

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

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SUBJECT: Age-dependent manifestations of central anticholinergic effects

DRUGS: Oxybutynin: Ditropan®, Ditropan® syrup, Ditropan XL® (J&J); Oxytrol™ (Watson)

RCM#: 2007-181

1. EXECUTIVE SUMMARY

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology. ****

Oxybutynin is an anticholinergic tertiary amine that was first approved in the U.S. in 1975 for the treatment of overactive bladder. Pediatric exclusivity was granted in 2002. A review of pediatric adverse events in association with oxybutynin completed for the November 16, 2006 Pediatric Advisory Committee (PAC) noted that there were a disproportionate number of central nervous system (CNS) adverse event reports in the pediatric population compared to adults. As a result, the Office of Pediatric Therapeutics (OPT) requested an in-depth review of all cases of CNS adverse events with oxybutynin and requested that the proportion of CNS adverse events in children should be assessed and compared to CNS adverse events in adults.

We reviewed 202 CNS adverse events cases in association with oxybutynin (37 pediatric, 143 adult and 22 no age reported). A significant portion (>12%) of all adverse event reports for oxybutynin involve a CNS adverse event.

Compared to the adult cases, the pediatric AERS cases in association with oxybutynin differ in both number and types of CNS events:

- Taking domestic usage by age group into account, there is a disproportionately higher number of CNS adverse event cases reported in pediatric patients as compared to adult patients. Also, pediatric CNS reports represent a greater percentage of total pediatric oxybutynin reports than adult CNS reports do for all adult oxybutynin reports (31% and 11%, respectively).
- Hallucination was the most common CNS event reported for pediatric patients (27% of cases). Hallucination was the second most common CNS adverse event (25% of cases) in elderly patients (ages 60+ yrs). Hallucination was reported in only 11% of cases in patients 17-59 yrs of age.
- Pediatric CNS cases reported agitation more than twice as often as adult cases (14% pediatric cases vs. 6% adult cases).
- Adult CNS cases reported sedation more than twice as often as pediatric cases (24% adult cases vs. 11% pediatric cases).
- Confusion was the most common CNS event reported for elderly patients (ages 60+yrs) and was reported three times as often vs. patients less than 60 yrs of age (30% elderly cases vs. 10% of cases in patients less than 60 yrs).

Although the adverse reactions sections of the Ditropan and Ditropan XL labels list some CNS events (i.e. somnolence, insomnia, nervousness, confusion, hallucinations), the current labeling does not explicitly describe the potential for CNS anticholinergic effects, or the age-dependent pattern of CNS effects that have been reported. We recommend that the labeling be revised to include the following points under **PRECAUTIONS**:

- ❖ Oxybutynin has the potential to cause anticholinergic central nervous system (CNS) effects, and these adverse effects have been reported postmarketing. Postmarketing reports describe a variety of CNS anticholinergic effects, with hallucinations and agitation prominent among pediatric cases, and confusion, hallucinations, and sedation prominent among reports involving geriatric use.
- ❖ Patients should be monitored for signs of anticholinergic CNS effects, particularly in the first few months after beginning treatment or increasing the dose. If patients experience anticholinergic CNS effects, drug discontinuation should be considered.

2. REASON FOR REVIEW

Pediatric Exclusivity was granted for oxybutynin on February 8, 2002. A review of pediatric adverse events reports was completed in May 2003¹ and focused on reports that were received in the first 13 months following the approval of pediatric exclusivity (February 8, 2002-March 19, 2003). At the June 12, 2003 Pediatric Advisory Committee Meeting (PAC), the PAC requested additional monitoring due to the small number of postmarketing adverse event reports. The follow-up review completed September 2006² for the November 16, 2006 PAC noted that there were a disproportionate number of central nervous system (CNS) adverse event reports in the pediatric population compared to adults. As a result, the Office of Pediatric Therapeutics (OPT) requested a review of all cases of CNS adverse events with oxybutynin and requested that the proportion of CNS adverse events in children should be assessed and compared to CNS adverse events in adults.

3. RELEVANT PRODUCT LABELING

Table 1: Relevant oxybutynin labeling

Section of label:	Current Oxybutynin Labeling:
Indications	<p>Ditropan® tabs/syrup (not age specific) indicated for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e. urgency, frequency, urinary leakage, urge incontinence, dysuria).</p> <p>Ditropan XL® pediatric: indicated in the treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida).</p> <p>Oxytrol™(transdermal patch) – no pediatric indication</p>
Precautions: Pediatric Use	<p>Ditropan® tabs/syrup - the safety and efficacy of Ditropan administration have been demonstrated for pediatric patients 5 years of age and older. The safety and efficacy of Ditropan Tablets and Ditropan Syrup were studied in 30 and 26 children, respectively, in a 24-week, open-label trial. Patients were aged 5-15 years, all had symptoms of detrusor overactivity in association with a neurologic condition (e.g. spina bifida). Study results demonstrated that the administration of DITROPAN was associated with improvement in clinical and urodynamic parameters (At total daily dose of 5mg to 15mg with Ditropan tablets and at total daily doses of 5mg to 30mg, treatment with Ditropan Syrup)...As there is insufficient clinical data for pediatric populations under age 5, Ditropan is not recommended for this age group.”</p> <p>Ditropan XL® The safety and efficacy of DITROPAN XL were studied in 60 children in a 24-week, open-label trial. Patients were aged 6-15 years, all had symptoms of detrusor overactivity in association with a neurological condition (e.g., spina bifida). Study results demonstrated that administration of DITROPAN XL 5 to 20 mg/day was associated with an increase from baseline in mean urine volume per catheterization from 108 mL to 136 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 189 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34% to 51%. Urodynamic</p>

¹ Farinas E. One year post-pediatric exclusivity postmarketing adverse event review: oxybutynin. DDRE/ODS. DFS May 8, 2003.

² Gish P. Post-pediatric exclusivity postmarketing adverse event review - update for Fall 2006 PAC: oxybutynin. DDRE/OSE. DFS September 15, 2006.

Section of label:	Current Oxybutynin Labeling:
	<p>results were consistent with clinical results. Administration of DITROPAN XL resulted in an increase from baseline in mean maximum cystometric capacity from 185 mL to 254 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 44 cm H₂O to 33 cm H₂O, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H₂O) from 60% to 28%. ...DITROPAN XL is not recommended in pediatric patients who can not swallow the tablet whole without chewing, dividing, or crushing, or in children under the age of 6.</p> <p>Oxytrol™(transdermal patch) - The safety and efficacy of OXYTROL in pediatric patients have not been established.</p>
Adverse Reactions	<p>Ditropan® tabs/syrup (not age specific) - somnolence, insomnia, nervousness, confusion, hallucinations, convulsions</p> <p>Ditropan XL® (not age specific) - somnolence, insomnia, nervousness, confusion, hallucinations, convulsions</p> <p>Oxytrol™(transdermal patch) – fatigue, somnolence</p>
Overdosage	<p>Ditropan® tabs/syrup - Overdosage with oxybutynin chloride has been associated with anticholinergic effects including CNS excitation (e.g. restlessness, tremor, irritability, convulsions, delirium, hallucinations)...coma. Ingestion of 100mg oxybutynin chloride in association with alcohol has been reported in a 13 year old boy who experienced memory loss, and a 34 year old woman who developed stupor, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients fully recovered with symptomatic treatment.</p> <p>Ditropan XL® - Overdosage with oxybutynin chloride has been associated with anticholinergic effects including central nervous system excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention. Ingestion of 100 mg oxybutynin chloride in association with alcohol has been reported in a 13-year-old boy who experienced memory loss, and a 34-year-old woman who developed stupor, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients fully recovered with symptomatic treatment.</p> <p>Oxytrol™(transdermal patch) – same as Ditropan XL®</p>
Dosage and administration	<p>Ditropan® tabs/syrup - in pediatric patients over 5 years of age: 5mg two times a day, maximum 5mg three times a day.</p> <p>Ditropan XL® - Pediatric patients aged 6 years of age and older: The recommended starting dose of Ditropan XL is 5mg once daily. Dosage may be adjusted in 5mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 20mg/day)</p> <p>Oxytrol™(transdermal patch) – no pediatric dosing</p>

4. DRUG USAGE

Table 2 provides U.S. oxybutynin use data, from Verispan, LLC, by age for the last 5 years. The table shows that consistently between 2002 and 2006, approximately 5% of users were pediatric patients (ages 0-16 yrs).

