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Review Article

Comparison of tolterodine with standard treatment in pediatric patients with non-neurogenic dysfunctional voiding/over active bladder : A systematic review

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Abstract

To examine the efficacy, safety and tolerability of tolterodine in children with overactive bladder in comparison with standard treatment i.e. oxybutynin as demonstrated in randomized clinical trials and other studies. A systematic search was done to screen the studies evaluating the effect of tolterodine in children with non-neurogenic overactive bladder. Results of studies were pooled and compared. Efficacy was determined from micturition diaries and dysfunctional voiding symptoms score. Safety and tolerability were assessed from the reported treatment emergent adverse events. A total of six randomized clinical trials and 11 other studies of tolterodine in children with urinary incontinence were included in the present systematic review. The dose of tolterodine used in different settings ranged from '0.5 to 8 mg/day' instead of '0.5 to 8 mg/kg per day' and the duration of studies ranged from 2 weeks to 12 months. Both extended and immediate release preparations of tolterodine were shown to have comparable efficacy and tolterodine proved to have comparable efficacy with better tolerability than oxybutynin in these studies. It can be concluded that tolterodine is efficacious in treatment of urinary incontinence in children. Moreover, its efficacy is comparable to oxybutynin, the most commonly prescribed anticholinergic in this condition, while having better tolerability. Hence, it can be considered as first line therapy for the treatment of urinary incontinence in children.

Introduction

Urinary incontinence is defined as the unwanted or involuntary passage of urine that is objectively demonstrable and is a social and hygienic problem (1). Incontinence has a negative effect on quality of life, emotional well-being, social function and general health. Left untreated, it can lead to skin inflammation, pressure ulcers, urinary tract infections, sleep deprivation, social withdrawal, depression and sexual dysfunction.

Daytime or nighttime incontinence in children can be embarrassing. Incontinence may occur as a result of abnormalities of the urethra (including the bladder outlet and urinary sphincter) or the bladder or from a combination of both. The most common group of pediatric patients with incontinence are those with overactive bladder disorder (2).

In normal individuals, incontinence during the bladder filling and storage phase of the micturition cycle is prevented by the urethral sphincters (proximal and distal), acting along with other factors like the urethral

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mucosa, submucosal spongy tissue, and the overall length of urethra, maintaining adequate resistance to the flow of urine from the bladder at all times until voluntary voiding is initiated. Also, bladder or detrusor smooth muscle activity is normally suppressed during the filling phase by centrally mediated neural reflexes. During the micturition phase, bladder emptying occurs due to coordinated contraction of bladder smooth muscle, resulting in rise in intravesical pressure concomitant with a decrease in urethral resistance (3, 4).

The primary motor input to the detrusor muscle of the bladder is along the pelvic nerves (S2-S4), acetylcholine being the primary neurotransmitter in the human lower urinary tract. Of the known subtypes of muscarinic receptors, M3 receptors are responsible for both the emptying contraction of normal micturition, as well as involuntary bladder contractions that may result in urinary incontinence. Thus, most pharmacologic antimuscarinic therapy is primarily anti- M3 based (3, 4).

Anticholinergics like oxybutynin, tolterodine, trospium, solifenacin and darifenacin have widely accepted clinical effectiveness for the treatment of overactive bladder. The efficacy of oxybutynin chloride has been sufficiently proved; however its dosage and side effects, although scarce in children, usually cause treatment discontinuation (5). Tolterodine, an anticholinergic specifically developed to treat overactive bladder has demonstrated greater specificity for bladder tissue in vitro and is believed to be superior to non-selective antimuscarinic drugs, with respect to adverse events, allowing more compliance and more effective treatment in children (5-9).

Keeping this in mind, the aim of the present study was to critically analyze the randomized clinical trials and other studies of tolterodine for evaluating its effectiveness and tolerability in children.

Material and Methods

A systematic literature search was carried out from 1966 to 24 December 2012. MEDLINE search employed a complex search strategy, including both ''MeSH'' (Medical Subject Heading) and ''free text'' protocols. Specifically, the MeSH search was conducted by combining the following terms retrieved from the MeSH browser provided by MEDLINE: ''urinary bladder, overactive'' and ''cholinergic antagonists''. Multiple free-text searches were performed applying singularly the following terms through all the fields of the records: overactive bladder, detrusor overactivity, bladder overactivity, urgency frequency syndrome, tolterodine and children. Subsequently, the searches were pooled and limited to randomized controlled trials (RCTs) and other studies in pediatric population. No temporal limits were used. Further, reference list of original reports and review articles were looked for finding desired studies. We also manually searched related journals in the National Medical Library (New Delhi), library of the institute and conference abstracts for 2003 to 2012 of international societies of pediatric surgery. Data were extracted separately and independently by two of the authors and were cross-checked.

