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Low Dose Oxybutynin in Childhood Nocturnal Enuresis

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Introduction: To evaluate the response to low dose oxybutynin in children with nocturnal enuresis.

Materials and Methods: Forty-one neurologically normal enuretic children who were visited in our nephrology clinic in a 3-year period (2007-2009) received low dose oxybutynin (2.5-10 mg/day depending on the weight) to define response to the drug in one and 3- month periods. No, partial, and full response were defined as 0-49%, 50-89% and ≥90% decrease in bed wetting, respectively.

Results: In the first month of treatment, full, partial, and no response were reported in 3 (7.3%), 14 (34.1%), and 24 (58.6%) patients, respectively. In the non-responder patients, 6 (25%) and 5 (20.8 %) patients showed full and partial response in the 3-month period whereas 13 (54.2%) had no response. The side effects of the drug were reported in 5 (12.2%) patients. Children with non-mono symptomatic nocturnal enuresis (NMNE) showed a better response to the drug than those with mono symptomatic nocturnal enuresis (MNE) (75% versus 25%). There was no significant differences in age, gender, family history of enuresis, and the presence or absence of daytime urinary or bowel symptoms between responder and non-responder groups (P>0.05 for all).

Conclusions: In this clinical report study, there was 68.3% treatment benefit and 12% risk (side effects of the drug) with low dose oxybutynin. Therefore, it may have a role in treating nocturnal enuresis, especially in patients with NMNE who experience adverse effects of standard treatment (Higher doses of the drug).

Keywords: Nocturnal Enuresis; Child; Oxybutynin; Risks and Benefits; Adverse effects.

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Running Title: Oxybutynin in Nocturnal Enuresis

Introduction

There is considerable controversy regarding the most appropriate treatment for nocturnal enuresis. Multidimensional behavioral therapy, pelvic floor exercise, and pharmacological therapy or combinations of them are main treatments that are used [1,2]. Pharmacological therapy consists of anti-cholinergic drugs (oxybutynin or tolterodine), musculotropic relaxants (flavoxate), tricyclic anti- depressants (imipramine) and desmopressin. Oxybutynin chloride is an anticholinergic and anti-spasmodic agent. It has a direct effect on the smooth muscle and is used for the management of urinary frequency, urgency, and incontinence in neurogenic bladder disorder, idiopathic detrusor instability, and for nocturnal enuresis [3,4]. Antimuscarinic agents have been

commonly used for the treatment of severe monosymptomatic nocturnal enuresis (MNE) refractory to standard treatment with oral desmopressin ± enuretic alarm [5]. Desmopressin alone or in combination with oxybutynin is effective in the treatment of diuresis-dependent enuresis (which is not related to detrusor over activity) [4,6]. A double-blind, placebo-controlled study in children showed that anticholinergic agents might play an important role in the treatment of some cases of mono symptomatic nocturnal enuresis (MNE) [7]. Although there is limited evidence supporting the use of oxybutynin in children with MNE, based on the available clinical studies and the long experience with oxybutynin, the beneficial risk ratio of this product has been considered favorable and the drug has been approved for the treatment of enuresis [4]. Despite the lack of prospective studies, anti-cholinergic and holding exercises have been proposed as successful ways to treat MNE [8-12]. The few controlled trials of oxybutynin for treatment of MNE have shown full response rates in 10-20% of the cases [2,8,13]. The recommended dose for oxybutynin is 5 to 10 mg at bedtime [14] or 5 mg BD in 6–9 year olds and 5 mg TDS in 10–14 year olds [1]. The adverse effects of the drug are common including dry mouth, dysphagia, dry eyes, blurred vision, diarrhea, constipation, and abdominal distention that may occur in up to 76% of the patients. Moreover, central nervous system complications have been reported in 31% of the pediatric reports [13, 15]. Regarding these findings which support the use of anticholinergic agents in MNE and as different our published clinical experiences with enuretic children strongly suggested that absence of day time symptoms in enuretic children are not good indicator for normal bladder function and abnormal urodynmic findings mainly over active bladder are not infrequence in MNE [16-17], we designed a case series study to evaluate the response to treatment and efficacy of low dose oxybutynin (0.2-0.3 mg/kg or 2.5-10 mg/day) in treating bedwetting in enuretic children.