Table 2: Drug Usage Information
(values are in thousands, add 3 zeros)

Projected number of total † prescriptions dispensed by retail pharmacies (mail-order excluded) <i>(values are in thousands, add 3 zeros)</i>										
Oxybutynin	2002		2003		2004		2005		2006	
	TRxs	% share								
Age band	5,373	100.0%	5,589	100.0%	5,741	100.0%	5,237	100.0%	4,881	100.0%
0-5 yrs	44	0.8%	44	0.8%	40	0.7%	35	0.7%	38	0.8%
6-16 yrs	223	4.1%	221	4%	215	3.7%	199	3.8%	203	4.2%
17-29 yrs	150	2.8%	157	2.8%	157	2.7%	144	2.8%	136	2.8%
30-39 yrs	237	4.4%	240	4.3%	224	3.9%	195	3.7%	187	3.8%
40-49 yrs	575	10.7%	584	10.5%	562	9.8%	497	9.5%	451	9.2%
50-59 yrs	859	16%	899	16.1%	904	15.8%	834	15.9%	789	16.2%
60-69 yrs	853	15.9%	916	16.4%	937	16.3%	865	16.5%	859	17.6%
70-79 yrs	1,157	21.5%	1,198	21.4%	1,237	21.5%	1,109	21.2%	1,025	21%
80+ yrs	1,241	23.1%	1,290	23.1%	1,393	24.3%	1,289	24.6%	1,168	23.9%
UNSPEC.	35	0.6%	40	0.7%	74	1.3%	71	1.4%	25	0.5%

Citation: Verispan Vector One®: National, data extracted 2-8-2007
Source Files: 2007-181 VONA Gish Oxybutynin molecule-age-product
Drug Use Specialist: LCDR Dave Money RPh
† Total includes New and Refill prescriptions

Pediatric use

Based on data from Verispan Vector One®: national, approximately 241,000 prescriptions were written for patients ages 0-16 years in 2006. At least 18% (43,000/241,000) of the pediatric prescriptions were for use in an unapproved patient population:

- Approximately 38,000 oxybutynin prescriptions were written for ages 0-5 in 2006. Oxybutynin is not approved for use in this age group.
- Approximately 5,000 prescriptions were written for Oxytrol patch for patients ages 6-16. Oxytrol patch is not approved for pediatric use.

Based on data from Verispan Vector one®: Total Patient Tracker, approximately 84,000 pediatric patients were prescribed an oxybutynin product during 2006. At least 23% of pediatric patients (19,500/84,000) were prescribed oxybutynin off-label³:

- Approximately 18,000 patients 0-5 years of age received a prescription for any oxybutynin product during 2006. Oxybutynin is not approved for use in this age group.
- Approximately 1,500 patients 6-16 years of age received a prescription for Oxytrol patch during 2006. Oxytrol patch is not approved for pediatric use.

5. SEARCH CRITERIA

³ Moeny D. Post-Pediatric Exclusivity Post-marketing Adverse Event Review: Drug Use Data Update: Oxybutynin. OSE/DSRCS. DFS February 12, 2007.

Anticholinergic CNS effects as described in the medical literature include sedation, confusion, cognitive impairment, delirium, agitation, and hallucinations.^{4,5}

AERS was searched on January 12, 2007 for reports of anticholinergic CNS adverse events in association with oxybutynin using the Preferred Terms (PTs) listed below.

<i>Abnormal behaviour</i>	<i>Disturbances in attention</i>	<i>Panic attack</i>
<i>Abnormal dreams</i>	<i>Drug toxicity</i>	<i>Panic reaction</i>
<i>Abnormal sleep-related event</i>	<i>Emotional disorder</i>	<i>Paranoia</i>
<i>Aggression</i>	<i>Fatigue</i>	<i>Personality change</i>
<i>Agitation</i>	<i>Hallucination</i>	<i>Personality disorder</i>
<i>Amnesia</i>	<i>Hallucination, auditory</i>	<i>Psychomotor hyperactivity</i>
<i>Anger</i>	<i>Hallucination, visual</i>	<i>Psychotic disorder</i>
<i>Anticholinergic syndrome</i>	<i>Initial insomnia</i>	<i>Restlessness</i>
<i>Anxiety</i>	<i>Insomnia</i>	<i>Sedation</i>
<i>Attention deficit/hyperactivity disorder</i>	<i>Irritability</i>	<i>Senile dementia</i>
<i>Cognitive disorder</i>	<i>Lethargy</i>	<i>Sleep disorder</i>
<i>Confusional state</i>	<i>Memory impairment</i>	<i>Sleep terror</i>
<i>Convulsion</i>	<i>Mental status changes</i>	<i>Sleep walking</i>
<i>Delirium</i>	<i>Middle insomnia</i>	<i>Somnolence</i>
<i>Delusion</i>	<i>Mood altered</i>	<i>Thinking abnormal</i>
<i>Dementia</i>	<i>Nervousness</i>	<i>Tremor</i>
<i>Dementia alzheimer's type</i>	<i>Obsessive thoughts</i>	
<i>Disorientation</i>	<i>Obsessive-compulsive disorder</i>	

Three-hundred forty-seven (347) reports (crude count – may contain duplicates) were retrieved from AERS.

6. AERS SEARCH RESULTS

Three-hundred forty-seven (347) reports were retrieved from AERS. Of these reports, 55 were pediatric patients (age 0-16 yrs) and 256 were adult patients (age 17 yrs and older) and 36 reports did not provide age information.

These reports were reviewed individually to exclude duplicate reports, reports with characteristics that made a causal relationship to oxybutynin use unlikely, and reports with inadequate information. Eighteen (33%) of the 55 pediatric reports were excluded, 113 (44%) of the 256 adult reports were excluded, and 14 (39%) of the 36 reports with no age information were excluded. Please refer to the Appendix for a complete listing of the reasons individual cases were excluded from the case series.

The remaining 202 cases (37 pediatric, 143 adult, 22 no age reported) reporting CNS adverse events were reviewed further.

⁴ Feinberg M. The problems of anticholinergic adverse effects in older patients. *Drugs Aging* 1993;3(4):335-48.

⁵ Brown J, Taylor P. Chapter 7: Muscarinic receptor agonists and antagonists. *Goodman & Gilman's the pharmacological basis of therapeutics*. 11th ed. /editors, Laurence Brunton, John Lazo, Keith Parker. The McGraw-Hill Companies, Inc 2006:183-200.

7. SUMMARY OF DATA

Table 3 summarizes the number of AERS reports of CNS adverse events in pediatric patients compared to adult patients. The Table shows:

- After exclusions at least 12% (202/1667) of all adverse events for oxybutynin involve a CNS adverse event.
- At least 31% (37/116) of all reports for pediatric patients involve a CNS adverse event as compared to 11% (143/1311) of adult reports.

**Table 3: AERS Reports – CNS adverse events
Oxybutynin**

*From date of product marketing through 1/12/2007. †
(# of U.S. reports is in parentheses)*

Oxybutynin † <i>(No. of U.S. reports are in parentheses)</i>	Peds (U.S.) (0-16 yrs)	Adults (U.S.) (17+ yrs)	Null (U.S.)	Total (U.S.)
Total # reports- all adverse events *	116 (88)*	1311(1084)*	240(213)*	1667(1385)*
# of reports –CNS adverse events*	55(39)*	256(194)*	36(33)*	347(266)*
Excluded reports	18(11)	113(63)	14(13)	145(87)
Duplicates	6(3)	26(14)	3(2)	35(19)
Other exclusions	12(8)	87(49)	11(11)	110(68)
# of cases of CNS adverse events	37(28)	143(131)	22(20)	202(179)

* Note: crude counts – may contain duplicates and one report may have more than one Preferred Term (PT)

† Note: Ditropan tablets/syrup and Ditropan XL were granted waivers for submitting forms 3500A for non-serious labeled events on April 20, 1998, and September 5, 2002, respectively.

7.1 Pediatric cases reporting CNS adverse events (N=37)

The characteristics of the 37 pediatric cases of CNS events are summarized below in Table 4. All 37 pediatric cases are detailed at the end of this document in Table 7.

