior to death. At the time was placed on observation and subsequently released on risperidone – this was discontinued 3 weeks later. Paroxetine dose was increased and atomoxetine was started. On fifth day afer starting atomoxetine – mother informed physician that patient was experiencing increase in depression, was "zonked out" and withdrawn. Atomoxetine was discontinued – 2-3 days later patient shot himself.	History of depression. Taking paroxetine.	Shot himself
	32/F	Unknown	1 week	After approximately 1 week of atomoxetine use, the patient died. Overnight, her partner had seen her up out of bed vomiting. She then went back to bed and died some time later. The cause of death on the autopsy was methadone overdose.	History of suicide attempt 6 to 7 years ago and long standing depression.	Overdosed methadone
	47/F	60 mg	Unknown	The patient had taken atomoxetine for an unknown duration. The police received a report that the patient was crawling around on the roof. The next day the patient was found dead. The final autopsy attributed the death to polysubstance toxicity.	Unknown medical history.	Overdosed atomoxetine and other drugs.
	15/M	80 mg	1 month	After a month on atomoxetine patient was reported to be doing well on atomoxetine – better than ever, stable and shown marked improvement. Seven days later was found hung in garage.	No history of depression. Having —very bad" scoliosis. Taking amphetamine/ dextroamphetamine.	Hung himself
	41/F	40 mg	7 months	Patient who had been on atomoxetine for 7 months was found dead in home. Police and medical examiner considered the cause of death to be suicide but her psychiatrist disagreed. Postmortem revealed high levels of unspecified drugs.	History of schizoaffective and bipolar disorder. Taking olanzapine, celecoxib, fluoxetine and sertraline	Unknown
	27/M		Unknown	Received atomoxetine for ADHD for unspecified duration. Committed suicide using a gun.	History of depression and anxiety. Taking escitalopram and methylphenidate.	Gun shot

Suicide attempt (Code 2)

A total of 40 reports were placed in this category. These cases involved 9 children (8 male and 1 unknown gender), 15 adolescents (8 male, 6 female and 1 unknown gender), and 16 adults (7 male, 9 female).

An overview of the information relating to the 24 reports involving children and adolescents is provided in table 2 below. In these reports potential risk or confounding factors were reported in 14 cases, such as pre-existing depression (in 6 cases), prior suicidal ideation or attempts (2 cases), other psychiatric disorders (sensory intergration disorder and "acting out"), or concurrent psychosocial stressors (3 cases). In other 6 case reports, the patients' medical history was not provided. There were 4 cases (GBS050417040, USA040259671, USA040363143, USA050597574) where there was no pre-existing psychiatric disorders present. Case narratives for the 9 case reports concerning children under 12 years of age are provided at Appendix C.

Of the 16 case reports involving adult patients, potential risk or confounding factors were reported in 14 cases, including pre-existing depression (7 cases), suicide attempts (4 cases), concurrent psychosocial stressors (2 cases), and/or other psychiatric disorder or conditions. There were two cases medical history and information on concomitant medication was not provided.

Table 3. Suicide Attempts in Children and Adolescents

Case ID	Age/ Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Suicide Attempt
	11/M	18 mg twice, 38 days	History of suicide attempt by hanging 5 months prior to his death. Having anxiety, depressive thought, impulsive and unable to concentrate. Had an argument with his family a day ago.	Tried to hang himself in his room, then called for help.
	11/M	60 mg, 5 œ 6 months	Unknown medical history. No concomitant medications.	Tried to climb out of the window at school.
	11/M	60 mg, 5 months	ADHD. Unknown if taking any concomitant medications.	Tried to commit suicide (no details)
	15/M	40 mg, Unknown	Unknown medical history. No concomitant medications.	Overdosed 1360 mg atomoxetine (34x 40-mg)
	17/M	Unknown	Got into a fight prior to his overdose. Unknown if having a history of suicide or depression. No concomitant medications.	Overdosed 1400 mg atomoxetine (14x 40-mg and 14x 60-mg)

Case ID	Age/ Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Suicide Attempt
	15/M	80 mg, ~2 months	History of major depression with concomitant bupropion, risperidone and alprazolam.	Overdosed 1200 mg atomoxetine (22 mg/kg)
	11/M	18 mg, 1 day	History of attempt to start fire once, hearing voices. Conner's rating showed a markedly elevated ADHD index, global restlessness, impulsive, cognitive problems/inattentive and social problems. Concomitant clonidine.	Attempted to hang himself with a rope in the closet at home. (He admitted this incident after he was arrested 18 days later, due to setting a fire in school.)
	13/F	60 mg, Unknown	History of depression, emotional and behavioral problems, being institutionalized in the past. Taking citalopram and clonidine.	Overdosed 840 mg atomoxetine (14x 60-mg)
	16/M	60 mg, <2 months	Medical history and concomitant medications were not provided.	Overdosed 1080 mg atomoxetine (18x 60-mg)
	15/F	40 mg, 6 days	History of depression and ADHD. No concomitant medications.	Overdosed 320 mg atomoxetine.
	16/M	Unknown	Unknown medical history. Concomitantly taking methylphenidate.	Overdosed atomoxetine and methylphenidate (unknown amount).
	15/F	Unknown	Prior to her overdose, had a fight with her mother. Concomitant medications were not provided.	Overdosed 600 mg atomoxetine (15x 40-mg)
	9/M	18 mg, 1 dose	Unknown medical history. No concomitant medications.	Tried to strangle himself with his crucifix and yelled —kill me, kill me", later diagnosed as a psychotic episode.
	10/M	40 mg, >5 weeks	History of sensory integration disorder, being emotional sensitive to medications. Taking methylphenidate.	Sticking his wet finger into a light socket.
	15/F	Unknown	Prior suicide attempt (not by overdose). No concomitant medications.	Overdosed 1560 mg atomoxetine (26x 60-mg)
	14/M	Unknown	No prior history of suicidal ideation or attempts. No concomitant medications.	Overdosed 800 mg atomoxetine (20x 40-mg)
	14/M	Unknown, ~1 month	History of depression, psychosis and ADHD with numerous medication treatments. Having been medication free for several months prior to atomoxetine initiation.	Asked his friends to set him on fire and suffered first and second degree burns on his chest, jaw and nose. Days later, threaten to self-harm.

Case ID	Age/ Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Suicide Attempt
	16/F	Unknown	History of depression. No prior history of suicide attempts. No ADHD. Atomoxetine was prescribed to her for an unknown indication. Taking hydrocodone/acetaminophen.	Overdosed atomoxetine, a tricyclic antidepressant and narcotic capsules (unknown amount).
	12/M	Unknown, 7 months	Negative for depression and prior suicide attempts. No concomitant medications.	Hanging himself
	14/un k	18 mg, 5 months	History of —acting out" and being in counseling before. Unknown if taking concomitant medication	Overdosed 270 mg atomoxetine (15x 18-mg)
	15/M	60 mg, Unknown	History of depression. Unknown if taking concomitant medications.	Overdosed 780 mg atomoxetine (13x 60-mg)
	12/un k	Unknown	Medical history and concomitant medications were not provided.	Overdosed atomoxetine (unknown dose).
	9/M	25 mg, ~ 1month	No family history of mental illness, no social stressors. No concomitant medications.	Slit his wrist with a butter knife as an act of self-harm.
	17/F	60 mg, <1 month	Exposed to trauma relating her father as firefighter. Having an argument with her teacher, learning difficulties, and questioning of her graduation.	Overdosed acetaminophen.

Preparatory Acts Toward Imminent Suicidal Behavior (Code 3)

A total of 5 reports were placed in this category. These case reports involved 2 female children, 2 male adolescents and 1 male adult. Of these 5 patients, 4 had a medical history of psychiatric disorder and/or conditions (2 with depression) other than ADHD. In a further reports there was a family history of psychiatric disorder.

The acts towards suicide behaviour in these cases are as follows:

i) Attempted to open the car door and threaten to put self in front of the car.
ii) Bought a gun and threatened to kill self.
iii) After the first dose, began hearing voices, acting like an animal and became suicidal. Had to be restrained by family so wouldn't hurt themself.
iv)Became depressed, crying. Came downstairs with a rope around neck.
v) Found at home with a belt around his neck, no injury. After the event commented, —if got hurt, parents would realize that they needed to be together for him.

Suicidal Ideation (Code 4)

A total of 143 reports were placed in this category. The majority of reports of suicidal ideation (69%; 99 out of 143 reports) occurred in children aged 12 years or below and adolescents. Of these case reports with suicidal ideation, potential risk or confounding factors were reported in 29 cases (38%), including pre-existing depression suicide attempt/ideation concurrent psychosocial stressors and/or other psychiatric disorder or conditions.