Materials and Methods

Patients: Forty-one neurologically normal pediatric patients were evaluated in a cases series study in a 3-year period (2007-2009). They were referred to the nephrology clinic of Dr. Sheikh Children's Hospital with a chief complaint of enuresis. The patients whose fasting urine specific gravity was normal (SG>1015) were considered as non polyuric nocturnal enuresis and were enrolled in the study. Patients with apparent neurologic deficits such as mentally retarded children, those with neurogenic bladder (such as myelomeningocele cases), and patients who received the drug during the last month were excluded from the study. The enrolled patients included 23 (56%) girls and 18 (44%) boys who were 5-17 (8.24 ± 2.6) years who wetted the bed 2-7 (5.9±1.7) nights per week. The form of enuresis was MNE in 12 (29.3%) and NMNE in 29 (70.7%) patients. Twenty two patients (53.7%) had day and night incontinence while 19 (46.3%) only wetted the bed during the night. Forty patients had primary and one had secondary enuresis. Eight of 41 (19.5%) children had bowel symptoms including constipation, encopresis, or both. Two out of 41 (4.9%) patients had urological abnormalities including vesicoureteral reflux, (1 patient) and posterior urethral valve (1 patient). One patient had attention deficit disorder (ADHD) who did not respond to the treatment and was referred for more evaluation, and one patient had respiratory problems during the night (snoring) because of nasal septum deviation.

Definitions used in the study:

Enuresis, its sub-types**,** constipation, and encopresis were defined as International Children Continence Society (ICCS) criteria [18]. Enuresis was defined as bed wetting ≥ 2 nights in a month in children ≥ 5 years, MNE was defined as bed wetting with no daytime urinary symptoms, and non mono symptomatic nocturnal enuresis (NMNE) was defined as enuresis accompanied by daytime urinary symptoms [18]. On ultrasound evaluation, bladder wall thickness (BWT) >3 mm in full bladder and post voiding residual urine volume (PVURV) ≥ 15cc were considered abnormal. Moreover, bladder volume (BV) was compared to its normal range for age and defined as normal, increased, or decreased [19]. No, partial, and full response were defined as 0-49%, 50-89%, and ≥90% decrease in bedwetting, respectively [20].

Laboratory examinations and imaging evaluations:

Initial evaluations including urine analysis (U/A), urine culture (U/C), kidney–bladder ultrasonography (US), and measurement of serum BUN and creatinine were done for all patients. Bladder US was used to estimate BV, BWT, and PVRUV.

We did not perform urodynamic studies (UDS) as part of the investigation but we used the results of

UDS which were done in a group of our patients (22 out of 41 subjects) who participated in another research study performed at the same time. Cystometrography (CMG) was done as a conventional method that involved a dual lumen urodynamic catheter and a rectal tube. Pelvic floor electromyography (EMG) was done by inserting a skin electrode and the Koff's formula was used to measure bladder capacity [Volume (ml) = (Age + 2× 30] [21]. The volume in the filling phase at which the patients felt the first desire to void (FDV) was used as bladder capacity. Capacities less than 65% and >150% of the age-calculated value were defined as small and large capacities, respectively [18]. Detrusor overactivity was defined as involuntary detrusor contractions during the filling phase with a detrusor pressure increase of >15 cm H2O above baseline [18,21]. Detrusor under-activity was defined as a contraction of decreased strength resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying [3]. Overactive bladder was defined as involuntary detrusor contractions, small bladder capacity, and urethral instability [3,18] Abnormal urodynamic findings were observed in 3 out of 5 (60%) partial responder and 10 out of 15 (66.3%) non-responder patients. Urodynamic studies were not reportable in 2 cases because of artifacts.

