

# Second generation antipsychotics & nocturnal enuresis in children

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## ABSTRACT

Nocturnal enuresis, or involuntary wetting during sleep, is an adverse drug reaction that may occur with numerous second generation antipsychotics (SGAs) and currently is underreported. This article reviews SGA-induced enuresis and its management.

## KEYWORDS

second generation antipsychotic, child, pediatric, nocturnal enuresis

## SECOND GENERATION ANTIPSYCHOTIC USE IN CHILDREN

Antipsychotic medication use has expanded as newer agents have been developed and there has been a broader acceptance of the newer antipsychotic medications. The use of prescription antipsychotics has increased six-fold from 1993 to 2002 for patients twenty years old and younger.<sup>1</sup> First generation antipsychotics (FGAs) have been largely replaced by second generation antipsychotics (SGAs) in children and adults over the last 20 years.<sup>1</sup> Much of the SGA use is attributed to less potential for extrapyramidal side effects compared to FGAs though there is some argument for differences in efficacy.<sup>2</sup>

There are five SGAs approved by the Food and Drug Administration (FDA) for use in children (Table 1). The oral formulations of aripiprazole, olanzapine, quetiapine (regular release), and risperidone are approved for patients with schizophrenia and bipolar I disorder.<sup>3,4</sup> Aripiprazole and risperidone are also approved for irritability associated with autistic disorder.<sup>3,4</sup> Paliperidone is approved for adolescents for schizophrenia only. The FDA SGAs approved for adults include asenapine, clozapine, iloperidone, lurasidone, and ziprasidone.

Across the United States, antipsychotic medications are increasingly being used for a wider range of disorders and are being used for indications that have not been approved by the FDA.<sup>2,6</sup> This off-label antipsychotic use has more than doubled from 4.4 million treatment visits in 1995 to 9 million in 2008 with an estimated cost of \$6 billion dollars in 2008.<sup>2</sup> This trend is also occurring in children and adolescents where antipsychotics are being used for indications other than those approved by the FDA. Non-FDA approved uses include aggression, pervasive developmental disorder, disruptive behavior

disorders, conduct problems, depression, personality disorders, and tics associated with Tourette's syndrome.<sup>2,7,8</sup> The lack of evidence for the use of antipsychotics for these indications and the increase in the use of SGAs requires the need for monitoring pediatric patients taking these medications.<sup>2,8</sup>

Parents and caregivers need to be engaged with the mental health provider to ensure appropriate monitoring of side effects from the antipsychotic medications.<sup>9</sup> Choosing effective medications early on in mental illness treatment may improve medication use.<sup>10</sup> A barrier to medication continuation often is the result of side effects or adverse drug reactions. Often overlooked, nocturnal enuresis is a potential side effect from antipsychotic medications which may be frustrating and stressful for children and their caregivers.

## NOCTURNAL ENURESIS

Nocturnal enuresis is involuntary wetting during sleep. Enuresis, according to the American Psychiatric Association, is defined as occurring in children over the age of five and wetting more than two times per week for 3 months in a row.<sup>11</sup> In the normally developing child, the incidence of bedwetting decreases with age and by the time children reach the ages of 3 to 5, they are dry through the night.<sup>11,12</sup> Twenty percent of children age 5 wet the bed on occasion compared to five percent of ten year olds.<sup>12</sup> Primary nocturnal enuresis is a child that has never been dry for 6 months and secondary enuresis is if the bedwetting has occurred in a child that previously had been dry for 6 months.<sup>11,12</sup> It is estimated that 5 million children in the US experience nocturnal enuresis.<sup>11</sup>

The cause of bedwetting is not known but may be related to the bladder not functioning appropriately, difficulty awakening from sleep, polyuria, sexual abuse, or a family history of bedwetting.<sup>11,12</sup> It may also be related to

**Table 1. FDA approved indications for pediatric age groups of second generation antipsychotics**

SGAs	Schizophrenia	Bipolar I Disorder	Irritability Associated with Autism
Generic Name	Age Group	Age Group	Age Group
Aripiprazole	13-17	10-17 (manic/mixed)	6-17
Olanzapine	13-17	13-17 (manic/mixed)	Not approved
Quetiapine	13-17	10-17 (manic)	Not approved
Risperidone	13-17	10-17 (manic/mixed)	5-17
Paliperidone	12-17	Not approved	Not approved