Self-Injurious Behaviour, Intent Unknown (Code 5)
A total of 34 reports were included in this category. These cases involved 14 children (11 male and 3 female), 13 adolescents (6 male and 7 female), 4 adults (3 male and 1 female), and 3 unknown age patients (2 male and 1 female). A brief overview of these cases can be found in the table at Appendix D.

Of these 34 patients, 15 had a medical history of psychiatric disorder (including 5 depression and 3 suicide attempt) other than ADHD, 3 were concurrently taking psychiatric medications. In 12 cases the medical history was not provided. There were 4 reports in which there is no relevant history or it is clear that there is no history of previous events.

Not Enough Information, Fatal (Code 6)
There were 4 case reports with a fatal outcome placed in this category. Two cases involved female patients (1 aged 35, 1 age unknown) who died after receiving atomoxetine therapy (1 after one week of treatment) - cause of death not specified and medical history not provided in these cases.

A further case concerns a 25 year old male with a history of anxiety, depression, seizure disorder, heroin and cocaine abuse and numerous drug overdoses. He received atomoxetine for about 2 months during which he complained of constant headaches, shortness of breath, and dizziness, and became swollen and heavy looking. He subsequently took an overdose of cocaine for which he was treated with naloxone and was in the intensive care unit for four days. About a month later, a day prior to his death, the patient reportedly contacted the prescribing psychiatrist to report feeling bad with constant headaches and dizziness. He died the next day it is thought that the death was a cardiac event related to an overdose of heroin.

The final case involves a 45-year-old male patient with a medical history including cardiovascular disease, hypertension, IDDM, kidney problems, mood problems, CHF, venous stasis, back pain, irritable bowel syndrome, sleep apnoea and drinking of alcohol. The patient began taking atomoxetine for ADHD at 40 mg daily and dose was increased due to not having the desired effect the patient wanted from the medication. About 4 months on atomoxetine, the patient died in his sleep. It was reported that the patient had begun drinking (alcohol) again prior to his death. Cause of death, as listed on the autopsy report, was complications of alcoholism, cardiomegaly, degeneration of mitral valve, morbid obesity, IDDM and venous stasis. The reporting psychiatrist stated that the atomoxetine did not contribute to the patient's death.

Self-Injurious Behaviour, No Suicidal Intent (Code 7)
A total of 10 reports were included in this category. These cases involved 3 children (2 male, 1 female), 4 adolescents (2 male, 2 female), 2 adults (1 male, 1 female) and 1 male patient of unknown age. Of these case reports, potential risk or confounding factors were reported in 8 cases, including pre-existing depression (2 cases), other psychiatric disorders or conditions. More details of these cases can be found in Appendix E.

Other: Accidental, Psychiatric, Medical (Code 8)
A total of 7 reports were placed in this category – 6 reports of accidental injury and a further report of self-inflicted injury due to his psychiatric conditions. In this later case a 20-year-old male who had taken atomoxetine for 2 years and concomitantly smoked hashish for 3 years, experienced persecutory delusion and aggression. He jumped out of the window, as he believed the police were chasing him. He was hospitalized in a coma, with cerebral haematoma, and liver and kidney injury. Both atomoxetine and cannabis were discontinued. At the time of reporting, the patient was recovering, but remained hospitalized.

Not Enough Information, nonfatal (Code 9)
There were 40 case reports placed in this category, of which 38 case reports were overdose cases from a literature publication (Spiller et al. 2005). This was case series concerning atomoxetine ingestion in children (aged ≤17 years) that had been conducted at 3 regional poison control centres in the US. In this publication, the authors specified that suicide attempt was the reason for exposure to atomoxetine in 4 of these cases, but did not provide background information on any individual case. The remaining 2 cases also involved overdose of atomoxetine, where the patients took 1 or 2 extra doses of atomoxetine, but their intent was unspecified.

3.0 Updated Review of Suicidal or Self-Injurious Behaviour associated with Atomoxetine (23 September 2005 – 25 October 2005)

This review covering the period 23 September 2005 – 25 October 2005 assesses the newly reported cases since the cut off date for the data discussed in the sections above (22 September 2005).

Using the same search methods as used in the review covering the period 26 November 2002 – 22 September 2005, a total of 135 case reports of 153 adverse events of possible suicide or self-injurious behaviour were identified in the atomoxetine safety database for the period 23 September 2005 – 25 October 2005. A total of 104 of the reports were reported by healthcare professionals, with 31 being reported by non-healthcare professionals.

Five case reports were excluded from the MAHs analysis. These were two reports of 'accidental overdose'; one report of 'overdose' in which a 6-year old male took and extra 13 capsules of atomoxetine after his first dose when he was unsupervised; one report of 'overdose' in which an adult patient adjusted the dose (100mg-120mg) in order to reach the desired drug effect; and one report of 'suicide attempt' in an adult female who was not prescribed atomoxetine but attempted suicide by taking her child's atomoxetine with acetaminophen.

The remaining 130 reports were reviewed and diagnosed into one of the same 10 diagnostic categories used in the previous review. Table 4 below provides further details of the diagnostic cateogorisation of the reported cases.

Table 4. Diagnostic Categorization and Seriousness of Case Reports (23 September 2005 – 25 October 2005)

Code	Diagnostic Category	Fatal	Serious	Non-Serious	Total
1	Completed suicide	7	0	0	7
2	Suicide attempt	0	23	0	23
3	Preparatory acts toward imminent suicidal behaviour	0	2	0	2
4	Suicidal ideation	0	27	61	88
5	Self-injurious behaviour, intent unknown	0	1	0	1
6	Not enough information, fatal	0	0	0	0
7	Self-injurious behaviour, no suicidal intent	0	2	2	4
8	Other: accidental; psychiatric; medical	0	0	0	0
9	Not enough information, nonfatal	0	0	0	0
10	Self-injurious ideation	0	0	5	5
Total Case Reports		**7**	**55**	**68**	**130**

Patient age distribution in these cases ranged from 5 to 66 years. Of the 120 cases where age was known, the average patient age was 14.6 years, and the median age was 13 years. The seven reports categorised as completed suicide occurred in children aged ≤12 years (n=1), adolescents aged 13-17 years (n=3) or adults aged 18-64 years (n=2). There was one report of completed suicide in which the age of the patient is unkown. The reports categorised as suicide attempts (n=23) were predominantly reported in adolescents aged 13-17 years (n=16), however there were reports of suicide attempts in children ≤12 years (n=3) and in adults aged 18-64 years (n=4).

The majority of reports of suicidal ideation (84%; 74 out of 88 reports), self-injurious ideation (80%; 4 out of 5 reports); and self-injurious behaviour (no intent) (100%; 4 out of 4 reports) occurred in children aged 12 years or below and adolescents aged 13-17 years). Information on the number of reports for each category broken down by age group can be found in Appendix A.

Of the 130 reports, a total of 96 were in males (74%), 30 in females (23%) and in 4 reports the gender was unspecified (3%). The ratio of male to female was higher in paediatric and adolescent patients with a ratio of four to one, compared with adult patients at a ratio of two to one.

Where the information was provided (94 out of 130 cases), the atomoxetine daily therapeutic doses ranged from 10 mg to 100 mg daily, with an average dose of 46.3 mg daily, and a median dose of 40 mg daily. In another 3 cases the daily dose of atomoxetine was 0.5, 1.5 or 2.0 mg per kg body weight.

The time to onset of the events was provided in 79 out of the 130 case reports and ranged from 1 day to more than 2 years. The time to onset was reported as within 2

weeks in 12 cases (15%), between 2 weeks and 2 months in 28 cases (36%), and between 2 months and 2 years in 39 cases (49%).

In 7 of the reports there was a fatal outcome – these reports will be considered in more detail in the discussion of the completed suicide category. In the remaining reports (n=123), 42% of cases were recovering or had fully recovered. The events resolved in 42 out of 78 of the cases in which atomoxetine was discontinued. Atomoxetine was continued in 18 cases, 9 of which reported resolution of the event.

Completed suicide (Code 1)

A total of 7 reports were placed in this category and a summary for the information for each case is provided in the table below. Narratives for the seven cases are presented in Appendix B.

As previously described these cases occurred in children (n=1), adolescents (n=3) and adults (n=2). The age of the patient was unknown in the remaining case. In 5 of the 7 cases there was a pre-existing or history of a psychiatric disorder (in 2 cases), and/or concomitant psychiatric medications (4 cases). In two further reports information on medical history or current psychosocial environment was not provided.