Methods of the study:

To avoid the anti-cholinergic effects, low dose oxybutynin was recommended (2.5mg QD or BD for children≤25 kg (1/2 of oxybutynin 5 mg tablet QD or BD) and 3.75-5 mg QD or BD for patients >25 kg (3/4-1 oxybutynin 5 mg tablet QD or BD)). The therapy also included mild restriction of fluids after dinner. In 8 patients with MNE, the drug was used as a single dose at night while 4 children with MNE and all of those with NMNE received the drug twice daily. The frequency of bedwetting in one- and three-month courses of treatment was recorded by parents. According to response to therapy, patients were divided in to 2 groups: responder (full or partial responder), and non responder**.** Six participants including 1 patient with vesicoureteral reflux (VUR) and 5 with recurrent urinary tract infection received prophylactic antibiotics in combination with oxybutynin. The parents recorded bedwetting and drying at night during the study in a simple chart which included the date and positive (+) and negative (-) signs for every night (+ and - indicated bedwetting and drying at night, respectively. Patients were evaluated for response to treatment at 1 and 3- month intervals. In the responder group, the drug was recommended for at least 6 months and was then discontinued. In patients with MNE, if no response was achieved after 3 months, the drug was discontinued. In non –responder children with NMNE, especially those who had day-time incontinence, the drug was administrated for a longer period of time (> 6 months) if the resolution of day-time symptoms was achieved.

Statistical analysis:

Descriptive statistics included mean values ± SD for continuous and percentages for categorical data. Fisher exact and chi - square tests were used for data analysis and P values <0.05 were considered significant. Univariate analysis was performed using a model with response to treatment based on dependent variables like age, gender, family history of enuresis, presence of daytime incontinence and bowel symptoms.

Results

In the first month, 17 (41.4%) patients responded to the drug; 3 patients (7.3%) showed full response and 14 (34.1%) showed partial response. Moreover, the majority remained responder during the follow-up. Enuresis relapsed in one patient who had partial response in the first month of treatment and the patient was categorized as non-responder in the rest of the therapy. Of 24 patients who were non-responder in the first month, 6 (25%) and 5 (20.8%) showed full and partial response after 3 months of treatment (figure 1, Diagram A). Five out of 8 (62.5%) patients who received the drug as a single night dose showed partial response after one month of treatment, 2 (25%) showed partial response after 3 months of therapy, and one (12.5%) did not respond to the drug after 3 months (non-responder). Overall, 28 of 41 (68.3%) children responded to low dose drug after long-term therapy (3 months of treatment). The condition of the patient at the final follow-up and the previous drug history of the patients for enuresis are presented in Table I (see on last page). Clinical parameters and US findings were compared between responder and non-responder groups (Table 2). Data analysis revealed no significant difference in age, gender, presence of day-time incontinence, bowel symptoms, family history of enuresis, and abnormal findings on US between responder and non-responder groups (P>0.05 for all). The patients were followed up for 1-34 months (mean: 9 months). Seven out of 8

Table 2. Clinical parameters and US findings in fast ▫ responder VS non-responder patients
▫ Fast responder: Those who responded to the drug in first month of treatment
1) US: ultrasonography 2) single doses of the drug just were used in cases with MNE
3) Divided doses were used in one case with MNE and all cases with NMNE

Variable		Responder group (N/ %)	Non-Responder group (N/%)	P-Value Measurement
Age(year)	≤10 yr	14(43.8)	18(56,2)	0.711
	> 10 yr	3(33.3)	6(66.7)	
Gender	Female	7(30.4)	16(69.6)	0.125
	Male	10(55.6)	8(54.4)	
Family history of enuresis	Positive	12(38.7)	19(61.3)	1
	Negative	2(40)	3(60)	
Presence of bowel symptoms		3(37.5)	5(62.5)	1
Absence of bowel symptoms		14(42.4)	19(57.6)	
Enuresis without day-time incontinence		9(47.4)	10(52.6)	0.537
Enuresis + day-time incontinence		14(63.6)	8(26.4)	
Normal bladder US[1]		8(53.3)	7(46.7)	0.336
Abnormal bladder US				
Single dose oxybutynin[2]		9(36)	16(64)	-----
Receiving oxybutynin in divided doses[3]		7(41.2) 10(58.8)	1(4.2) 23(95.8)	
Total number		17(41.5)	24(58.5)	