Table adapted from FDA Approved Indications for Oral Second Generation Antipsychotics and the Approved Age Group from AHRQ Clinician Research Summary on Atypical Antipsychotics (August 2012).<sup>5</sup>

decreased bladder capacity, increase in night time urine production, constipation, psychological issues like stress, or a medical condition.<sup>9,12</sup> Other possible causes of bedwetting need to be considered such as new-onset urgency, stress incontinence, or voiding issues.<sup>13</sup> A comprehensive assessment should be performed to rule out other possible causes of enuresis. In addition to these organic causes of enuresis, bedwetting may be an adverse drug reaction from SGAs that may be unrecognized and underreported.<sup>13</sup>

### REVIEW OF SGAS AND NOCTURNAL ENURESIS

The exact mechanism of antipsychotic induced bedwetting is not well understood. There are numerous theories surrounding antipsychotic-induced enuresis. These include “decreased internal bladder sphincter tone due to alpha 1 adrenergic blockade, reduced dopamine transmission in the basal ganglia, urinary retention and subsequent overflow incontinence due to anti-muscarinic properties of antipsychotics, and blockade of pudendal reflexes via antagonism of 5-HT<sub>2</sub> or 3 and the activation of neuronal 5-HT<sub>4</sub> receptors in the detrusor muscle.”<sup>14</sup> Psychosis itself may cause urinary incontinence.<sup>15</sup> Activating muscarinic receptors in the bladder results in micturition due to smooth muscle contractions.<sup>16</sup> Antipsychotic enuresis may be from an imbalance of dopamine and norepinephrine in that area since the basal ganglia normally inhibits bladder contractions.<sup>16,17</sup> The regulation of bladder control involves multiple neurotransmitters, the parasympathetic, and sympathetic systems.<sup>13,16</sup> The broad pharmacologic actions of SGAs make it difficult to identify the exact action of the drug inducing the enuresis.<sup>17</sup> Another theory is that sleeping too deeply either from the sedating effects of antipsychotics alone or in combination with other CNS depressants leads to the child’s inability to wake when the bladder is full.<sup>13</sup> Another hypothesis is that antipsychotics may lower the seizure threshold at night which would cause a seizure during sleep resulting in loss of bladder control.<sup>13</sup> The exact mechanism of nocturnal enuresis may not be known, but gathering this

information from the caregiver or child is important since it may be underreported.<sup>18</sup>

Reported nocturnal enuresis rates for SGAs vary in the literature and most of the available information is in adolescents and adults. A comparative cohort study of patients in New Zealand aged 15 to 64 years looked at clozapine, risperidone, olanzapine, and quetiapine causing bedwetting. The study found 17 of 82 (20.7%) patients taking clozapine, 11 of 115 (9.6%) taking olanzapine, 7 of 105 (6.7%) taking quetiapine, and 12 of 195 (6.2%) taking risperidone caused bedwetting.<sup>18</sup> The nocturnal enuresis developed within the first few days or within the first three months of starting the antipsychotic and resolved without any treatment intervention.<sup>18</sup>

Aripiprazole is the antipsychotic thought to have the least likelihood of causing nocturnal enuresis since it can “act as a dopamine partial agonist and has no appreciable affinity for cholinergic muscarinic receptors.”<sup>17</sup> During the premarketing research of this medication, enuresis was a very rare adverse drug reaction.<sup>19</sup> One case report listed aripiprazole induced nocturnal enuresis which resolved once the medication was discontinued.<sup>19</sup>

Micromedex® does not provide any genitourinary side effect listings for the SGAs therefore Lexicomp was used as a source. Lexicomp® lists nocturia for aripiprazole with an incidence of less than 1% and lists incontinence for olanzapine though no percentage or frequency is provided.<sup>20</sup> Lexicomp® does not list genitourinary effects for quetiapine and this may be a reflection of underreporting and lack of recognition of enuresis resulting from SGA use.<sup>20</sup> Lexicomp® lists urinary incontinence in children for risperidone with 5 to 22% incidence.<sup>20</sup> Reported risperidone related enuresis rates in children vary from 1 to 31%.<sup>21</sup>

Clozapine is unapproved for use in children though is used for various indications. It is known to cause both daytime urinary incontinence and enuresis.<sup>22</sup> Enuresis induced by clozapine occurs in 6 to 44.3% of patients.<sup>19</sup> Lexicomp® lists incontinence as 1 to 2% which is significantly lower

than the previous statistic, potentially indicating lack of consistent assessment for this side effect.<sup>20</sup>