Table 5. Code 1 – Completed Suicide (N=7)

Case ID	Age/ Sex	Daily dose	Time-to-onset	Brief descriptor of event	Risk or Confounding Factors	Cause of Death
	19/unk	Unk	Unk	Ingested venlafaxine, ziprasidone, atomoxetine and other unlisted substances in an intentional suicide. Experienced pre-hospital cardiac and/or respiratory arrest resulting in a fatal outcome.	Unknownmedical history. Possibly taking venlafaxine and ziprasidone concomitantly.	Mixed overdose
	14/unk	Unk	Unk	Ingested amphetamine/dextroamphetamine, atomoxetine, and sertraline for an unkown chronicity toxic exposure for an unspecified reason. Experienced pre-hospital cardiac and/or respiratory arrest resulting in a fatal outcome.	Unknown medical history. Possibly taking sertraline, amphetamine/dextroamphetamine.	Mixed overdose
	17/M	40mg	30 weeks	Patient committed suicide approximately 7 months after starting atomoxetine 40mg. No further information provided. MAH has requested additional information.	History of musclar dystrophy (undetermined type), bipolar disorder, sleep apnoea, Pierre Robin sequence, Stickler syndrome, restless leg, attention disorder, and sleep disorder. Concomitant lithium, oxcarbazepine, ranitidine and alprazolam.	Unknown
	14/M	40mg	2 years	Committed suicide by hanging after 2 years on atomoxetine 40mg for ADHD. MAH has requested additional information.	Unknown medical history. No concomitant medications.	Hanging
	12/M	60mg	<90 days	'No signs of a suicide background'. Patient committed suicide about less than 90 days after starting atomoxetine. MAH is unable to obtain further information regarding this case.	History of oppositional defiance disorder (ODD) and possible bipolar I disorder. Unknown if taking concomitant medication.	Unknown
	Unk/M	Unk	Unk	Non healthcare professional report. Reportedly atomoxetine was not effective for the patient and was discontinued. The patient committed suicide. On company follow up.	Unkown medical history. Taking sertraline, valproate and escitalopram.	Unknown, after atomoxetine was discontinued.
	Adult/ M	Unk	8 weeks	Non healthcare professional report. After starting atomoxetine the patient started writing suicide poems for weeks. Committed suicide about 8 weeks after	Unknown medical history. Unknown if taking concomitant medications.	Unknown

				starting atomoxetine. On company follow up.		

Suicide attempt (Code 2)

A total of 23 reports were placed in this category. These cases involved 3 male children, 16 adolescents (8 male, 8 female), and 4 adults (3 male, 1 female).

An overview of the information relating to the 23 reports is provided in table 6 below. In these reports potential risk or confounding factors were reported in 17 cases, such as pre-existing depression or anti-depressant treatment (in 6 cases), prior suicidal ideation or attempt (4 cases), and other psychiatric disorders or concurrent psychosocial stressors (7 cases). In the remaining 6 case reports, the patients'medical history was not provided.

Table 6. Suicide Attempts in Children and Adolescents

Case ID	Age/ Sex	ATX Daily dose/ Time to onset	Potential Confounding Factors	Actions of Suicide Attempt
	8/M	Unknown	Had a long history of unspecified different problems. Prior to the events, while at school, reportedly his teacher said something he did not like.	Claimed he wanted to die, and picked up a knife and attempted to kill himself with the knife.
	13/F	60 mg, 6 weeks	History of threatening suicide prior to atmoxetine. Family history of psychotherapy (mother). No concomitant medications.	Intentional overdose of 1680mg atomoxetine. After the event, she claimed that she wanted to frighten her parents, but not kill her self.
	13/M	40 mg, 4 months	History of social behaviour and emotional disorders, and learning disability.	Climbed outside of a building and refused to come down.
	13/M	50mg, 12 days	Being treated for ADHD with methylphenidate with a non-satisfactory effect. Concomitantly taking methylphenidate. Prior to the event he had some problems in school and been confronted for threatening his classmates.	Intentional overdose of 15-20 tablets of 30-mg methylphenidate.
	16/F	40 mg, 2 months	History of previous impulsive overdoses and past substance misuse. The event occurred after an argument.	Overdose of atomoxetine (unspecified amount).
	9/M	60 mg, 16 months	History of possible bipolar or pervasive developmental disorder and being in therapy twice a month for 3 years. Unknown if taking concomitant medications.	Tried to strangle himself and hospitalised.
	15/F	60 mg, Unknown	Unknown medical history and concomitant medications	Intentional overdose of 30 capsules of 60-mg atomoxetine (1800mg).
	15/M	80 mg, 2 weeks	History of ADHD and bipolar disorder. No diagnosis of depression previously. No concomitant medications. Prior to the event, had an argument with his sister.	Intentional overdose of the amount of 15-days worth of atomoxetine.
	16/M	80 mg, 11 days	History of mild depression (prior treated with escitalopram), and self-injury (cutting self 59 times) when taking Adderall. Concomitantly taking amphetamine/	Intentional overdose of 23 pills of 50-mg trazodone and 4 pills of Adderral.

			dextroamphetamine.	
	14/F	Unknown	History of taking Adderral and unspecified tricyclic antidepressants (but unknown if taking at the time of the events).	Intentional overdose of amphetamine/ dextroamphetamine, tricyclic antidepressants and atomoxetine (unspecified amount).
	15/M	80 mg, 28 months	Unknown medical history. No concomitant medications. Had a positive tuberculosis skin test result.	Trying to hang him self.
	7/M	25 mg, 2 days	History of spastic cerebral palsy and spastic dyslogia. Taking baclofen.	He said "I want to kill my self", wanted to put a knife to his stomach, and jumped off the second storey balcony.
	15/F	10 mg, 3 months	History of depression and suicidal ideation, being hospitalised for suicidal ideation 3 months prior to atomoxetine initiation. Concomitantly taking fluoxetine.	Taking a bottle of naproxyn (unspecified amount).
	16/M	60 mg, 1 month	History of depression, but no suicide attempt. Family history of mental illness. Concomitant methylphenidate was discontinued 5 days prior to the events.	Hanging him self with a belt.
	17/F	60 mg, 50 days	History of depression or other (unspecified) mental disorder. Unknown if taking concomitant medications.	Overdosed on ibuprofen (unspecified amount) at bedtime.
	14/F	40 mg, Unknown	Unknown medical history and concomitant medications.	Overdose of up to 20 times the prescrtibed dose of atomoxetine (possible 800mg).
	33/M	60 mg, 2 months	History of irritability and "focus issue".	Called his physician about having psychotic thoughs and symptoms. Later reported by police that he became psychotic and slit his wrist in a suicide attempt.
	46/M	Unknown	Unknown medical history. Taking quetiapine. Taking atomoxetine due to the pharmacy dispense error.	Hanging him self.
	16/M	100 mg, 5 months	History of depression, social anxiety, bipolar disorder and lack of impulse control. Prior suicide attempts 3 times. Taking venlafaxine, valproate, esomeprazole, fexofenadine and amphetamine/dextroamphetamine.	Attempted suicide with a knife to his wrist. (The event occurred 2 days after Adderral was discontinued).
	15/F	43 mg, Unknown	Unknown medical history. No concomitant medications. Had a fight with her boyfriend prior to the event.	Overdose of 54 capsules of 25-mg or 18-mg atomoxetine.
	51/F	50 mg, Since started 2 years ago	History of being postmenopausal, cancer, and a head injury. Taking estradiol, progesterone, montelukast and midodrine.	Experienced worsening of depression, and swam out of the bay and did not care if she could swim back. Using a corkscrew to cut/scrape her arm and thought about getting an infection and dying.

	18/M	100 mg, 1 year	Attended 1st year college away from home, broke up with girlfriend, and possibly failed a class.	Tried to slit his wrist and stopped him self due to pain. No suture required.
	14/M	40 or 60 mg, 1 year	Unknown medical history and concomitant medications.	Tried to hang him self.

Preparatory Acts Toward Imminent Suicidal Behavior (Code 3)

A total of 2 reports were placed in this category (Table 7). These reports involved a male adolescent and a male adult. Both patients had pre-existing psychiatric disorders and concurrent social stresses.

Table 7. Code 3 – Preparatory Acts Toward Imminent Suicidal Behaviour (N=2)

Case ID	Age/ Sex	Atomoxetine Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Suicide Attempt
	13/ M	40 mg, 1 month	Prior history of suicide attempt. Attending a special class for behaviorally difficult children and suspended 4 times for fighting. His parents were not together. Strong family history of suicidal ideation and attempts (his cousin committed suicide several months prior). Prior to the event, he got into fight with a boy. His mother threatened to send him to his father, and his father said the patient would have to go to military school.	The patient grabbed an electric cord and stated he was going to hang himself. His mother took the electric cord away. He then grabbed a knife, held the knife to his throat and threatened to kill himself/cut his throat.
	30/ M	80 mg, 3 months	History of depression. Divorced, unemployed, and lived with his brother and sister-in-law. Taking paroxetine and methylphenidate.	He stated that he had been feeling extremely suicidal and had bought a rope and gone into the woods to hang himself. He did not act on his plan because of a contract he made not to harm himself.