MNE cases who received the drug as a single night dose were categorized as responder, whereas one MNE subject and 23 cases with NMNE who received the drug at divided doses were non responder. Overall, bedwetting relapsed during treatment or after drug withdrawal in 4 out of 28 patients (14.3%) who responded to the drug. The remaining of the patients did not experience a relapse in enuresis or change in the pattern of response to treatment during follow-up. The patient with posterior urethral valve achieved partial response after one month of treatment with valve ablation and oxybutynin while the patient with VUR remained a non responder. The patient with ADHD responded partially to treatment after 3 months of therapy. One of the patients who was a partial responder and 2 of the patients who were full responders experienced disease recurrence after drug withdrawal and no response was achieved when the drug was administrated again (they became non responders). Urodynamic evaluation [uroflowmetry, cystometrography (CMG) and pelvic floor electromyography (EMG)] were performed in one full responder, 5 partial responders and 15 non- responders. (Tables 3 and 4). Few non-serious complaints were reported by parents or older children during the treatment. Five patients (12.2%) complained about drug side effects such as fever (1 patient), fever and flushing (2 patients), blurred vision (1 patient), vertigo, and constipation (1 patient).

Table 3. Response to treatment and urodynamic findings in one –month treatment

Findings of urodynamic Studies	Full responder (Number)	Partially responder (Number)	Non responder (Number)
Group 1 (normal UDS)	-	1	-
Group 2 (OAB)	1	2	
Group 3 (OAB +detrusor hyperactivity)	-	1	1
Total	1	4	1

Table 4. Response to treatment and urodynamic findings in 3–month treatment

Findings of urodynamic Studies	Full responder (Number)	Partially responder (Number)	Non responder (Number)
Group 1 (normal UDS)	-	1	1
Group 2 (OAB)	-	-	3
Group 3 (OAB + detrusor hyperactivity)	-	-	5
Group 4 (detrusor hyperactivity)	-	-	1
Total	0	1	10