TABLE 4: Characteristics of Pediatric CNS Adverse Event Cases (N=37) Oxybutynin			
<i>From date of product marketing through 1/12/2007.</i>			
Age (years)	<ul style="list-style-type: none"> • 0-<1 mo - 0 • 1 mo- < 2 yrs - 2 • 2-5 yrs - 12 • 6-11 yrs - 17 • 12-16 yrs - 5 • Unk - 1 <p>Mean: 6.7, Median: 6 Range: 15 mos to 16 yrs</p>	Report year (number of cases)	1975-1 1993-1 1977-1 1994-1 1979-1 1996-4 1982-1 1997-4 1985-1 2000-3 1988-2 2001-1 1989-5 2002-3 1990-2 2005-3 1992-1 2006-2
Gender (number of cases)	<ul style="list-style-type: none"> • Males: 18 • Females: 18 • Unk: 1 	Location (number of cases)	<ul style="list-style-type: none"> • US – 28 • Foreign – 7 • Unknown - 2
Reporter (number of cases)	<ul style="list-style-type: none"> • Health care professional-29 • Literature report -4 (foreign-3, domestic-1) • Consumer/Parent-3 • Not reported-1 		
Total daily dose (number of cases)	≤10mg - 20 (including accidental exposure-1) ≤20mg - 7 (including accidental overdose/med error-1)		

TABLE 4: Characteristics of Pediatric CNS Adverse Event Cases (N=37) Oxybutynin <i>From date of product marketing through 1/12/2007.</i>	
	21mg - 1 15mg vesicular + 10mg oral - 1 25mg - 1 (accidental overdose/med error) 50mg - 1 (accidental overdose/med error) 60mg - 1 (intentional overdose) 100mg - 1 (intentional overdose) 225mg - 1 Not reported - 3 (including accidental exposure-1)
Reported indication (number of cases)	Nocturnal enuresis - 4 Isolated enuresis - 1 Enuresis - 5 Incontinence - 2 Neurogenic bladder - 7 Post urological surgery - 2 Relaxation of bladder muscles - 1 Overactive bladder - 1 Bladder spasms - 2 Dysfunctional bladder - 1 Accidental exposure - 2 Not reported - 9
Time to onset (number of cases)	<ul style="list-style-type: none"> • ≤1 day - 9 • ≤1 week - 4 • ≤1 month - 7 • ≤3 months - 3 • ≤6 months - 1 • ≥1 year - 5 • Not reported - 8
Concomitant meds/ Psychiatric history	14 of the 37 reported one or more of the following: <ul style="list-style-type: none"> • Psychiatric/neuro history-5 (ADHD-1, disruptive behavior-1, anxiety-1, brain damage-1, multiple sclerosis-1) • Concomitant psychoactive meds-6 (pemoline-1, Ritalin-1, benzodiazepines-1, alcohol-1, meperidine-1, carbamazepine-1)) • Concomitant anticholinergic meds-3 (Benadryl-2, Triaminic-1) • Other-2 (recently started school-2)
Dechallenge (number of cases)	<ul style="list-style-type: none"> • Positive - 23 • Negative - 0 • Did not discontinue oxybutynin - 6 • Not applicable/Not reported – 8
Rechallenge (number of cases)	<ul style="list-style-type: none"> • Positive - 4 • Negative - 0 • Not applicable/Not reported – 33
Outcome (number of cases)	<ul style="list-style-type: none"> • Hospitalized - 6 • Disability - 2 • Life-threatening - 1 • Required intervention - 1 • Other (considered “medically significant”) - 6

Most common Preferred Terms reported

The most common PTs relating to CNS events for pediatric patients were hallucinations (27% or 10/37 CNS cases), followed by agitation (14%), sedation (11%), confusion (11%), amnesia (11%), and abnormal dreams (11%).

Cases accompanied by other (non-CNS) anticholinergic effects

Eight of the 37 cases of CNS events were accompanied by non-CNS anticholinergic effects (8/37 cases reported one or more of the following: dilated pupils-3, tachycardia-3, dry mouth-3, flushing-2, constipation-1, urinary retention-1, peripheral edema-1, dry skin-1, anhydrosis/overheating-1).

Positive dechallenges/rechallenges

Twenty-three of the 37 cases reported the CNS events abated after oxybutynin was discontinued or the dose was reduced (positive dechallenge).

Four of the 37 cases reported the CNS events reappeared after oxybutynin was reintroduced (positive rechallenge). The 4 cases are summarized below:

Case #4637374, ISR 568057-6, MFR# 890632 - [redacted] 1989

A 4-year-old female began treatment with oxybutynin syrup 10mg/day for enuresis on June 24, 1988. The same day the child experienced visual hallucinations. The drug was administered again the following evening and the hallucinations recurred. Oxybutynin was discontinued and the hallucinations stopped.

Case #4745444, ISR 690817-1, MFR# 9013017 - France 1990 (Literature ⁶)

A 6-year-old male began treatment with oxybutynin tablets 5mg twice a day (10mg total daily dose) for isolated enuresis. Four days later the child awoke with nightmares and visual hallucinations. The mother stopped the drug, and the events abated. She resumed oxybutynin several days later. She gave the child one tablet at 5pm and one tablet at 10pm. At about 4am the child awoke with elaborate visual hallucinations. He saw large beast moving all over his body, causing pain, tonic seizures at the moment of the pain, agitation and crying. He was admitted to the hospital. The child stated he had swellings over his entire body but clinical examination showed no skin anomaly.

On admission at 10am he was highly agitated and suffering from extreme anguish and had severe and persistent hallucinations. He was constipated and his mouth was dry. His pupils were normal and his pulse was 80 beats per minute. He had no fever. The reaction abated 12 hours after hospitalization. Blood levels 12 hours after the last dose revealed oxybutynin chloride: 11ng/ml.

Case #4637376, ISR 568059-X, MFR# 881823 - [redacted] 1989

A 4-year-old male began treatment with oxybutynin syrup 10mg twice daily (20mg total daily dose) for uninhibited bladder on August 14, 1987. The patient had a history of daytime enuresis, dysuria, and X-ray bilateral vesicoureteral reflux. Three weeks later, on September

⁶ Choulot J, Mensire A, Saint Martin J. Overdosage of atropine drugs and confusional syndrome. Ann Pediatr (Paris) 1989;36(10):714.

4th, the patient developed hyperactivity. The hyperactivity abated after stopping oxybutynin and reappeared after reintroduction. Oxybutynin was permanently discontinued 4 months later in January, 1988.

Case #5547778, ISR 1903322-9, MFR97001470 - [redacted] 1997 (Literature ⁷)

A 3-year-old female began treatment with oxybutynin tablets 5mg/day for neurogenic bladder. One week later the patient began treatment with Triaminic (75 mg phenylpropanolamine, 12mg chlorpheniramine), at a dose of 1 capsule a day. Three weeks later the patient manifested bizarre behavior, sleep disturbances with nightmares, hyperactivity, anorexia and incoherent speech. When the medications were discontinued, her symptoms subsided within 24 hours.

At 6-years of age she was again started on the same two drugs at comparable doses for six weeks, until her neuropsychiatric symptoms led to her hospitalization. On admission, the child was anxious, agitated and had pressured speech. She had slightly dilated pupils. She complained of insomnia, nightmares and visual hallucinations about plants turning red and violent death scenes. She was preoccupied with death and feared she might be harmed by television actors. The parents denied any possibility of drug overdose or acute family crisis. A urine drug screen showed no trace of hallucinogens or stimulants. Both medications were discontinued and within one to two days the symptoms subsided.

Cases with psychiatric/neurologic medical history and/or concomitant psychotropic medications

Fourteen of the 37 reported one or more of the following:

- Psychiatric/neuro history-5 (ADHD-1, disruptive behavior-1, anxiety-1, brain damage-1, multiple sclerosis-1)
- Concomitant psychoactive meds-6 (pemoline-1, Ritalin-1, benzodiazepines-1, alcohol-1, meperidine-1, carbamazepine-1)
- Concomitant anticholinergic meds-3 (Benadryl-2, Triaminic-1)
- Other-2 (recently started school-2)

Although these cases may be considered confounded, in many of these reports a causal relationship to oxybutynin was suggested by one or more of the following: the events began shortly after oxybutynin therapy was added (e.g. 5 days) (n=8); the events abated after oxybutynin was discontinued (n=8); the events were considered due to additive effects of multiple anticholinergic medications (n=3); the events were accompanied by other classical anticholinergic toxicity events (e.g. overheating, tachycardia, dilated pupils) (n=3).

⁷ Hamdan-Allen G, Nixon M. Anticholinergic psychosis in children. A case report. *Hosp Commun Psych* 1991;42(2): 191-193.