Suicidal Ideation (Code 4)

A total of 88 reports were placed in this category. The majority of reports of suicidal ideation (84%; 74 out of 88 reports) occurred in children aged 12 years or below and adolescents aged 13-17 years. Of these 88 reports of suicidal ideation, potential risk or confounding factors were reported in 34 cases (39%), including pre-existing depression (8 cases), suicide attempt/ideation (4 cases), concurrent psychosocial stressors (7 cases) and/or other psychiatric disorder or conditions. Details of the patient's medical history were not provided in 39 cases.

Self-Injurious Behaviour, Intent Unknown (Code 5)
There was 1 report included in this category. This case involved a male patient of unknown age who took atomoxetine 60 mg daily for an unknown length of time. The patient experienced self-mutiltation after starting atomoxetine (intent unspecified). His medical history was unknown and it was unknown if he was receiving concomitant medication.

Not Enough Information, Fatal (Code 6)
None.

Self-Injurious Behaviour, No Suicidal Intent (Code 7)
A total of 4 reports were included in this category. These cases involved 2 children (2 male), and 2 adolescents (1 male, 1 female). Of these case reports, potential risk or confounding factors were reported in 2 cases. Details regarding medical history were not provided in the remaining 2 cases. More details of these cases can be found in Appendix E. There are an additional 4 case reports in Code 4 in which the patients had non-suicidal self-injurious behaviour with suicidal ideation. Further details of these four additional reports are provided in Table 8 below.

Table 8. Suicidal Ideation with non-suicidal Self-Injurious Behaviour.

Case ID	Age/ Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Self-Injury
	12/M	40 mg, 5 months	History of ADHD, low self-esteem, social anxiety, aggressive/violent behaviour to others. Family history of mental illness (mother). No concomitant medications.	Experienced a gradual onset of increased anxiety, leading to frank paranoid psychosis. Had a low mood, hopelessness, suicidal thoughts, repetitive self-harming (no details), and aggression. The reporting child psychiatrist stated that the patient's intent to kill self was questionable and his motive was also questionable.
	Unk/ M	Unknown	Unknown medical history and concomitant medications.	Started harming himself, cut him self with blades, bit him self to the point drawing blood. And told his mother "life wasn't worth living," "hates him self" and "wanted to die."
	7/F	25 mg, 1 month	No prior suicidal thought. No concomitant medications.	Verbalized suicidal thoughts to her mother, stating that "she would kill herself", and began hitting herself. The reporting pediatrician stated that the patient's intent to kill herself was questionable, but she had a definite intent to provoke others.
	8/M	18 mg, ~ 2 years	History of ADHD and having mood swings with Adderall treatment. He was adopted and his parents were divorced. No concomitant medications.	Experienced hallucinations, hearing voices, wanting to harm himself, wanting to drown in the bathtub, wanting to jump off the balcony, wanting to die. And was found sticking a safety pin into his thumb trying to make himself bleed.

Other: Accidental, Psychiatric, Medical (Code 8)
None

Not Enough Information, nonfatal (Code 9)
None.

Self-Injurious Ideation (Code 10)
A total of 5 case reports were placed in this cateogy. These five cases involved 4 children (3 males, 1 unknown gender) and one male patient of unknown age. One of the cases reported anxiety, tic and obsessive compulsive disorder as medical history. Medical history was unknown in the remaining 4 cases.

4.0 Overall Discussion

Up to 25 October 2005, a total of 431 reports of suicidal and behaviour have been received (301 cases during the period 26 November 2002 – 22 September 2005, 130 cases during the period 23 September 2005 – 25 October 2005).

These reports include 20 classified as completed suicide, 63 classified as suicide attempt, 231 classified as suicidal ideation, 35 classified as self-injurious behaviour and 10 classified as self-injurious ideation.

In the cases where patient age was provided (369/431; 86%), the patient age distribution ranged from 5 to 69 years and the majority of the suspected ADRs were in males (67%). In the cases where age is known, the majority of the completed suicides (95%) and the majority of suicide attempts (81%) occurred in adolescents or adults. There was one completed suicide in a 12 year old male with a history of ADHD, oppositional defiance disorder (ODD) and possible bipolar I disorder. Further details regarding the case (including the manner of suicide) are not available. The majority of reports of suicidal ideation (81%) and self-injurious behaviour (87%) occurred in children aged 12 years or below and adolescents.

The time to onset of the events ranged from 1 day to more than 2 years. In the reports where information on the time to onset is provided, just under two thirds (61%) of the events occurred within 2 months of starting treatment. There was no apparent trend in the dose.

Where information is provided, there are confounding factors such as previous history, underlying illness or concomitant medication in the majority of reports of completed suicide (15 out of 15 cases), suicide attempt (45 out of 49 cases) and suicidal ideation (63 out of 92 cases). Based on these data, however, one cannot exclude the possibility that atomoxetine may have exacerbated the individuals underlying condition in these cases.

If the cumulative number of reports (26 November 2002 – 25 October 2005) of suicidal and self-injurious behaviour are considered in the context of exposure to date (3.5 million patients) then such reports have been reported rarely (<0.1%). The overall reporting rate has changed from "very rare" (<0.01%) for the first set of data covering the period 26 November 2002 – 22 September 2005) to "rare" (≥0.01% - <0.1%) for the total period covered by the two reviews (26 November 2002 – 25 October 2005). The increase in reporting rate observed during the period 23 September 2005 – 25 October 2005 is not unexpected following the healthcare communications/public advisories and press coverage concerning this issue during that time. The reporting rates should be interpreted with caution given that they are based upon spontaneous reporting data and thus are subject to the same biases/limitations including under reporting and publicity surrounding the drug.

as stated above, the possibility that atomoxetine may have exacerbated the individual's underlying condition in these cases can not be excluded.

With regards to reports of other psychiatric adverse events associated with atomoxetine, the table provided in Section 1.0 of this reports provides an overview.

Conclusion

A total of 431 spontaneous reports of suicidal and self-injurious behaviour associated with atomoxetine were reported during the period 26 November 2002 – 25 October 2005. There were 20 reports of completed suicide, the majority of which were in adolescents and adults although there was one report in a 12-year old male. There was no apparent trend in dose and time to onset varied from 1 day to more than 2 years although almost two thirds of the events occurred within 2 months of starting atomoxetine.

Whilst a significant number of reports had confounding factors such as previous history, underlying illness or concomitant medication, the possibility that atomoxetine may have exacerbated the individuals underlying condition in these cases cannot be excluded.

The overall reporting rate has changed from "very rare" (<0.01%) to "rare" (≥0.01% - <0.1%). The increase in reporting rate observed during the period 23 September 2005 – 25 October 2005 is not unexpected following the healthcare communications/public advisories and press coverage concerning this issue during that time.

14 November 2005

Appendix A

Patient Demographics of reports with Suicidal or Self Injurious Behaviours (26 November 2002 - 22 September 2005)

Code	Diagnostic Categorization	Age Groups (years)					Total
		≤12	13-17	18-64	≥65	Unk	
1	Completed suicide	0	4	9	0	0	13
2	Suicide attempt	9	15	16	0	0	40
3	Preparatory acts toward imminent suicidal behavior	2	2	1	0	0	5
4	Suicidal ideation	64	35	32	1	11	143
5	Self-injurious behaviour, intent unknown	14	13	4	0	3	34
6	Not enough information, fatal	0	0	3	0	1	4
7	Self-injurious behaviour, no suicidal intent	3	4	2	0	1	10
8	Other: accidental; psychiatric; medical	3	2	2	0	0	7
9	Not enough information, nonfatal	1	2	1	0	36	40
10	Self-injurious ideation	3	1	0	0	1	5
Total of Case Reports		**99**	**78**	**70**	**1**	**53**	**301**
Age Grouping Percentage of Reports		**32.9%**	**25.9%**	**23.3%**	**0.3%**	**17.6%**	**100%**
Atomoxetine Patient Exposure (cumulative)		**44.3%**	**22.3%**	**32.7%**	**0.6%**	**0.1%**	**100%**

Patient Demographics of reports with Suicidal or Self Injurious Behaviours (23 September 2004 - 25 October 2005)

Code	Diagnostic Categorization	Age Groups (years)					Total
		≤12	13-17	18-64	≥65	Unk	
1	Completed suicide	1	3	2	0	1	7
2	Suicide attempt	3	16	4	0	0	23
3	Preparatory acts toward imminent suicidal behavior	0	1	1	0	0	2
4	Suicidal ideation	49	25	7	1	6	88
5	Self-injurious behaviour, intent unknown	0	0	0	0	1	1
6	Not enough information, fatal	0	0	0	0	0	0
7	Self-injurious behaviour, no suicidal intent	2	2	0	0	0	4
8	Other: accidental; psychiatric; medical	0	0	0	0	0	0
9	Not enough information, nonfatal	0	0	0	0	0	0
10	Self-injurious ideation	4	0	0	0	1	5
Total of Case Reports		**59**	**47**	**14**	**1**	**9**	**130**
Age Grouping Percentage of Reports		**45%**	**36%**	**11%**	**1%**	**7%**	**100%**