Discussion

There are two main types of enuresis in children: diuresis-dependent and detrusor-dependent enuresis. In dieresis-dependent enuresis, excessive nocturnal urine production and in detrusor type nocturnal detrusor hyperactivity and impaired arousal mechanisms are responsible for bedwetting. Desmopressin is usually effective in the dieresis type but not in the detrusor type. Two first-line therapies in nocturnal enuresis in children have been recommended: the enuresis alarm and desmopressin and anticholinergic drugs, treatment of occult constipation and urotherapy [22]. Oxybutynin may be applied in different forms including oral, transdermal or intravesical forms [4]. For intravesical application, crushed tablets or oxybutynin powder are dissolved in NaCl or sterile water prior to administration [23,24] although this method of administration is not approved for day-to-day pediatric practice [4]. Medications can help to control the symptoms of enuresis but they generally do not provide a cure and the high relapse rate is a common problem in medical therapy of enuresis [7]. A randomized, double-blind, placebo-controlled study in children with MNE showed that anticholinergic agents may play an important role in a subset of children with enuresis who have a restricted bladder capacity and thickened bladder wall [7]. Detrusor hyperactivity plays a part in the pathogenesis of nocturnal enuresis. Due to the beneficial effects of oxybutynin as an anti-spasmodic agent with a direct effect on the smooth muscle, it is suggested for the treatment of enuresis. Although there is limited evidence supporting the use of oxybutynin in children with MNE which is not related to detrusor over activity [4], based on the available clinical studies and the long experience with this product, the beneficial risk ratio of oxybutynin has been considered favorable and it has been approved for the treatment of children >5 years old with neurogenic bladder disorders and enuresis [4]. Some researchers have recommended oxybutynin as a second-line treatment, mainly as a combined drug when the child does not respond to first-line treatments or in cases of NMNE [15]. It may be asked why we recommended the drug at a dosage lower than the standard recommended dose? Actually, the majority of the patients who are visited in our clinic are residents of geographic regions with hot and dry climates and according to our unpublished clinical experience with oxybutynin in treating children with neurogenic bladder, when we prescribe the standard dose of the drug, anti-cholinergic side effects especially fever and flushing are the main adverse symptoms that seem to be dose dependent and frequently resolve with reducing the dose. We used oxybutynin as the first line of treatment since the majority of our patients had NMNE; on the other hand, previous studies have also shown the efficacy of the drug in treating MNE [9,11,12]. Moreover, oxybutynin is easily available and is not expensive (when compared to nasal spray and melt of Minirin), and fluid restriction during treatment is not essential (which is needed when desmopressin is administered). In our series, full and partial response to oxybutynin was observed in 7.3% and 34.1% of the patients in the first month of the study which increased to 22% and 46.3% after 3 months, respectively (Figure 1, Diagram A). It should be considered that the favorable response to the drug in our cases may be related to the type of enuresis in our enrolled subjects; the majority of our patients had NMNE which is supposed to be related to detrusor overactivity [18]. In our series of 12 patients with MNE, 6 (50%), 5 (41.5%), and 1 (8.5%) patient showed partial, no, and full response to the drug, respectively. Van Hock et al reported a full response rate of 2% by placebo and 12% by oxybutynin treatment and concluded that oxybutynin was superior to placebo although the difference was not statistically significant [2]. The efficacy of oral oxybutynin at a dose of 5 mg bid for the treatment of neurogenic bladder in children >5 has been demonstrated but most placebo-controlled studies in pediatric patients with enuresis have not clearly reported the beneficial therapeutic effect of oxybutynin [4]. One double-blinded study compared oxybutynin with placebo for the treatment of MNE [8]. The results showed that the frequency of bed wetting episodes did not differ between the drug regimen period and the placebo period whereas several studies have reported that it is effective in patients with NMNE and those with abnormal urodynamic studies [9,12]. These findings are consistent with our report. In our series which mainly consisted of children with NMNE (29; 70%), 28 patients responded to the treatment [7 (25%) children with MNE and 21 (75%) patients with NMNE]. Based on the Rapporteur's reports for pediatric patients, oxybutynin should be indicated in nocturnal enuresis associated with detrusor overactivity in conjunction with non-drug therapy when other treatments have failed [4]. We prescribed the drug at a dose about 1/2-