Off-label use

Fifty-one percent (19 of the 37 cases) reported off-label use due to one or more of the following:

- unapproved age (< 6 yrs) - 13
- unapproved indication (nocturnal/isolated enuresis) - 5
- prescribed daily dose exceeded maximum recommended pediatric dose (> 20mg/day) - 3

Hospitalizations

6 cases reported the events resulted in hospitalization:

- 6-year-old female receiving oxybutynin for neurogenic bladder: developed agitation/hallucinations/abnormal dreams/personality disorder (Case #5547778)
- 9-year-old male receiving oxybutynin for unknown indication: developed hallucinations/edema of face and hand (Case #3483209)
- 6-year-old male receiving oxybutynin for isolated enuresis: developed hallucinations/abnormal dreams/convulsions (Case #4745444)
- 23-month-old child receiving oxybutynin for recent hypospadias surgery; patient received accidental overdose/medication error: developed antimuscarinic intoxication (Case #5833321)
- 15-month-old female was accidentally exposed to oxybutynin: developed somnolence, tachycardia, urinary retention, pyrexia (Case #6056158)
- 7-year-old male receiving oxybutynin for neurogenic bladder: developed agitation (Case #4362700)

Reporters

The majority of cases (89% or 33/37) were reported by health care professionals (including 4 literature reports). Three cases (8%) were reported by consumers/parents.

Polypharmacy

Two cases reported the events were treated by adding another medication:

- hydroxyzine was added to treat insomnia (Case #3797797)
- paroxetine was added to treat anxiety (Case #3805625)

7.2 Comparison of Pediatric and Adult CNS Cases

The following table displays by age group the number of domestic AERS adverse event reports (crude counts), and domestic CNS cases in our case series (for which age was reported) compared to domestic prescriptions for 2006. As reflected in the figures below, the proportion of total adverse event reports in pediatric age groups is slightly higher than the proportion of pediatric prescriptions. However, the proportion of CNS adverse event cases in pediatric age groups has been significantly higher relative to the proportion of pediatric prescriptions. (Although for this comparison we show only 2006 prescription data, the proportion of pediatric use has been relatively stable in recent years, as seen in Table 2 above).

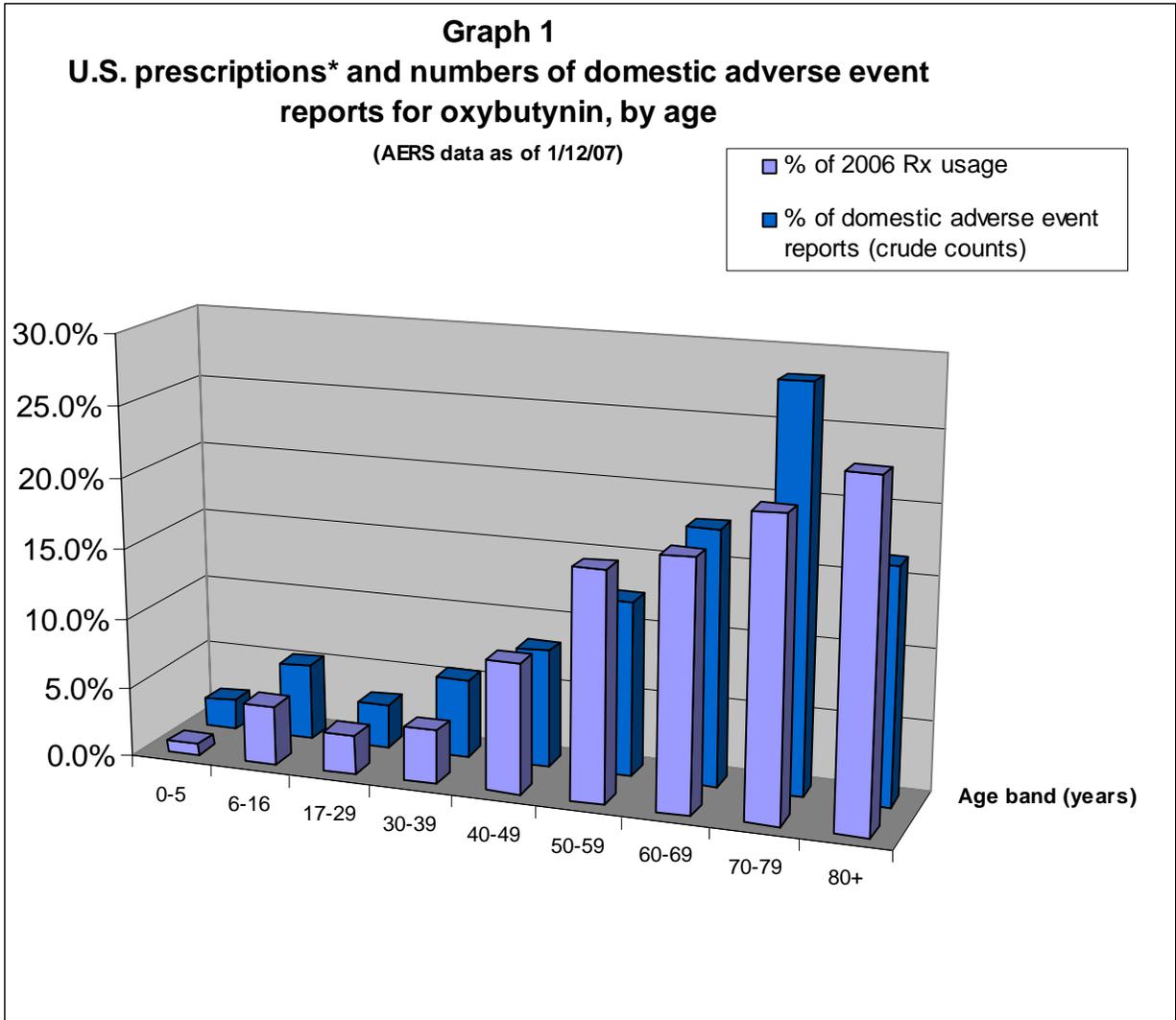
Table 5: U.S. retail prescriptions (mail-order excluded), numbers of domestic adverse event reports and numbers of domestic CNS adverse event cases for oxybutynin, by age

Age group (yrs)	0-5	6-16	17-29	30-39	40-49	50-59	60-69	70-79	80+	Total
Total Rx's (mail-order excl), 2006, in thousands (add three zero's) (source: Verispan)	38	203	136	187	451	789	859	1025	1168	4,856
% of 2006 Rx usage	0.8%	4.2%	2.8%	3.8%	9.2%	16.2%	17.6%	21%	23.9%	99.6%
Number of domestic reports – all adverse events (crude counts, may contain duplicates)	25	63	37	65	98	146	211	332	195	1,172
% of domestic reports	2.1%	5.4%	3.2%	5.5%	8.4%	12.5%	18%	28.3%	16.6%	100%
Number of domestic CNS cases	12*	15*	3	12	13	15	20	40	28	158
% of domestic CNS cases	7.6%	9.5%	1.9%	7.6%	8.2%	9.5%	12.7%	25.3%	17.7%	100%

*Note: Total number domestic CNS pediatric cases in Table 5 totals 27 instead of 28 (from Table 3) because one pediatric case only stated the patient was “a child” and therefore the age band could not be determined.