Appendix B

Case narratives for all reports categorised as completed suicide (26 November 2002 – 22 September 2005)

Case *(completed suicide)*, reported by a physician, concerned a 39-year-old Caucasian male patient. The patient had schizotypal personality disorder and ADHD as a child. He had a history of depression, suicide ideation and previous inpatient psychiatric treatment. He had previously received treatment with methylphenidate, but discontinued it due to symptoms of psychosis. Concomitant medication included oral olanzapine, escitalopram and diazepam. Per the reporter, the patient's mother had read about atomoxetine and requested to get a prescription of atomoxetine for her son. The physician resisted and told the mother "that at this stage it would be dangerous to start Strattera." However, both the mother and patient further requested treatment. The patient first received atomoxetine 40 mg daily while he was still hospitalized (reason for hospitalization was not provided). On the first weekend of vacation at home, the patient committed suicide by using several different unspecified medications. It was unknown if an autopsy was performed. According to the reporter, "it was obvious that the suicide was planned," and the patient had a definite intent to die, but the reporter did not know the patient's motive.

Case *(drug interaction, overdose, completed suicide)*, was reported by a toxicologist, with additional information provided by a medical examiner and a psychiatrist. A 17-year-old male patient had a history of suicide attempt, and overdosed on zoldipem about 6 months prior to his death. His concomitant medications included paroxetine, zoldipem, lamotrigine and quetiapine. While he had taken atomoxetine 80 mg daily for 4 months and paroxetine for 1 month, the patient had a disagreement with his parents and left home. The next day, he was found dead in a park faced down. It was reported his death appeared to be suicide. The autopsy revealed an elevated blood level of atomoxetine at 16 mg/L, which the toxicologist suggested could have resulted from the patient taking 24 capsules of 40-mg atomoxetine. Paroxetine blood level was reported as less than 0.1 mg/L. The cause of death was not identified. The physician did not feel that foul play could be attributed to the death. The reporting medical examiner, toxicologist, and psychiatrist did not provide an opinion of relatedness.

Case *(intentional misuse, completed suicide)*, reported by a psychiatrist, concerned a 42-year-old male patient with a history of ADD, depression, hypothyroidism and back pain. He was concomitantly taking escitalopram, levothyroxine and carisoprodol. The patient received atomoxetine 40 mg daily for treatment of ADD. The dose was titrated up to 80 mg daily then later increased to 120 mg daily within a month. Approximately a month after atomoxetine initiation, the patient took an overdose of possible atomoxetine and escitalopram in a suicide attempt and died. It was unknown exactly how much of each medication was ingested. An autopsy was performed and the results were not known. The reporter stated that due to the fact this may be a legal case, he declined to provide additional information and did not wish to be contacted again.

Case [redacted] (*completed suicide*) was initially reported by a funeral home director with additional information from the medical examiner and a consumer, concerns a 13-year-old Caucasian male patient with an unknown medical history. He was not receiving any concomitant medications. The patient discontinued a 4-year therapy of methylphenidate around the time atomoxetine was initiated. The patient began receiving atomoxetine with a daily dose titrated from 20 mg to 60 mg. According to the consumer reporter, the patient was tolerating atomoxetine therapy; his grades were improving, he was in choir, and there were not any signs of depression. He was coming out of his shell and becoming more involved. About one month after atomoxetine initiation, the patient went into his back yard and hung himself with an electrical cord. The reporting consumer believed that because the electrical cord was wrapped around his neck but not tied to anything else this hanging was an accident. She felt he was acting out a drama as he often did. According to the medical examiner, the patient was found hanging from a deck at his family's home at 1:30 pm. He was last seen a day before at 11:00 pm. Reportedly there was no suicide note found and the patient had not made any suicidal ideations to his family. An autopsy was performed. The cause of death was ruled as hanging. The manner of death was ruled a suicide.

Case [redacted] (*completed suicide, drug toxicity*), reported by a medical examiner, concerned a 35-year-old female patient weighing 103.9 kg. Her medical history included bipolar disorder, psychosis, possible schizophrenia, previous unspecified suicide attempts, type II diabetes mellitus, obesity, chronic obstructive pulmonary disease, and degenerative disc disease. Concomitantly, the patient was prescribed hydrocodone, topiramate, citalopram, oxycodone, zafirlukast, risperidone, zolpidem, loratadine, gabapentin, metformin, alprazolam, and prochlorperazine. In addition chlorpropramide and chlorpromazine was found upon autopsy. It was unspecified which, if any, of the medications had been discontinued. The patient was prescribed atomoxetine 60 mg daily for an unspecified indication and duration. The patient was found dead in her apartment. An empty pill bottle and syringe was found nearby. A note of intent was also found. Upon autopsy oxycodone, hydrocodone, citalopram, gabapentin, atomoxetine, chlorpropamine, and chlorpromazine were found in the patient's system. There was a contusion on the anterior left forearm and two contusions on the anterior left thigh. The cause of death was mixed drug intoxication. The manner of death was suicide.

Case [redacted] (*intentional misuse, completed suicide*), reported by a pathologist, concerned a 35-year-old male patient with a medical history included previous attempts of suicide, chronic back pain and varicose vein surgery 2 months prior to his death. Concomitant medication included hydrocodone/acetaminophen. While he was taking atomoxetine 60mg daily for ADHD for an unknown duration, the patient took an intentional overdose of atomoxetine, 2880 mg (an estimated 48 pills of the 60-mg capsule) and an undetermined amount of hydrocodone/acetaminophen. The patient was found dead the next day. The cause of death was listed as drug overdose from atomoxetine and hydrocodone/acetaminophen. Blood level of atomoxetine was 4400 ng/ml, hydrocodone 420 ng/ml and acetaminophen 174 ng/ml. The patient had not been hospitalized recently, and the autopsy did not show any complications from his varicose vein surgery.

Case [redacted] (*completed suicide*), reported by a physician, concerned a 17-year-old Caucasian male patient with a medical history included depression or other mental disorders

(bipolar/manic depression). The patient attended a private boarding school away from where his family lived. He had no history of previous suicide ideations or attempts, no previous history of inpatient psychiatric treatment, alcohol/substance abuse, or psychotic behavior, no history of criminal charges, child abuse or neglect and no family history of mental illness or suicide. He had no emotional stressors at the time. Concomitant medications included escitalopram. The patient began taking atomoxetine 25 or 40 mg for an unknown indication on an unknown date. The patient committed suicide by hanging himself. He had been playing Frisbee golf, and about 30 minutes later he went and hung himself.

Case (*completed suicide, depression, social avoidant behaviour, somnolence*), reported by a physician, concerned an 18-year-old male patient with a medical history including anxiety and depression. He had a history of cocaine, marijuana, and alcohol abuse. The patient had been seen in the emergency room approximately 3 months prior to his death, the patient experienced drug induced psychosis with suicidal ideation. He was placed in observation for 10 to 12 hours. He recovered well. Upon having no more suicidal thoughts the patient was released on risperidone 1 mg daily and paroxetine 12.5 mg daily. Upon, the next office visit, the patient was doing very well. He had no further hallucinations or paranoia. His risperidone dose was decreased down to
0.5 mg daily then three weeks later risperidone was discontinued. The patient complained of poor concentration at the time of risperidone discontinuation. Then, his paroxetine dose was increased up to 20 mg daily and atomoxetine was started at 10 mg daily. The patient had not taken any other medications for the treatment of ADHD in the past. About the fifth day after beginning atomoxetine, the physician received a telephone call from the patient's mother stating the patient was experiencing an increase in depression, and was —zonked out", withdrawn, and not talking much. Reportedly no situational stresses were present. Atomoxetine was discontinued while paroxetine was continued. Two to three days after the discontinuation of atomoxetine, the physician received a telephone call from a medical examiner stating the patient had shot himself. There was no evidence of illicit drug or alcohol use at the time of suicide. The patient had been sober for two months prior. The reporting physician related the event to the use of atomoxetine. He was unaware of anything else that could have effected the patient's depression.

Case (*death, vomiting*), reported by a physician, with additional information from a nurse, concerned a 32-year-old black female patient. Her medical history included a suicide attempt 6 years ago and longstanding depression. Concomitant medications were not provided. After approximately a week of atomoxetine use (dose unspecified), the patient died. Overnight, the patient's significant other had seen her up out of bed and vomiting. She then went back to bed and died sometime later. The cause of death on the autopsy report was methadone overdose. The reporting physician did not prescribe methadone. The patient received reportedly the methadone from a friend. There was no indication that the patient took an overdose of atomoxetine.