1/3 of the usual recommended dose and since most of the drug side effects are dose related, it is logical that the side effects were very uncommon in our patients when compared to previous studies [25,26]. Fortunately, none of our patients developed severe CNS side effects of the drug (hallucinations, agitation, sedation, confusion, amnesia). Gish et al. reported that long-term administration of oxybutynin in young children (<5 years) could produce neuro developmental effects [25]. Neuropsychological function tests in children with diurnal incontinence treated with oxybutynin have revealed no cognitive impairment [27]. Another study found no negative long-term effects of oxybutynin on short-term memory and attention span [28]; however, these studies included small sample sizes and lacked long-term follow-up. The side effects of oxybutynin often include atropinic and allergic reactions. The side effects are 4 times more frequent in children (1/4,000 prescriptions) than in adults. The higher frequency of atropinic reactions in children may be due to the higher dose of the drug used and/or to differences in hydroxylation metabolism that is genetically determined in adults [27,28]. We aimed to test the efficacy (benefits) and adverse effects (risks) of low dose oxybutynin in treating NE because literature review does warn about anti-cholinergic adverse effects as common complaints in patients who receive the standard dose of oxybutynin [25,26-29,30]. One open randomized parallel-group study [31] evaluated the efficacy of transdermal and oral oxybutynin in 49 children who were 6-15 years old with nocturnal detrusor overactivity. Treatment resulted in a significant improvement in all measured urodynamic parameters in both groups, but the ratio of N-desethyl oxybutynin-to-oxybutynin plasma concentrations was substantially lower with transdermal than with oral oxybutynin. In a 3-year retrospective study [23], 101 children who were 0.25-10 years old and had uncoordinated detrusor-sphincter function and low compliance were treated with both oral or intravesical oxybutynin and clean intermittent catheterization (CIC). The results showed that both protocols were equally effective for managing neurogenic bladder dysfunction, but intravesical administration was safer and better tolerated than oral oxybutynin. In a prospective study [24], the intravesical application of oxybutynin (0.3 mg/kg/day up to 0.9mg/kg/ day) was found to be an efficacious therapy as oral oxybutynin which could increase the efficiency to 87%. An overview of 25 studies conducted in pediatric patients with enuresis shows that the drug therapy does not improve the detrusor hyperactivity which is regarded as a pathogenic factor in nocturnal enuresis [4]. Sehgal et al. used oxybutynin in enuretic children who were categorized based on urodynamic findings into 2 groups of patients with normal urodynamic studies and those with urodynamic abnormalities. The patients received the drug at a dose of 5 mg BD (6–9 years) or 5mg TDS (10–14 years) for 3 months and then the drug was tapered during one month. They found a response (50% reduction in the frequency of enuresis) rate of 94.2% in patients with urodynamic abnormalities. When compared to imipramine and flavoxate, oxybutynin had the best immediate outcome [1].

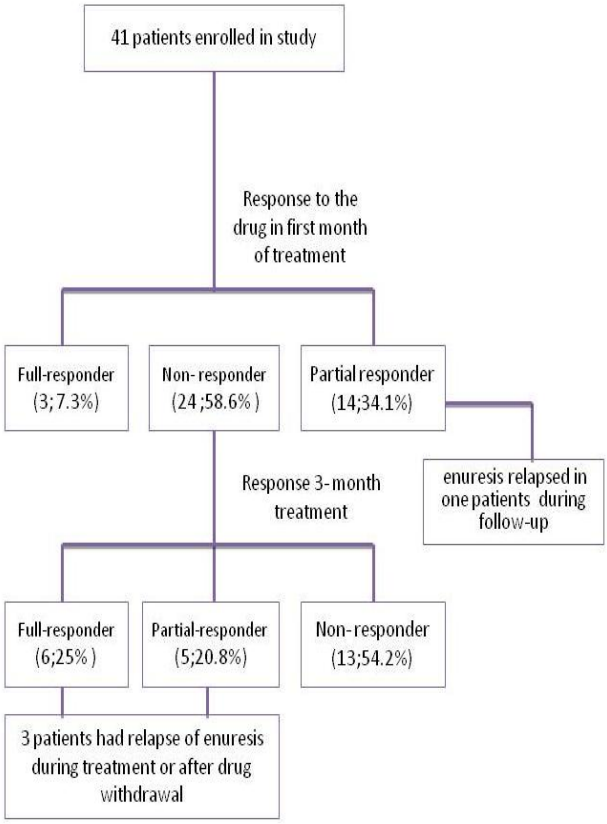

Figure 1. Diagram A: Response to treatment in study group

The results of this study showed that oxybutynin was effective in patients with and without urodynamic abnormalities. Hjälmås believes that detrusor relaxing drugs (such as oxybutynin) alone are not efficient against nocturnal enuresis and should be used as adjuncts to urotherapy and

enuresis-specific therapy such as alarm and/or desmopressin [20]. Long term follow-up of enuretic children has shown a spontaneous resolution rate of 15% per year [32-33]. In our series, although during short term (3 months) follow –up 9 of 41 patients (22%) reached full response (≥90% reduction in bed wetting), after 1-34 months (mean 9 months) follow up, in 3 patients enuresis recurred during course of treatment or after drug withdrawal. The spontaneous resolution rate of enuresis in one-year follow-up is estimated 15% [32-33], which is lower than that of our study (22% in the 3-month follow-up). The main limitations of our study were the lack of a control group, the small sample size, and lack of long-term follow-up. Further double-blind placebo-controlled studies in larger groups of pediatric enuretic patients with long-term follow-up are needed to compare the benefits and psychosomatic adverse effects of the low dose of oxybutynin versus its standard dose.