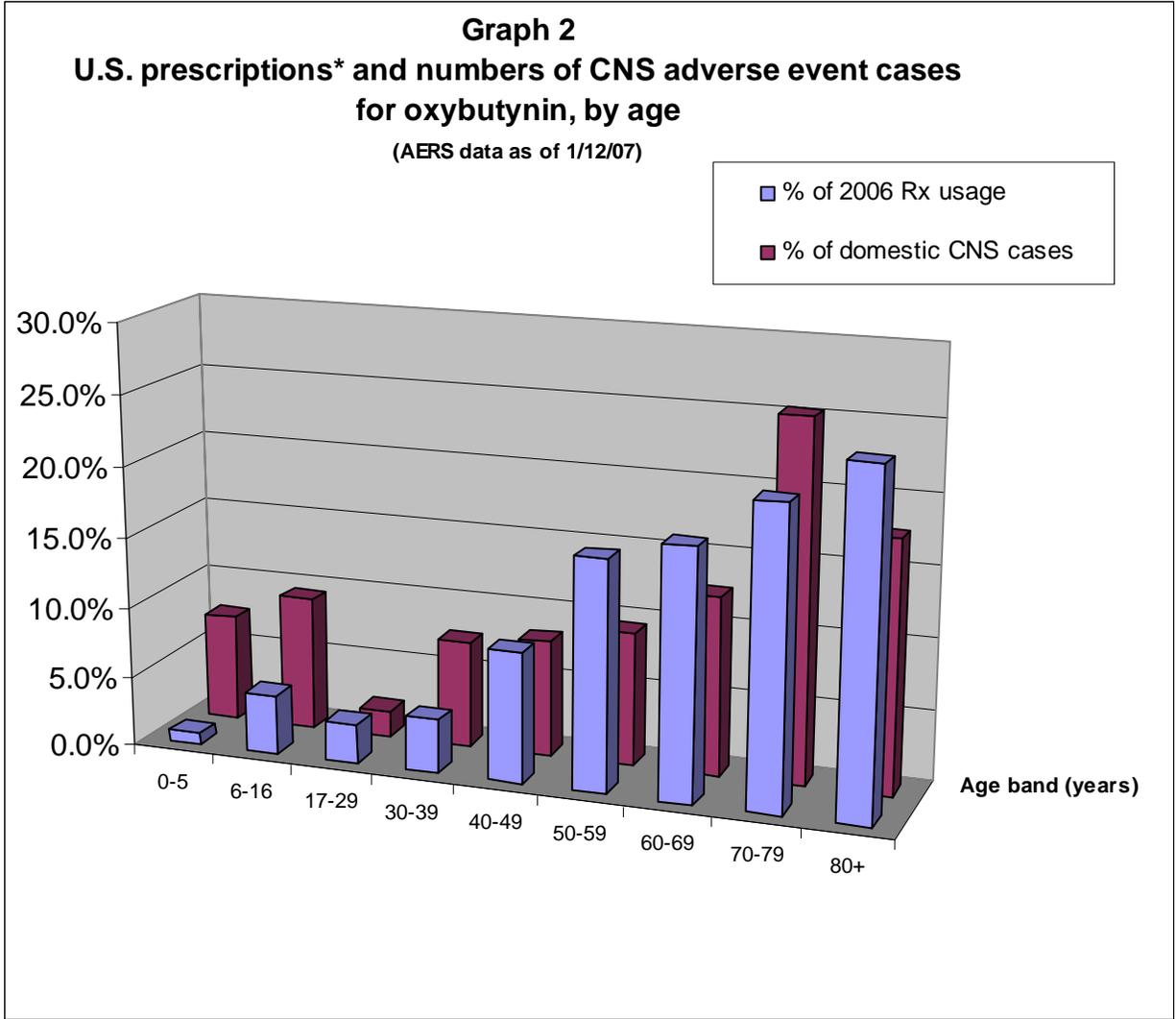
The following two graphs display the same data.

In Graph 1 the proportion of total adverse event reports in pediatric age groups is slightly higher (7.5%) to the proportion of pediatric prescriptions (5%). The proportion of total adverse event reports (92.5%) in adult age groups is approximately the same as the proportion of adult prescriptions (94.6%):



* Projected number of Rxs dispensed by retail pharmacies (mail-order excluded) Source: Verispan Vector One®

However, in Graph 2 the proportion of CNS adverse event cases in pediatric age groups is significantly higher (17.1%) relative to the proportion of pediatric prescriptions (5%). The proportion of CNS adverse event cases in adult age groups (82.9%) is slightly less than the proportion of adult prescriptions (94.6%):



* Projected number of Rx's dispensed by retail pharmacies (mail-order excluded) Source: Verispan Vector One®

The data shown above reflect the case series after review and exclusion of cases based on various characteristics, as was described above. If the same comparison is made using the numbers of reports with only duplicate reports excluded, the disproportion in the number of pediatric cases is still present (data not shown).

Table 6 summarizes the most common CNS Preferred Terms by age. The Table shows that:

- Hallucination was the most common CNS event reported for pediatric patients (27% of cases). Hallucination was the second most common CNS adverse event (25% of cases) in elderly patients (ages 60+ yrs). Hallucination was reported in only 11% of cases in patients 17-59 yrs of age.
- Pediatric cases reported agitation more than twice as often as adult cases (14% pediatric cases vs. 6% adult cases).
- Adult cases reported sedation more than twice as often as pediatric cases (24% adult cases vs. 11% pediatric cases).

- Confusion was the most common CNS event reported for elderly patients (ages 60+yrs) and was reported three times as often vs. patients less than 60 yrs of age (30% elderly cases vs. 10% of cases in patients less than 60 yrs).

**Table 6: Most common CNS Preferred Terms reported by age (N=180)
Oxybutynin**

From date of product marketing through 1/12/2007

Table 6: # of CNS adverse event cases by age band and PT - Oxybutynin <i>(# of U.S. cases in parenthesis)</i>	0-16 yrs N=37 (28)	% of CNS cases <i>0-16 yrs</i>	17-59 yrs N=46(43)	% of CNS cases <i>17-59 yrs</i>	60+ yrs N=97(88)	% of CNS cases <i>60+ yrs</i>	TOTAL N=180 (159)	% of CNS cases - all ages
HALLUCINATION	10(7)	27%	5(5)	11%	24(23)	25%	39 (35)	22%
SEDATION	4(4)	11%	13(13)	28%	21(20)	22%	37(36)	21%
CONFUSIONAL STATE	4(4)	11%	4(4)	9%	29(24)	30%	37(32)	21%
AGITATION	5(3)	14%	3(1)	7%	6(5)	6%	14(9)	8%
ANXIETY	1(0)	3%	6(6)	13%	6(6)	6%	13(12)	7%
AMNESIA	4(2)	11%	3(3)	7%	6(6)	6%	13(11)	7%
ABNORMAL DREAMS	4(3)	11%	2(2)	4%	3(3)	3%	11(8)	6%
THINKING ABNORMAL	3(3)	8%	2(2)	4%	2(2)	2%	7(7)	4%
DISORIENTATION	1(0)	3%	-	-	6(3)	6%	7(3)	4%
CONVULSION	2(1)	5%	3(3)	7%	1(0)	1%	6(4)	3%
PSYCHOTIC DISORDER	1(0)	3%	2(1)	4%	2(2)	2%	5(3)	3%
PERSONALITY DISORDER	3(3)	8%	1(1)	2%	-	-	4(4)	2%
ATTENTION DEFICIT/HYPERACTIVITY DISORDER	2(2)	5%	1(1)	2%	-	-	3(3)	2%
ABNORMAL BEHAVIOR	2(1)	5%	-	-	1(1)	1%	3(2)	2%
HALLUCINATION, VISUAL	2(0)	5%	-	-	1(1)	1%	3(1)	2%
DRUG TOXICITY	2(1)	5%	-	-	-	-	2(1)	1%

8. DISCUSSION

Oxybutynin crosses the blood-brain barrier, as evidenced by its effects on quantitative EEG in two controlled studies.^{8,9} In addition, oxybutynin was associated with cognitive impairment in older volunteers administered the drug in a laboratory study.¹⁰

Anticholinergic CNS effects as described in the medical literature include sedation, confusion, cognitive impairment, delirium, agitation, and hallucinations.^{4,5} The package insert for atropine states

⁸ Pietzko A, Dimpfel W, Schwantes U, Topfmeier P: Influence of trospium chloride and oxybutynin on quantitative EEG in healthy volunteers. Eur J Clin Pharmacol 1994;47:337-343.

⁹ Todorova A, Vonderheid-Guth B, Dimpfel W. Effects of tolterodine, trospium chloride, and oxybutynin on the central nervous system. J Clin Pharmacol 2001;41(6):636-44.

¹⁰ Katz IR, Sands LP, Bilker W, Di Filippo S, Boyce A, D-Angelo K: Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. JAGS 1998;46:8-13.

*“adverse events seen in pediatrics are similar to those that occur in adult patients, although central nervous system complaints are often seen earlier and at lower doses.”*¹¹

Data from placebo-controlled pediatric studies of tolterodine (another anticholinergic used to treat overactive bladder in adults) lend further support for the potential of CNS stimulation in pediatric patients. A total of 710 pediatric patients (486 on Detrol LA, 224 on placebo) aged 5-10 with urinary frequency and urge incontinence were studied in two phase 3 randomized, placebo-controlled, double-blind, 12-week studies. Aggressive, abnormal and hyperactive behavior and attention disorders occurred in 2.9% of children treated with Detrol LA compared to 0.9% of children treated with placebo.¹² In addition, an AERS review of 29 pediatric adverse event cases in association with tolterodine found 10/29 reported events associated with CNS stimulation (aggression, hyperactivity, insomnia) and recommended the potential for pediatric patients to develop CNS stimulation be included in the labeling for Detrol and Detrol LA.¹³

In the pediatric exclusivity studies with oxybutynin, there were no placebo controls. In the larger trial, Study 042 (n=116), one child experienced each of the following CNS adverse events: nervousness, insomnia, somnolence and asthenia. In the smaller trial (Study 043, n=16), there were no CNS adverse events.¹⁴

We reviewed 202 CNS adverse events cases in association with oxybutynin (37 pediatric, 143 adult and 22 no age reported). A significant portion (>12%) of all adverse event reports for oxybutynin involve a CNS adverse event. More than 31% of pediatric reports and 11% of adult reports involve a CNS adverse event.