Case (*drug toxicity, abnormal behaviour, excoriation*), reported by a medical examiner, concerned a 47-year-old Caucasian female patient weighing 72 kg. The patient's medical history included asthma. Concomitant medications were not provided. The patient had taken atomoxetine for an unknown duration. She had two prescriptions for atomoxetine, one for a 40-mg dose and the other for a 60-mg dose. The police received the report that the patient was

crawling around on the roof. The next day, the patient was found dead. The autopsy report stated that the patient had multiple minor blunt force injuries (abrasions) of her face and upper and lower extremities. But the injuries were not contributory to her death. The final autopsy report attributed the patient's death to polysubstance toxicity, while the manner of death was undetermined. Post mortem toxicity report showed blood positive for atomoxetine at 8.2 mg/L, ibuprofen, paroxetine 0.62 mg/L, ethanol 0.06% and cannabinoid metabolites. Gastric contents showed 28.6 mg of atomoxetine and 489.7 mg of paroxetine.

Case (*completed suicide*), reported by a physician, concerned a 15-year-old male patient (weighing 58 kg) with a "very bad" scoliosis but no history of depression. He was one of two children and lived at home with both parents. Concomitant medications included mixed amphetamine/dextroamphetamine. The patient also previously took methylphenidate that was discontinued prior to the start of atomoxetine. The patient started atomoxetine for the treatment of ADHD, at a dose of 40 mg daily for 4 days, and then titrated up to 80 mg daily. Amphetamine was tapered when atomoxetine was started. About 1 month later, the patient visited the physician's office for regular follow-up. The patient was reportedly better than ever, stable, had marked improvement, and was taking increased responsibility. Amphetamine was discontinued at that date. Seven days after his office visit, the patient was found hung in the garage. No autopsy was performed. The reporting physician stated it was a sad and unfortunate event, and he did not relate the event to the use of atomoxetine.

Case (*death, drug level increased*), reported by a psychiatrist, concerned a 41-year-old female African American patient with a medical history of schizoaffective and bipolar disorder. She was concomitantly taking olanzapine, celecoxib, fluoxetine and sertraline. The patient was found dead in her home about 4 days after her death. Both police and the medical examiner considered the cause of death to be suicide, but her psychiatrist disagreed. Postmortem blood tests revealed high levels of unspecified drugs. At the time of her death, she had taken atomoxetine at 25 mg to 40 mg daily for 7 months, and olanzapine for almost 7 years.

Case (*completed suicide*), reported by a physician, concerned a 27-year-old male patient of unknown race. The patient's medical history included ADHD, anxiety and depression. Concomitant medications were methylphenidate and escitalopram. The patient received atomoxetine for ADHD at an unspecified dose for an unknown duration. The patient committed suicide by using a gun. Reportedly atomoxetine was discontinued but the date was not provided.

Case narratives for all reports categorised as completed suicide (23 September 2005 – 25 October 2005)

Case *(completed suicide, drug toxicity)*, described in the literature (Watson W et al. 2005) and reported from a poison control center, concerned a 19-year old patient (gender unknown) with an unspecified medical or psychiatric history. It was reported that the patients ingested venlafaxine, ziprasidone, atomoxetine (dose unknown) and other unlisted substances for an intentional suicide. The patient experienced a pre-hospital cardiac and/or respiratory arrest resulting in a fatal outcome. Postmortem blood

leveles included venlafaxine 100,000 ng/ml, no-metabolites 19,900 ng/ml, ziprasidone 140ng/ml and atomoxetine 8.3 ug/ml. No other information was provided. The authors noted that the rug exposure was "probably" or "undoubtedly" responsible for the fatality.

Case *(drug toxicity),* described in the literature by the same reported (Watson W et al. 2005) and reported from a poison control center, concerned a 14-year ol patient (gender unknown) with an unspecified medical or psychiatric history. It was reported that the patient ingested amphetamine/dextroamphetamine, atomoxetine (dose unknown), and sertraline for an unknown chronicity toxic exposure for an unspecified reason. The patient experienced a pre-hospital cardiac and/or respiratory arres resulting in a fatal outcome. No other information was provided. The authors noted that the drug exposure was "probably" or "undoubtedly" responsible for the fatality.

Case (*completed suicide*), reported by a regulatory agency, concerned a 17-year-old male patient with a medical history including muscular dystrophy (undetermined type), bipolar disorder, sleep apnea, Pierre Robin sequence, stickler syndrome, restless leg, attention disorder, and sleep disorder. Concomitant medications included lithium, oxcarbazepine, ranitidine and alprazolam. The patient received atomoxetine 40 mg daily for the treatment of attention. Approximately seven months after starting atomoxetine, the patient committed suicide (the manner of death was not provided). Additional information has been requested.

Case (*completed suicide*), reported by a physician, concerned a 14-year old male patient with an unspecified medical history. He took no concomitant medications. The patient received atomoxetine 40 mg for treatment of ADHD. About 2 years on atomoxetine, the patient committed suicide by hanging himself. It was reported the he was still taking atomoxetine at the time of death. The reporting physician did not provide a statement of relatedness. Additional information has been requested.

Case (*completed suicide*) was reported by a company attorney and a physician (no relation with the patient) separately. This case was posted on a plaintiff attorney's website. A 12-year-old male patient had a medical history including ADHD, oppositional defiant disorder (ODD) and possible bipolar I disorder. Reportedly he had no signs of a suicide background. Concomitant medication was not provided. The patient received atomoxetine 60 mg daily for treatment of ADHD. About less than 90 days after starting atomoxetine, he committed suicide (the manner of death was not provided). At the time of his death, he was 2 weeks away from his 13th birthday.

Case (*completed suicide, drug ineffective*), reported by a consumer via an electronic mail message, concerned a male patient of unknown age whose medical history was not provided. The patient was receiving sertraline, valproate and escitalopram. The patient had received atomoxetine at an unspecified dose for an

unspecified indication. Reportedly atomoxetine was not effective for the patient. On an unspecified date, the atomoxetine was discontinued. After an unspecified duration of atomoxetine discontinuation, the patient committed suicide (the manner of death was not provided). At the time of his death, he was receiving escitalopram and valproate. Additional information has been requested.

Case [redacted] (*completed suicide*), reported by a consumer via an electronic mail message, concerned an adult male patient whose medical history and concomitant medications were not provided. The patient was receiving atomoxetine at an unspecified dose. After starting atomoxetine, the patient began to write suicide poems for weeks. About eight weeks after starting atomoxetine, the patient committed suicide (the manner of death was not provided). Additional information has been requested.

Appendix C

Case narratives for all reports in children (≤12 years) categorised as suicide attempt (26 November 2002 – 22 September 2004)

Case (*suicide attempt*), reported by a physician, regarded an 11-year-old male patient with a history of a prior suicide attempt, about 5 months prior to his death. His medical history also included anxiety and depressive thoughts especially in the evenings. The patient was reported to be very uneasy, impulsive, unable to concentrate, and very variable in behavior (from being reflective with a lot of self-insight to acting like a clown or being very sad). The patient achieved normal scores in cognitive tests, but continued to have difficulty in multiple subjects. Concomitant medications included melatonin and methylphenidate. After 38 days of receiving atomoxetine 18 mg twice daily, the patient attempted suicide by trying to hang himself in his room after an argument with his family members the previous day. During the attempt, the patient became afraid and called for his mother, who along with the patient's brother, subsequently managed to get the patient down. The patient was hospitalized, and corrective treatment was not reported. The patient recovered. At the hospital, the patient denied having planned to take his life, however, the patient had installed a hook in the ceiling. Two days after the event, the patient stated during his consultation with his therapist that he should have taped his mouth so he would not be able to cry out for help. He also stated that he does not think he will attempt to commit suicide again, but could not be certain. The patient's mother reported that the patient was doing better while on atomoxetine since the patient was no longer depressed in the evening. However, the patient's mother discontinued atomoxetine 3 days following the event.

Case (*suicide attempt*) involved an 11-year-old male patient whose medical history was unknown. He did not receive any concomitant medications. After approximately 5 to 6 months of receiving atomoxetine 60 mg daily, the patient had a suicidal episode, described as attempting to climb out of the window at school. At the time of the report, the patient was recovering. Atomoxetine was continued.

Case (*depression suicidal, suicide attempt*), reported by a healthcare professional, involved an 11-year-old male patient with a history of ADHD. It was unknown whether he received any concomitant medications. Approximately 5 months after receiving atomoxetine 60 mg, the patient experienced suicidal depression and attempted to commit suicide (method unspecified). Atomoxetine was discontinued 12 days after the event occurred. At the time of reporting, the patient was recovering.