### MANAGEMENT & TREATMENT OF ENURESIS

The National Institute for Health and Clinical Excellence (NICE) 2010 clinical guidelines for nocturnal enuresis list key priorities for nocturnal enuresis which include informing caregivers that the child is not to blame for bedwetting, to provide support, and to determine appropriate therapy.<sup>12</sup> Treatment for bedwetting doesn't usually begin until the child is seven or older. An initial assessment of when the bedwetting started, and whether the child has previously stayed dry at night should be performed.<sup>12</sup> Also the frequency of bedwetting such as nights per week and times per night should be assessed.<sup>12</sup> Other key priorities include a discussion on fluid intake, toileting patterns, and a reward system.<sup>9,11,12</sup> A urinalysis should only be done if there are daytime symptoms, signs or symptoms of a urinary tract infection, or a history of diabetes mellitus.<sup>12</sup> Other conditions that may affect bedwetting include constipation, developmental or learning difficulties, behavior or emotional problems, or family problems.<sup>12</sup> The caregiver or parent may also need support if they are showing signs of anger or frustration toward the child.<sup>9,11,12</sup>

Health care professionals can provide advice in regards to fluid intake, diet, and toileting patterns. Fluid restriction should occur between the evening meal and bedtime so that most of the daily fluid intake requirements are throughout the morning and afternoon.<sup>9,11,12</sup> Daily fluid intake monitoring is important especially if the child lives in a warm climate or is very physically active so that they are not thirsty before bedtime.<sup>12</sup> The recommended amount of fluid per day depends on the child's age and gender as noted in Table 2.<sup>12</sup> Caffeinated drinks should also be avoided.<sup>9,11,12</sup> Professionals can recommend that the child be reminded to use the toilet at regular intervals throughout the day and right before bedtime, approximately four to seven times total per day.<sup>9,12</sup> A reward system such as sticker charts should be used to motivate and encourage the child to modify his/her drinking pattern and toileting behavior.<sup>12</sup> The child should be praised for drinking enough fluids during daytime hours and using the toilet before bedtime rather than just dry nights.<sup>12</sup> Punitive action should not be taken for bedwetting.<sup>12</sup>

Oral desmopressin is FDA approved for primary nocturnal enuresis. It is a modified form of vasopressin (antidiuretic hormone) which results in decreased urine production.<sup>20</sup> The FDA issued an alert in 2007 regarding the desmopressin nasal spray formulation due to the risk of

seizures and hyponatremia.<sup>23</sup> As a result of this warning, desmopressin nasal spray is no longer a recommendation for the treatment of primary nocturnal enuresis. The oral formulation can be used in children ages 6 and older starting with a 0.2 mg tablet taken by mouth at bedtime.<sup>21</sup> The clinician should review the response in one to two weeks and at week four. Follow up assessment includes inquiring to see if the child is responding with smaller wet areas, less nights wet, or a decrease in the number of episodes per night.<sup>11</sup> The dose can be titrated up to 0.4 mg at bedtime if after the first couple weeks there has not been improvement in nighttime dryness.<sup>12,20</sup> Rather than increasing the dose, the timing of the medication can be changed so that it is taken one or two hours before bedtime and fluid restriction starts an hour before the medication is taken.<sup>9</sup>

**Table 2. Suggested daily intake of drinks for children and young people<sup>12</sup>**

Age	Sex	Total drinks per day
4–8 years	Female	1000–1400 ml
	Male	1000–1400 ml
9–13 years	Female	1200–2100 ml
	Male	1400–2300 ml
14–18 years	Female	1400–2500 ml
	Male	2100–3200 ml

Table from NICE clinical guidelines 2010 nocturnal enuresis<sup>12</sup>

An enuresis alarm can be considered if after three months of behavioral modification bedwetting is still occurring more than two nights per week.<sup>11,12</sup> The alarm should not be used if the bedwetting is not occurring very often or if the caregivers are having a difficult time coping with the bedwetting.<sup>12</sup> The use of the alarm should be reviewed at four weeks, and also after three months of use.<sup>12</sup> If the child has not achieved complete dryness or improvement in bedwetting then discuss adding oral medication.<sup>11,12</sup>