Of the 37 pediatric cases reporting CNS adverse events in association with oxybutynin, 28 were from the US. Twenty-three of the 37 pediatric AERS cases reported the CNS events abated after oxybutynin was discontinued or the dose was reduced (positive dechallenge). Four of the 37 cases reported the CNS events [hallucinations, abnormal dreams, attention deficit/hyperactivity disorder, agitation, personality disorder (psychosis)] reappeared after oxybutynin was reintroduced (positive rechallenge). The positive dechallenges and rechallenges along with the plausible mechanism of action (anticholinergic toxicity) increase the likelihood of attribution to oxybutynin.

Fourteen of the 37 pediatric cases reported psychiatric/neurologic medical history and/or concomitant psychotropic medications. Although these cases may be considered confounded, causality to oxybutynin could not be excluded in these cases because the events began shortly after oxybutynin therapy was added, the events abated after oxybutynin was discontinued, the events were considered due to additive effects of multiple anticholinergic medications, and/or the events were accompanied by other classical anticholinergic toxicity events.

¹¹ AtroPen®Auto-Injector (atropine injection) U.S. package insert, King Pharmaceuticals, revised August 2004.

¹² Detrol ®LA (tolterodine) U.S. package insert, Pfizer, revised October 2005.

¹³ Gish P. Overview of AERS data for pediatric patients: tolterodine. DDRE/ODS. DFS March 18, 2004.

¹⁴ Hirsch M. Medical Team Leader's Memo: Pediatric Efficacy Supplements NDA 20-897 SE8-009, NDA 17-577 SE8-033, NDA 18-211 SE8-016. DRUDP/OND. DFS April 10, 2003.

Four of the 37 cases described memory impairment associated with oxybutynin exposure, and in two of these the impairment was documented by neuropsychological tests. This raises the issue of whether oxybutynin administered chronically to young children might produce long term neurodevelopmental effects. Such effects were observed in the classic long-term, placebo controlled trial of phenobarbital for febrile seizures, in which the phenobarbital treatment group had a lower mean IQ score versus placebo at 2 years.¹⁵

Compared to the adult cases, the pediatric AERS cases in association with oxybutynin differ in both number and types of CNS events:

- Taking domestic usage by age group into account, there is a disproportionately higher number of CNS adverse event cases reported in pediatric patients as compared to adult patients (see Graph 2). Also, pediatric CNS reports represent a greater percentage of total pediatric oxybutynin reports than adult CNS reports do for all adult oxybutynin reports.
- Hallucination was the most common CNS event reported for pediatric patients (27% of cases). Hallucination was the second most common CNS adverse event (25% of cases) in elderly patients (ages 60+ yrs). Hallucination was reported in only 11% of cases in patients 17-59 yrs of age.
- Pediatric CNS cases reported agitation more than twice as often as adult cases (14% pediatric cases vs. 6% adult cases).
- Adult CNS event cases reported sedation more than twice as often as pediatric cases (24% adult cases vs. 11% pediatric cases).
- Confusion was the most common CNS event reported for elderly patients (ages 60+yrs) and was reported three times as often vs. patients less than 60 yrs of age (30% elderly cases vs. 10% of cases in patients less than 60 yrs).

Although the adverse reactions sections of the Ditropan and Ditropan XL labels list some CNS events (i.e. somnolence, insomnia, nervousness, confusion, hallucinations), these are not currently described in the context of central anticholinergic pharmacologic effects.

Of course, the discrepancies between adult and pediatric reporting of CNS events could be due to some type of reporting bias. As is always the case with spontaneous reporting data, it is not possible to estimate the actual incidence of such adverse reactions to oxybutynin in pediatric patients. However, the pediatric clinical trial data from a pharmacologically similar compound (tolterodine) suggest that milder CNS symptoms are not infrequent. It seems probable that there is a spectrum of severity of adverse CNS effects from anticholinergic compounds, and that the spontaneous reports we have described with oxybutynin may well include examples of the more severe but less frequent types of CNS reactions.

9. CONCLUSION/RECOMMENDATIONS

A significant portion of all adverse event reports for oxybutynin involve a CNS adverse event. The types of CNS adverse events reported vary by age. The current labeling does

¹⁵ Farwell JR, Lee YJ, Hirtz DG, Sulzbacher SI, Ellenberg JH, Nelson KB. Phenobarbital for febrile seizures-effects on intelligence and on seizure recurrence. *N Engl J Med.* 1990 Feb 8;322(6):364-9.

not explicitly describe the potential for CNS anticholinergic effects, or the age-dependent pattern of CNS effects that have been reported. We recommend that the labeling be revised to include the following points under **PRECAUTIONS**:

- ❖ Oxybutynin has the potential to cause anticholinergic central nervous system (CNS) effects, and such adverse effects have been reported postmarketing. These postmarketing reports have described a variety of CNS anticholinergic effects, with hallucinations and agitation prominent among pediatric cases, and confusion, hallucinations, and sedation prominent among reports involving geriatric use.
- ❖ Patients should be monitored for signs of anticholinergic CNS effects, particularly in the first few months after beginning treatment or increasing the dose. If patients experience anticholinergic CNS effects, drug discontinuation should be considered.

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TABLE 7 – CNS adverse event cases for ages 0-16 years: oxybutynin (N=37)

Case # ISR# Mfr Report # Initial rpt yr	Age- yrs/Sex/ Location	Indication/Daily dose/Time to onset	Adverse events	Concomitant drugs	Psychiatric /neurologic history	Outcome/Comments
1 6056158 5008565-6 (dup 4960270-8) RB-277-2006 2006	15 mos (1.3 yrs) F France	N/A-accidental exposure Dose not reported (accidental exposure) <12 hrs	Child ingested family member’s buprenorphine and possibly oxybutynin; became lethargic; hospitalized in intensive care. “Atropinic signs” of tachycardia, urinary retention, fever noted	Ingestion of buprenorphine at same time as oxybutynin	NR	Positive dechallenge Accidental exposure Hospitalized , recovered.
2 5833321 4707388-2 USP 57230 2005	23 mos (1.9 yrs) M US	Hypospadias surgery 20mg (med error) 2 hrs	“Signs and symptoms of antimuscarinic toxicity”	NR	NR	Unknown if oxybutynin discontinued altogether. Medication error: 4X overdose Hospitalized (overnight), outcome unknown.
3 4850708 808382-4 9101926 1992	2M US	Relaxation of bladder musculature 10mg Unk	Insomnia Vasodilatation	NR	NR	Unknown if oxybutynin discontinued. Outcome unknown.
4 5509737 1864059-8 Direct 1996	2F US	Unk 12mg 1 day	Described as anticholinergic syndrome with agitation and disorientation.	Benadryl Tylenol	NR	Positive dechallenge, recovered after oxybutynin dose decreased and Benadryl discontinued.
5 4698999 638340-4 PDR 1990	3F US	Post ureteral surgery 9mg <1 day	Confusional state Visual disturbance (“seeing things”)	Meperidine (post op)	NR	Positive dechallenge (Ditropan only)

TABLE 7 – CNS adverse event cases for ages 0-16 years: oxybutynin (N=37)

Case # ISR# Mfr Report # Initial rpt yr	Age- yrs/Sex/ Location	Indication/Daily dose/Time to onset	Adverse events	Concomitant drugs	Psychiatric /neurologic history	Outcome/Comments
6 5522476 1877184-2 96004355 1997	3M US	Unk 7mg 7 days	Sedation	NR	NR	Oxybutynin was not discontinued. Outcome unknown.
7 5547778 1903322-9 97001470 1997 Literature ¹⁶	3F US	Neurogenic bladder 5mg 1 st exposure: 3 weeks 2 nd exposure: < 6 weeks	1 st exposure at 3 yrs old: nightmares, hyperactivity, bizarre behavior, incoherent speech, anorexia 2 nd exposure at 6 yrs old: nightmares, agitation, , pressured speech, anxiety, visual hallucinations (of red plants, violent death), feared harm from TV actors.	Triaminic (phenylpropanolamine, chlorpheniramine)	NR	Positive dechallenge, rechallenge 1 st exposure at 3 yrs of age: recovered within 24 hrs. when both oxybutynin and Triaminic were discontinued 2 nd exposure to same two drugs at 6 yrs of age: Hospitalized , recovered two days following discontinuation of both oxybutynin and Triaminic Peripheral signs of anticholinergic toxicity absent. .
8 3805625 3955993-3 13485 2002	4F Unk	Neurogenic bladder 10-21mg 6mos-1 yr	Irritability, anxiety, tantrums, physical aggression, suicidal depression, personality change	Paroxetine 15 mg/d added, but appeared to exacerbate psychiatric symptoms; later restarted at lower dose	Congenital hypotonia, developmental ly delayed in speech, gait, eye movements	Patient also had peripheral signs of anticholinergic toxicity (anhidrosis, heat sensitivity, flushed skin, dry mouth) Positive dechallenge when patient switched to Detrol.