Conclusions

In the present study, there was 68.3% treatment benefit and 12% risk (side effects of the drug) with low dose oxybutynin. We believe that low dose oxybutynin may have a role in treating enuresis, especially in patients with NMNE who experience anti-cholinergic adverse effects of the standard treatment.

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Conflict of Interest

None declared

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Table 1. Duration of treatment and condition of the patients at final follow up

Patient	Duration of treatment (month)	Duration of Follow-up (month)	Patient at final follow-up	Prior medical treatment for enuresis
Case 1	6	8	Relapse with drug withdrawal	No treatment
Case2	12	23	Relapse with drug withdrawal	No treatment
Case3	5	6	Relapse with drug withdrawal	No treatment
Case4	12 (interrupted)	12	Relapse with drug withdrawal	No treatment
Case 5	7	7	Relapse with drug withdrawal	No treatment
Case 6	1	1	Relapse with drug withdrawal	No treatment
Case 7	3	3	Relapse with drug withdrawal	No treatment
Case 8	3	4	Relapse with drug withdrawal	No treatment
Case 9	2	2	No enuresis with Oxybutynin Consumption	Imipramine
Case 10	4	5	Relapse with drug withdrawal	Imipramine
Case 11	1	1	Relapse with drug withdrawal	Imipramine
Case 12	1	22	Partial resolution unrelated to the drug	No treatment
Case 13	10	32	Partial resolution unrelated to the drug	No treatment
Case 14	2	11	Spontaneous resolution unrelated to the drug	No treatment
Case 15	1	1.5	Relapse with drug withdrawal	Imipramine + Minirin
Case 16	3.5	11	No enuresis with Oxybutynin consumption	No treatment
Case 17	13	22	Relapse with drug withdrawal	No treatment
Case 18	18	22	Relapse with drug withdrawal	No treatment
Case 19	3	3	Relapse with drug withdrawal	No treatment
Case 20	8	10	Relapse with drug withdrawal	No treatment
Case 21	4	8	Relapse with drug withdrawal	Minirin
Case 22	7	26	Relapse with drug withdrawal	No treatment
Case 23	3	5.5	Relapse with drug withdrawal	No treatment
Case 24	4	8	No enuresis despite drug withdrawal	No treatment
Case 25	3	5	Relapse with drug withdrawal	Imipramine
Case 26	6	7	Relapse with drug withdrawal	Minirin
Case 27	6	6	No enuresis with Oxybutynin consumption	؟
Case 28	8	34	No enuresis despite drug withdrawal	No treatment
Case 29	2	5	Relapse with drug withdrawal	No treatment
Case 30	3	4	Relapse with drug withdrawal	Imipramine
Case 31	2	2	No enuresis with Oxybutynin consumption	؟
Case 32	4	5	Relapse with drug withdrawal	؟
Case 33	1	1	Relapse with drug withdrawal	؟
Case 34	2	3	Relapse with drug withdrawal	No treatment
Case 35	4	8	Relapse with drug withdrawal	Imipramine + Minirin
Case 36	2.5	8.5	Relapse with drug withdrawal	No treatment
Case 37	19	19	No enuresis with Oxybutynin consumption	No treatment
Case 38	17	23	No enuresis despite drug withdrawal	Minirin
Case 39	5	5	Relapse with drug withdrawal	No treatment
Case 40	3	3	Relapse with drug withdrawal	Minirin
Case 41	3	3	Relapse with drug withdrawal	Imipramine