Case (*anger, feeling abnormal, fight in school, hallucination auditory, insomnia, pyromania, aggression, suicide attempt, impulsive behaviour*), reported by a family practitioner, involved an 11-year-old male patient with a medical history of an attempt to start a fire while receiving dextroamphetamine, which was discontinued about 2 years ago. The patient received dextroamphetamine for about 12 to 18 months, during which he did not hear any voices. There were no further occurrences with starting fires after dextroamphetamine discontinuation. Additionally, his medical history included hearing voices (prior to receiving atomoxetine), ADHD, and Conner's ratings that revealed a markedly elevated ADHD index, global restlessness, impulsiveness, cognitive problems, lack of concentration, and social problems. The patient did not have a history of depression

or other mental disorders, previous suicide attempt or ideation, previous inpatient psychiatric treatment, alcohol and/or substance abuse, aggressive or violent behaviour, or been a victim of child abuse or neglect. There was no family history of mental illness, suicide or suicide attempts, personality disorder, or antisocial disorders. Concomitant medications included clonidine. On the same day that the patient received atomoxetine 18 mg, he attempted to hang himself with a rope in the closet at home. It was reported that the patient had a definite intent to die and a clear motive for the attempt. However, he had not experienced any trauma, death of a family member or friend, chronic illness, prior to the event. Sometime after initiating atomoxetine, the patient felt weird and started hearing voices intermittently. The patient may have heard voices prior to atomoxetine treatment, but he was able to ignore them without difficulty. These voices were telling the patient to do unspecified —bad things". Three days after starting atomoxetine, the patient started a fire in his backyard and was expelled from school on the next day. Atomoxetine was increased to 25 mg daily. The patient began experiencing increased attitude problems at home, which required police assistance. Three days after the dosage increase, the patient was charged with starting a fire, but then restarted school the next day. However, the patient was thrown out of school again for 2 days for reportedly threatening a teacher. After returning to school, the patient started a fight in the bathroom at school, was placed in school detention, and was arrested for starting a fire at school. Atomoxetine was discontinued after approximately 1 month of atomoxetine treatment. On the same day of discontinuation, the patient denied any auditory hallucination, visual hallucination, urge to burn things, or urge to injure others or himself. The patient had no explanation for his behaviour apart from hearing voices telling him to do bad things. Additionally, the patient thought he might have been angry prior to atomoxetine discontinuation. All events resolved after atomoxetine discontinuation.

Case (*vision blurred, nervousness, hyperhidrosis, vitreous floaters, screaming, headache, sensation of heaviness, psychotic disorder, suicide attempt, aggression, abnormal behaviour, sudden onset of sleep*), reported by a nurse, involved a 9-year-old male patient whose medical history was not provided. The patient did not receive any concomitant medications, but previously received methylphenidate and amphetamine/dextroamphetamine. One hour after receiving his first dose of atomoxetine 18 mg, the patient's legs felt heavy and subsequently experienced a headache. While the feeling of heavy legs and the headache worsened, the patient was violently screaming, —off the wall", and wanted to kill himself. He tried to strangle himself with his crucifix. The patient's mother held the patient down while the patient was yelling, —kill me, kill me". Additionally, the patient was diaphoretic, aggressive, violent, and would throw himself against the wall. Finally, the patient went limp and fell asleep in his mother's arms. The patient's breathing eventually became regular, and he became less diaphoretic. Atomoxetine was discontinued. The patient continued to experience headache and blurred vision with floaters on the following day, but these events resolved within a few days later.

Case (*depressed mood, distractibility, emotional disorder, dysgraphia, headache, drug ineffective, sensory integrative dysfunction, suicidal ideation, suicide attempt*) involved a 10-year-old male patient (weight 24 kg) with a medical history of sensory integrative disorder and being emotionally sensitive to medications. Concomitant medication included methylphenidate. The patient began atomoxetine 18 mg daily several months ago. Since beginning atomoxetine, the patient's handwriting worsened, but the patient was much happier. Several months later, atomoxetine was reportedly not effective. The patient began showing the same symptoms he had before starting atomoxetine and had sensory integration problems. Atomoxetine was increased to 25 mg, and then 40 mg daily.

Four to 5 weeks after the 40 mg dose increase, the patient was —at an emotional low", had sensory integration symptoms, and was suicidal. It was reported that the patient did not want to feel anymore and attempted suicide by placing his wet finger into a light socket. Atomoxetine was immediately decreased to 25 mg. Subsequently, the patient experienced a headache for 4 days and was distracted and hyperactive. Methylphenidate was prescribed as corrective treatment, and atomoxetine continued. The headaches resolved, but the event outcomes for sensory integration disorder symptoms, suicidal ideation, distraction, and hyperactivity were unknown.

Case (*mental status changes, suicide attempt*) was initially reported by a physician with additional information from a nurse. This case concerned a 12-year-old male patient with a history of possible ADHD and weight loss with previous use of methylphenidate. The patient had no history of depression or previous suicide attempts. He was not receiving any concomitant medications. The patient began an unspecified dose of atomoxetine, which he received only when he went to school. At the time about 8 months on atomoxetine treatment, the patient attempted suicide by hanging himself. He was found blue and unconscious. The patient's mother, who was a nurse, administered rescued breathing. The patient exhaled, gagged, and choked after he was flipped over. The reporting nurse stated —the patient said he met Jesus and was going towards the light. Jesus told him that this was not his time and to go back." The patient was admitted to the pediatric intensive care unit for an unspecified time and was released to a psychiatric hospital, where he received an unspecified antidepressant. Atomoxetine was discontinued. The antidepressant was tapered and later discontinued. Three months after the suicide attempt, the patient gained 25 pounds. As the latest follow-up received 5 months after the event, the patient was reported psychologically better. The physician did not believe atomoxetine was related to the event and would use atomoxetine again.

Case (*overdose, suicidal ideation*), reported by a pediatrician, concerned a 12-year-old patient. The patient's medical history and concomitant medications were not provided. The patient overdosed on an unspecified dose, and the patient was taken to the emergency room for suicidal tendencies. It was not reported that the patient actually overdosed on atomoxetine. The prescribed dose of atomoxetine and time to onset were also not provided. No further information has been provided.

Case (*intentional self-injury*) concerned a 7-year-old male patient who did not have a history of death of a family member, relationship failure, chronic illness, recent surgery, exposure to trauma, social stressors, depression, suicide attempt, suicidal ideations, inpatient psychiatric treatment, alcohol or substance abuse, aggressive or violent behaviour, or been a victim of child abuse or neglect. Additionally, there was no family history of mental illness, suicide, or suicide attempt. The patient was not receiving any concomitant medications. Within a month after the initiation of atomoxetine 25 mg daily, reportedly the patient slit his wrists with a butter knife as an act of self-harm. The patient was not hospitalized, but atomoxetine was discontinued. The patient fully recovered. No further information was available.

Appendix D

Reports of Self-Injurious Behaviour, Intent Unknown (Code 5) – 26 November 2002 – 22 September 2005

Case ID	Age/ Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Self-injury
	9/M	25 mg, 3 weeks	Mildly cognitive deficit. No other medical history was provided. Unknown if taking concomitant medications.	Getting very defiant, and hitting his head more than normal.
	14/M	120 mg, 2 months	Medical history was not provided. No concomitant medications.	Overdosed an unspecified amount of atomoxetine. Unknown if overdose was intentional.
	24/M	40 mg x2, 6 months	History of depression. Taking citalopram and paracetamol.	Took an intentional overdose of 3 to 4 extra doses of atomoxetine and a few citalopram and paracetamol (actual amount unspecified). Went to ER.
	Unk/ M	Unknown	Medical history was not provided. Taking an unidentified stimulant.	Became violently aggressive and began hitting himself excessively.
	14/F	40 mg, 7 months	History of depression, intermittent mood lability, oppositional defiant behaviours, victim of abuse, and hurting herself. Having problems with primary support and social environment (peers). No concomitant medications.	Scratching herself and thought about banging her head against objects. Had depression, suicidal ideation, and oppositional behaviors.
	16/F	80 mg, 2 months	History of ADHD. Taking methylphenidate.	Had uncontrollable rage, anger, self-destruction and property destruction leading to hospitalization in a crisis center.