¹⁶ Hamdan-Allen G, Nixon M. Anticholinergic psychosis in children. A case report. Hosp Commun Psych 1991;42(2):191-193.

TABLE 7 – CNS adverse event cases for ages 0-16 years: oxybutynin (N=37)

Case # ISR# Mfr Report # Initial rpt yr	Age- yrs/Sex/ Location	Indication/Daily dose/Time to onset	Adverse events	Concomitant drugs	Psychiatric /neurologic history	Outcome/Comments
9 4637374 568057-6 890632 1989	4F US	Enuresis 10mg <1 day	Visual hallucinations; no further description	NR	NR	Positive dechallenge, rechallenge The drug was administered again the following evening and the hallucinations recurred. Oxybutynin was discontinued and the hallucinations stopped.
10 4637376 568059-X 881823 1989	4M US	Uninhibited bladder, daytime enuresis, dysuria, bilateral vesicoureteral reflux 20mg 3 weeks	Hyperactivity (not further described)	NR	NR	Positive dechallenge, rechallenge
11 5615282 70002487-2 Direct 1977	4M US	Nocturnal enuresis 5mg 1 dose	Hallucinations involved snakes, insects, other animals in his room, and crawling on him.	NR	NR	Unknown if discontinued. Outcome unknown.
12 5802433 4731198-3 2005AP000393 2005	4F US	Neurogenic bladder/bladder instability 10mg 1 hr after first dose	“Severe hallucinations” not further described; headache	“None”	NR	Positive dechallenge, recovered within 1-2 days. Parents gave child diphenhydramine on advice of poison control center.
13 4637375 568058-8 890475 1989	5F US	Unk 10mg 9 days	Sedation	NR	NR	Positive dechallenge Pt assessed at local ER. No further details provided.

TABLE 7 – CNS adverse event cases for ages 0-16 years: oxybutynin (N=37)

Case # ISR# Mfr Report # Initial rpt yr	Age- yrs/Sex/ Location	Indication/Daily dose/Time to onset	Adverse events	Concomitant drugs	Psychiatric /neurologic history	Outcome/Comments
14 5579446 1935941-8 199710687HMRI 1997	5F US	Bladder incontinence 25mg (med error) <10 weeks	Hallucinations (daytime and nighttime) of monsters out to get her, nightmares	NR	Lupus	Positive dechallenge for hallucinations, however counseling has been initiated because pt is still fearful. Medication error: 5X overdose
15 4745444 690817-1 9013017 1990 Literature ⁶	6M France	Primary enuresis 10mg 4 days	1 st exposure: Abnormal dreams Hallucinations 2 nd exposure days later: Hallucinations, agitation, pains, convulsion? (also constipation, dry mouth) ; required hospitalization	NR	NR	Positive dechallenge, rechallenge 1 st exposure- abated upon drug discontinuation. 2 nd exposure: hallucinations of large beasts moving all over his body causing pain. Recovered 12 hours after hospitalization. Blood levels 12 hours after the last dose revealed oxybutynin chloride: 11 ng/ml.
16 3479319 3504558-6 6256 2000	6F Unk	Incontinence from injury in auto accident 5-10mg 2 weeks post dose increase to 10 mg/d	Agitation, visual hallucinations of insects, thought hands and feet were bleeding, personality change, fearfulness	NR	NR	Positive dechallenge

TABLE 7 – CNS adverse event cases for ages 0-16 years: oxybutynin (N=37)

Case # ISR# Mfr Report # Initial rpt yr	Age- yrs/Sex/ Location	Indication/Daily dose/Time to onset	Adverse events	Concomitant drugs	Psychiatric /neurologic history	Outcome/Comments
17 3037342 3007433-9 199712184HMRI 1997	6M US	Bladder spasms, causing daytime incontinence 15mg vesicular + 10mg oral <1 month after adding 15mg vesicular to regimen	Behavior problems, restlessness reported by teacher; no further details	Prazosin	.	Oxybutynin was not discontinued. Pt has not recovered.
18 4295539 71080-1 Direct 1975	6M US	Enuresis 20mg <1 day	Abnormal dreams (nightmares) after first dose	“nil else”	NR	Unknown if Oxybutynin discontinued. Outcome unknown.
19 5346802 1696308-3 95000353 1996	6F US	Spastic bladder 15mg 14 months	Short term memory loss, confusion	Carbamazepine Nitrofurantoin	Spina Bifida Recently started kindergarten	Oxybutynin was not discontinued. Outcome unknown.
20 6173448 5157218-2 (dup 5173190-3) TR-JNJFOC- 20061104047 2006 Literature ¹⁷	7M Turkey	N/A - accidental exposure Single 10mg dose (accidental exposure) 2 days	Brief Psychotic Disorder (including anxiety, auditory and visual hallucinations of monsters, chaotic thoughts, increased psychomotor activity, loss of appetite, headache).	NR	PE, blood chemistry, hematology, endocrinology , brain CT and EEG all normal.	Physical exam, clinical laboratories, CT, EEG unremarkable. Neuropsychiatric symptoms lasted approximately 3 days, then resolved.

¹⁷ Gulson M Pinar M, Sabanci U. Psychotic disorder induced by oxybutynin. Clinical Drug Investigation 2006;26(10):603-606.

TABLE 7 – CNS adverse event cases for ages 0-16 years: oxybutynin (N=37)

Case # ISR# Mfr Report # Initial rpt yr	Age- yrs/Sex/ Location	Indication/Daily dose/Time to onset	Adverse events	Concomitant drugs	Psychiatric /neurologic history	Outcome/Comments
21 4362700 141025-4 PCA22327 1982	7M US	Neurogenic bladder 10mg 5 days	Agitation Urinary incontinence	Pemoline (indication NR)	NR	Unknown if oxybutynin discontinued. Hospitalized. Outcome unknown.
22 4585675 509607-5 880820 1988	7M US	Unk 15mg <10days	Attention deficit/hyperactivity disorder aggravated; Abdominal pain	Ritalin	ADHD (well controlled)	Positive dechallenge “Ditropan caused previously well controlled hyperkinetic syndrome symptoms to recur”
23 4585676 509608-7 890632 1989	7M US	Enuresis 10mg 1 year	Visual hallucinations of bees, bugs, flies; fearful	“None”	NR	Positive dechallenge Pt had been treated with oxybutynin for 1 year, after first dose out of new bottle developed hallucinations
24 3744856 3842357-6 11903 2001 Literature ¹⁸	8M Turkey	Nocturnal enuresis 60mg (intentional OD) 4 hrs	Disorientation, agitation, hallucinations, amnesia following intentional overdose of oxybutynin prescribed to patient for enuresis	NR	Disruptive behavior	Other signs of anticholinergic toxicity present included lethargy, tachycardia (140 bpm), mydriasis, dry mouth. Treated with chloral hydrate in ER. Recovered (but unknown if oxybutynin de’d altogether). Authors speculated that oxybutynin exacerbated patient’s underlying psychiatric problems. Intentional overdose

¹⁸ Coskun S, et al. Is attempting suicide an adverse effect of oxybutynin in a child with enuresis nocturia? Pediatric Emergency Care 2001;17(5)398.