Anticholinergics and tricyclic antidepressants (TCAs) are also alternative options for bedwetting.<sup>12,13</sup> Oxybutynin is an anticholinergic medication that is FDA approved for overactive bladder in adults. It is used for bladder spasms in children ages 5 and older starting with the immediate release tablets 5mg by mouth twice per day. Children ages 6 and older can take the 5 mg extended release once per day.<sup>20</sup> The dose can be titrated up to a maximum dose of 15 mg per day for the immediate release and 20 mg per day for the extended release.<sup>20</sup> Anticholinergic medications decrease the number of involuntary bladder contractions.<sup>23</sup> Imipramine is an FDA approved tricyclic antidepressant approved for nocturnal enuresis in children ages 6 and older starting with 25 mg by mouth

per day and titrating up for efficacy with maximum doses based upon age.<sup>20,23</sup> TCAs stimulate vasopressin secretion, decrease the time in REM sleep, and relax the detrusor muscle.<sup>23</sup> The risk-benefit of combining TCAs and SGAs should be evaluated due to the risk of cardiac QT prolongation.

## MANAGEMENT AND MONITORING OF ENURESIS RELATED TO SECOND GENERATION ANTIPSYCHOTICS

Management of bedwetting as an adverse drug reaction related to SGAs must start with patient and caregiver education. Mental health professionals need to provide counseling about bedwetting possibly occurring within the first few days to months of starting antipsychotic medication. Mental health practitioners should ask patients directly about bedwetting and discuss management options if it is occurring.<sup>18</sup> Determining any underlying cause for enuresis or incontinence can be hard to determine and may involve an invasive urodynamic diagnostic test.<sup>13</sup> Other possible causes of urinary incontinence or nocturnal enuresis need to be considered and a comprehensive assessment should be done to rule these out.<sup>13</sup> Health care professionals can recommend non-pharmacological approaches such as limiting fluids before bedtime, limiting caffeine, toileting right before bedtime, and a reward system.<sup>11,12</sup> Bedwetting alarms are also a non-pharmacologic option.<sup>12</sup> Stress reduction, psychotherapy, or bladder therapy may also be appropriate for some children.<sup>11</sup>

Performing a medication review is also important. A review should include the following: potentially sedating medications, medications that may lower the seizure threshold, or medications that may act on the lower urinary tract.<sup>13</sup> The lower urinary tract is controlled by various neurotransmitter pathways such as serotonin, dopamine, acetylcholine, and norepinephrine.<sup>13</sup> Managing nocturnal enuresis related to the SGA include continuing the SGA at the same dose as the side effect may resolve spontaneously.<sup>13,16</sup> Another option may be reducing the dose if possible, or keeping the total daily dose the same but reducing the dose given at night. Switching antipsychotics to one which has less potential for enuresis may also be considered.<sup>13,16</sup> Pharmacologic agents could also be considered to treat the nocturnal enuresis with awareness of the potential for drug-drug interactions. An option to consider is adding an anticholinergic or TCA medication. Managing constipation issues with adequate daytime fluid intake, daily fiber, or medications like polyethylene glycol may also help resolve enuresis at bedtime. Patients and caregivers should be encouraged to report any genitourinary issues that arise related to

taking SGAs. Health professionals are encouraged to report enuresis as an adverse event related to taking SGAs to FDA's MedWatch program.<sup>24</sup>

Mental health professionals are encouraged to add direct questioning about bedwetting to their monitoring protocols. Managing and monitoring antipsychotics in children requires an assessment at baseline, during titration of the medication, and follow up at 3 months, 6 months, 9 months, and annually.<sup>13,25</sup> Monitoring SGAs includes documenting personal history, family history, height, weight, blood pressure, EPS monitoring, as well as laboratory monitoring such as fasting glucose, fasting lipids, and complete blood counts. Renal and liver function should also be assessed.<sup>13,25</sup> Prolactin levels and electrocardiogram may be needed if the patient is symptomatic.<sup>13,25</sup> Assessment of medication tolerance such as sedation should also be performed at each visit.<sup>13</sup>

## CONCLUSION

Overall, the use of SGAs is increasing in the pediatric population. Due to the limited safety and efficacy studies of SGAs in children and adolescents, the adverse effects in children are not fully known therefore clinical and laboratory monitoring is critical.<sup>26,27,28</sup> Bedwetting is an adverse drug reaction or side effect that may occur with numerous SGAs and currently is underreported. Nocturnal enuresis associated with antipsychotics should be part of the monitoring plan for healthcare providers. Direct questioning of the patient and caregivers will improve reporting of this side effect. Managing and treating bedwetting related to an adverse effect from SGAs may help improve the quality of life for children experiencing bedwetting as well as their caregivers.

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