Case ID	Age/ Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Self-injury
	14/F	Unknown	Medical history was not provided. No concomitant medications.	Overdosed 480 mg of atomoxetine for an unknown reason. One of the 41 literature cases (Spiller et al. 2005).
	12/M	Unknown	Medical history and concomitant medications were not provided.	Claimed to his parents that he swallowed four 25-mg capsules of atomoxetine. Went to ER and had gastric lavage.
	11/M	40 mg, 8 days	History of autism and ADHD. Unknown if taking concomitant medications.	Possibly ingested 10 capsules of 40-mg atomoxetine. Was found standing over the toilet with an open bottle of atomoxetine and 10 capsules were missing.
	15/M	Unknown	History of depression. Unknown if taking concomitant medications.	Overdosed an unspecified amount of atomoxetine for an unknown reason.
	23/M	40 mg x 2, Unknown	Medical history was not provided. No concomitant medications.	Overdosed possible 800 mg atomoxetine (20x 40-mg) for an unknown reason, slept over night.
	18/M	Unknown	History daily use marijuana and excessive drinking over weekend.	Brought to ER via ambulance after taking 480 mg atomoxetine (12X 40-mg).
	10/M	40 mg x 2, <2 months	History of tics while on methylphenidate. No concomitant medications.	He was hitting his head on everything.
	11/M	25 mg, 10 days	Was adopted. History of generalized anxiety disorder and panic attacks. Taking risperidone and bupropion.	Became very psychotic, was trying to hurt himself (unspecified) and was completed disinhibited. Hospitalized.
	7/F	40 mg, 1 month	History of bipolar disorder, oppositional defiant disorder, depression, Asperger's syndrome, ADHD and mood disorder.	Her head pounding tripled in frequency. Was attacking, biting and crying a lot more.
	7/M	25 mg, 10 days	History of ADHD.	At school, acting unruly and was beating his head on the desk. The teachers could not handle him.

Case ID	Age/ Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Self-injury
	10/M	Unknown, 3 to 4 weeks	History of ADHD and an emotional component. Unknown if taking concomitant medications.	Began harming himself and self-scratching to the point of drawing blood.
	<18/F	40 to 60 mg, Unknown	Medical history and concomitant medications were not provided.	Overdosed atomoxetine (unspecified amount and reason) and were to the hospital.
	13/M	40 mg, Unknown	Medical history and concomitant medications were not provided.	Ingested 320 mg atomoxetine (8X 40-mg).
	6/M	25 mg, 12 days	No prior history of similar events. Taking sertraline.	Jumped out of a 15-foot high window and got ran over by a car. Hospitalized.
	14/M	40 mg, 11 days	History of suicide attempts and ADHD. Expelled from 8 schools and was at a school away from home. Taking methylphenidate and lithium. Had over 18 different medications over the years.	The consumer reporter initially stated that the patient talked about suicide, stepped on his own glasses and attempted to cut him self. Follow-up with the consumer claimed that he never talked of suicide while he was on atomoxetine, and he did not try to cut his wrists.
	12/M	18 mg, 1 dose	History of autism, hyper, prone to agitation and non-verbal. Taking risperidone and guanfacine.	On the first day after taking atomoxetine, he sat around and bit and hit himself while crying.
	12/M	60 mg, Unknown	History of autism and seizure. No concomitant medications.	Four days with dose increase, he was hitting and biting himself. He started having seizures.
	12/M	40 mg, 1 dose	History of abnormal EEG without seizure or treatment. No concomitant medications.	After the first dose, he threw up all night, experienced delirium, hitting himself with his fist, hit his brother and father, and trashed his brother's room.
	13/F	Unknown	Medical history was not provided. Taking aripiprazole and fluoxetine.	Intentionally taking aripiprazole 10 mg, atomoxetine 80 mg, and fluoxetine 20 mg, and the next day, taking another 10 mg fluoxetine.

Case ID	Age/ Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Self-injury
	Unk/F	Unknown if she was prescribed ATX	Medical history and concomitant medications were not provided.	Taking 10 capsules of atomoxetine (unknown strength)
	13/F	40 mg, 23 days	History of oppositional defiant disorder, ADHD, explosive temper and a sleep disorder. Experienced traumatic events during the last year. No concomitant medications.	After her brother physically removed her from computer, she reportedly ingested 680 mg atomoxetine (17X 40-mg), started paper on fire, and sat unsafely on the balcony.
	15/M	80 mg, Since started	History of anxiety, which was resolved with sertraline. Methylphenidate was discontinued when atomoxetine started.	The patient cut himself on his wrists and forearms.
	6/M	25 mg, Unknown	Concomitant use of dexmethylphenidate.	Experienced extreme mood swings and aggression, throw himself to the floor, and beat his head on the floor.
	12/F	Unknown, 1 to 2 months	No history of suicidal ideation or attempts, no chronic illness. No concomitant medications.	The ER report stated —the patient inadvertently taken too many atomoxetine".
	12/F	60 mg, 2 to 3 weeks	Unknown medical history. Taking methylphenidate and risperidone.	Got violent toward herself, like hitting her self.
	13/F	50 mg, Unknown	History of mild mental retardation, ADHD, bipolar, anxiety, depression, suicide attempt and hallucination. Taking sertraline, paroxetine, haloperidol, lorazepam, and lithium, olanzapine, several other meds.	Experienced irritation, suicidal thoughts, hurt her self (unspecified), and had an episode of —running around naked."
	Unk/ M	Unknown	Medical history and concomitant medications were not provided.	Became more aggressive, depressed and harmed him self (unspecified).
	Adult/ F	40 mg x 2, 8 days	History of schizophrenia, chronic mental illness, and suicide attempts, setting fires, and inpatient psychiatric treatment. Taking clonazepam, quetiapine, escitalopram, oxcarbazepine and ziprasidone.	Set fire to her self as an act of self-harm.

Appendix E

Reports of Self-Injurious Behaviour, No Suicidal Intent (Code 7) – 26 November 2002 – 22 September 2005

Case ID	Age / Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Self-Injury
	Un k/M	40 mg x 2, Unknown	Drug abuser. Taking olanzapine for treatment of psychosis.	Overdose of cocaine and —possible other substances"
	17/ M	60 mg, 45 days	History of autism (high functioning), Tourette's syndrome and ADHD.	Claimed overdosing 350 mg atomoxetine (14X 25-mg) and methylphenidate (7-8X 10 mg), as he "felt bored" and proved atomoxetine making no impact on ADHD and autism.
	40/ F	60 mg, <1 month	History of depression, ADHD, sleeping problem and self-mutilation. Taking bupropion and trazodone.	Became more anxious, depressed and started self-mutilating (unspecified).
	32/ F	Unknown	History of depression and illegal drug use. Taking citalopram and risperidone.	Crushed atomoxetine capsule and injected antecubially. She claimed due to anger, not to obtain a high.
	5/M	25 mg, Unknown	No prior history of aggression. Taking clonidine.	Reportedly he started biting himself to try to curb the urges to be aggressive and hitting/pinching others.
	17/ F	40 mg, <1 month	History of impulsive behavior and cutting herself a year ago. Taking methylphenidate and citalopram.	She scraped her arm with a pair of tweezers. She claimed she did not know why she did this and stated she —could not help it."
	10/ F	25 mg, 3 days	Unknown medical history. No concomitant medications.	She complained of headaches and stomach aches. She was banging her head on the couch because her head hurt so badly.
	9/M	25 mg, 2 to 3 weeks	History of obsessive-compulsive disorder, tics and ADHD. Taking sertraline, clonazepam and clonidine.	He experienced an erection that was not sexually stimulated and would not go away. He did not understand what happened and tried to cut his penis with a pair of scissors. No damage reported.
	15/ M	25 mg, 5 days	History of ADHD, learning disorder and acne. Taking amphetamine /dextroamphetamine.	He took the pole off his weight bench and destroyed his room by breaking glass/windows, almost put his head through the wall. He scratched his face and put his fingers in his mouth.
	15/ F	60 mg, ~2 weeks	Suspected being sexual abused as a child. No history of alcohol or drug abuse. Taking zoldipem.	She took a Q-tip and dipped it in alcohol, set it on fire and used it to write on her arm.

Reports of Self-Injurious Behaviour, No Suicidal Intent (Code 7) – 23 September 2005 – 25 October 2005)

Case ID	Age / Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Self-Injury
	15/F	40 mg, Unknown	History of Tourette's and ADHD. Unknown if taking concomitant medications.	She had outbursts of anxiety at school and did not go to school for two weeks. She had an episode where she started hurting herself, pulling her hair and alternately laughing.
	5/M	10 mg, Unknown	Unknown medical history and concomitant medications.	He exhibited self injurious behaviour by biting him self and an increase in hyperactive behaviour.
	14/M	40 mg, 2 weeks	History of anxiety, low self-esteem, a little bit aggressive and learning, speech and language difficulties. Weight 32.5kg. Taking dexamfetamine (stopped a couple of days prior to the events).	He was aggressive, and pulled out his hair from the crown of his head, leaving a one-inch diameter bald circle, and put his hand through a window. He said his "head was medded up" and he "did not feel right".
	9/M	18 mg, ~2 months	Unknown medical history. No concomitant medications.	He became disturbed, moody, and tearful, and ran off. He then climbed a 25 feet wall (but was not suicidal, more "daring" according to the reporting doctor). He also self-harmed – hitting his head and sticking in pins (no detail).