TABLE 7 – CNS adverse event cases for ages 0-16 years: oxybutynin (N=37)

Case # ISR# Mfr Report # Initial rpt yr	Age- yrs/Sex/ Location	Indication/Daily dose/Time to onset	Adverse events	Concomitant drugs	Psychiatric /neurologic history	Outcome/Comments
25 4328770 104725-8 Direct 1979	8F US	Enuresis 10mg 2 months	Hallucinations, mydriasis, tachycardia diagnosed as anticholinergic toxicity by reporting MD	“None”	NR	Oxybutynin discontinued. Outcome unknown.
26 5460416 1813236-0 96000201 1996	8F US	Dysfunctional bladder 10mg Unk	Possible attention deficit hyperactivity disorder	Bactrim	NR	Oxybutynin not discontinued. Outcome unknown. Pt being evaluated for ADHD.
27 5877112 4762204-8 (dups 4760226-4, 4700964-2) TR-JNJFOC-2006 2006	8F US	Overactive bladder, urinary frequency 5mg <1 month	Confusion, hallucinations, mood changes, obsessive thoughts, delusions, disorientation	“none”	NR	Positive dechallenge within 3 days of Ditropan XL discontinuation.
28 3483209 3518217-7 SE51-00163 2000	9M France	Unk NR 1 year	Visual hallucinations, edema of face and hands; no further details	Desmopressin (was not discontinued)	NR	Positive dechallenge when oxybutynin discontinued. Hospitalized , recovered.
29 3846608 3983099-6 (dup 3507921-2) ALZ-6372 2002	9F US	Unk 5mg Unknown duration of oxybutynin; single dose of concomitant Benadryl	Convulsion, attributed by ER physician to drug interaction (oxybutynin and Benadryl)	Benadryl (one dose)	NR	Oxybutynin not discontinued. Benadryl discontinued and pt recovered.

TABLE 7 – CNS adverse event cases for ages 0-16 years: oxybutynin (N=37)

Case # ISR# Mfr Report # Initial rpt yr	Age- yrs/Sex/ Location	Indication/Daily dose/Time to onset	Adverse events	Concomitant drugs	Psychiatric /neurologic history	Outcome/Comments
30 3797797 3935913-8 EMADSS2002003 499 2002	10M Switzerland	Nocturnal enuresis 5mg 2-3 months	Night terrors, biting/hitting self, insomnia, visual hallucinations (monsters, little green men with knives), paranoia	Hydroxyzine added later to treat insomnia, Risperdal added later to treat depression	Anxiety Recent stressful events	Positive dechallenge (only Ditropan dc'd). Pt continues on Risperdal, hydroxyzine.
31 4666013 600825-4 890206 1989	10F US	Neurogenic bladder 7.5mg 7 years	Short term auditory memory deficits, fine motor coordination impaired	Bactrim	Spina Bifida	Positive dechallenge. Deficits seen on neuropsychological assessment; results of retesting off drug not reported.
32 5157788 1499257-9 94002657 1994	12M US	Nocturnal enuresis 10mg 1 year	Behavior problems and mood swings; no further details provided	Desmopressin	NR	Unknown if oxybutynin discontinued. Outcome unknown.
33 4651181 583839-2 893400 1989	13M Canada	Unk 100mg (intentional OD) Unk	Memory loss, fire setting	Also took Vitamin C and alcohol as part of intentional OD	No previous history of mental disturbances	Pt hospitalized for psychiatric care, no physiological signs/symptoms reported; no further details Intentional overdose, after OD pt set fires in 3 buildings.
34 5460380 1813199-8 96000535 1996	13M US	Neurogenic bladder from spinal cord injury Unk Unk "since starting oxybutynin"	Insomnia	Diazepam Unspecified antibiotic	Spinal cord injury	Oxybutynin not discontinued. Outcome unknown. Pt does not drink caffeine, does not nap and does not have ADHD.

TABLE 7 – CNS adverse event cases for ages 0-16 years: oxybutynin (N=37)

Case # ISR# Mfr Report # Initial rpt yr	Age- yrs/Sex/ Location	Indication/Daily dose/Time to onset	Adverse events	Concomitant drugs	Psychiatric /neurologic history	Outcome/Comments
35 4445639 348460-X 2841989 1985	14M US	Neurogenic bladder 15mg Unk (gradual)	Memory impairment (short term)	Septra	Spina bifida	Positive dechallenge. Pt was administered sections of Wechsler Memory Scale before and after Ditropan discontinued; documented an improvement in memory off Ditropan.
36 5040527 1374000-2 93002673 1993	16F US	Unk 225mg Unk	Thinking abnormal (“fogginess”); evaluated in ER; no further details	NR	Multiple sclerosis	Positive dechallenge after dose decreased from 15 tablets (75mg) tid to 9 tablets (45mg) tid.
37 3531571 3563852-3 USP 081328 2000	Child (sex/age unk) US	Unk 50mg (med error) Unk	Sedation, dizziness, leg pain	NR	NR	Unknown if oxybutynin discontinued altogether. Outcome unknown. Med error: 5X overdose

Appendix: Reasons for exclusion of AERS oxybutynin CNS event reports from the case series

Pediatric: 18 (33%) of the 55 pediatric reports were excluded

- 6 duplicate reports
- 2 reports of seizures in patients with underlying conditions (seizure disorder-1, hyponatremia-1)
- 2 reports with a poor or unclear temporal relationship to drug administration (hallucinations-1, seizure-1)
- 2 reports with a negative dechallenge (tremor-1, paranoia-1)
- 1 report of CNS effects that appeared to be due to another drug (i.e. Concerta)
- 1 report of “mood problems”
- 1 report of decreased REM sleep
- 1 report of hallucinations in patient with possible illicit drug use
- 1 report in patient whose behavior was normal at home, but disruptive at school
- 1 report of in utero exposure in child with ADHD

Adult: 113 (44%) of the 256 adult reports were excluded

- 26 duplicate reports
- 33 reports of CNS events in conjunction with the following: acute infection-5, electrolyte imbalance-5, stroke/cerebral ischemia-3, fulminant hepatitis/liver toxicity-3, hyperthermia-2, neuroleptic malignant syndrome-2, decreased oxygen saturation-1, hypotension-1, cardiac events-1, hyperventilation-1, schizophrenia-1, CHF exacerbation-1, sepsis/hyperthermia-1, pulmonary embolism/hepatitis-1, leukemia (fatigue)-1, lactic acidosis-1, migraine (memory impairment)-1, dystonic reaction-1, agranulocytosis (fatigue)-1
- 16 reports of CNS events that appeared to be due to another drug (fentanyl-2, carbamazepine-2, doxazosin-1, Effexor-1, Embrel-1, propranolol/clozaril-1, galantamine-1, halcion-1, pregabalin-1, Topamax-1, Requip-1, Risperdal-1, tryptan-1, pregabalin/quetiapine/Edronex/Diamox/codeine-1)
- 7 reports with a poor or unclear temporal relationship to oxybutynin administration
- 6 reports of tremor/shakiness only
- 6 reports of negative dechallenge, event recurred after oxybutynin discontinued (depression/psychosis-2, sleepiness-1, seizure-1, insomnia-1, restless leg syndrome-1)
- 5 reports of intentional overdoses involving multiple medications: morphine (1), lorazepam/doxepin(1), lorazepam (1), baclofen/Dipyron/terazosin/ASA (1), phenylethylamine/gabapentin/melatonin/paroxetine/tizanidine (1)
- 4 reports of seizures in patients with history of seizures/epilepsy
- 3 reports in which the CNS event was not described/specified
- 2 reports of patients that continued oxybutynin therapy and the events resolved (confusion-1, mental status changes-1)
- 2 reports with a negative rechallenge (hallucinations-1, confusion-1)
- 2 reports of insomnia due to pain (1) and rash (1)
- 1 report of “nervous chill”

Unspecified: 14 (39%) of the 36 reports with no age information were excluded

- 3 duplicate reports
- 6 reports of CNS events in conjunction with the following: stroke-2, heat exhaustion-1, hyponatremia-1, urosepsis/hyperammonia-1, Parkinson’s (tremor)-1
- 3 reports with a poor or unclear temporal relationship to oxybutynin administration
- 2 reports of CNS events that appeared to be due to another drug (meperidine-1, sertraline-1)

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/s/

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3/5/2007 03:36:21 PM
DRUG SAFETY OFFICE REVIEWER

Rosemary Johann-Liang
3/5/2007 04:36:30 PM
MEDICAL OFFICER