Inclusion and exclusion criteria

Both randomized controlled clinical trials and other studies (include non randomized open label studies, single arm studies, observational studies and retrospective studies) evaluating the use of tolterodine in pediatric population with overactive bladder are included in the present review. Studies including pediatric population up to the mean age of 14 years and presence of voiding dysfunction defined as incontinence, frequency, urgency and various holding maneuvers with or without recurrent nonfebrile urinary tract infection in the absence of an obvious anatomical or neurogenic cause. Studies evaluating the drug in conditions with obvious anatomical or neurogenic abnormality, history of febrile urinary tract infection were excluded from the review.

Data extraction and outcome measure

Data was extracted in a specially designed format. Dysfunctional voiding scoring system is defined as primary efficacy end point. Other efficacy parameters like urodynamic parameters, Visual analogue scale (VAS) and incontinent episodes and tolerability profiles are also discussed.

Results

The search terms like "urinary bladder" AND "tolterodine" AND "incontinence" showed 186 items in pubmed. MeSH term "Urinary Bladder" under treatment related subheadings and with additional filters like Clinical Trial, Comparative Study, Randomized Controlled Trial, Humans, Child: birth-18 years showed 61 articles in PubMed. The search from this and other sources led to 72 articles to be screened. Out of these, the articles satisfying inclusion and exclusion criteria were six randomized controlled trials (RCTs) and 11 studies other than RCTs including non randomized open label studies, single arm studies, observational studies and retrospective studies. After considering characteristics of randomized controlled clinical trials and other studies of tolterodine in children with urinary incontinence are depicted in Table I and II respectively.

Randomized controlled clinical trials (RCTs) of Tolterodine in children with Urinary Incontinence (UI)

1. Ayan et al. conducted a randomized blinded clinical study to compare the efficacy of tolterodine treatment combined with behavioral modification, behavioral modification alone and behavioral modification plus placebo in children with non-neurogenic, non-anatomical voiding dysfunction. A total of 72 children divided into 3 groups. First group was given tolterodine (1 mg twice daily) along with behavioral modification, second group was given behavioral modification only and the third one was given placebo with behavioral modification. Assessment was done with Dysfunctional voiding symptom score (DVSS) for a period of 12 wks. Headache & dry mouth were noted in some. The study concluded that tolterodine along with behavior modification can be recommended as a first line treatment for voiding dysfunction in children without neurological or anatomical abnormality before invasive evaluation (10).

2. Nijman et al. in 2005 conducted two large randomized controlled trials to evaluate the efficacy and safety of tolterodine extended release in children with symptoms of urinary urge incontinence suggestive of detrusor overactivity. Children 5 to 10 years old with incontinence suggestive of detrusor overactivity (1 or more diurnal incontinence episodes per 24 hours) were randomized to tolterodine (2 mg daily) or placebo for 12 weeks. The assessment was based on the number of incontinence episodes per week. Changes from baseline in the number of voids per 24 hours and volume of urine per void were also evaluated. The study suggested that a weight adjusted dosing regimen is required for optimal response among older and heavier children (11).

3. Kilic et al. conducted a study to assess the effectiveness and tolerability of tolterodine and oxybutynin in children with detrusor instability (DI). A total of 60 children (mean age 7.97±2.71 years) were enrolled. Out of these, 30 were given tolterodine and the rest 30 received oxybutynin for at least 6 months. Assessment was done with urodynamic parameters. Similar reductions in urge urinary incontinence episodes were observed with tolterodine and oxybutynin but side-effects were more common with oxybutynin. The results showed that tolterodine is better tolerable and may enhance children's compliance during long-term treatment (12).

4. Deng et al. performed a head to head comparison of tolterodine and oxybutynin along with a placebo group in 204 children with idiopathic overactive bladder (n = 68 each). Drugs were administered as Tolterodine daily 0.1 mg/kg (maximum dose does not exceed 2 mg/d) orally for 14 d, Oxybutynin Daily 0.25 mg/kg (maximum dose does not exceed 5 mg/d) orally for 14 d. Parents daily recorded voiding diary, micturition frequency, time, urine output and the number of wet pants from 7 days before treatment to 2 weeks after treatment. Adverse reactions were also noted down. The efficacy rate was not significantly different among tolterodine and oxybutynin groups (89% and 92%, respectively) but was significantly ($P<0.05$) more than placebo group (25%). The incidence of adverse events in the tolterodine-treated group 18 (28%) was significantly lower than that in the oxybutynin-

TABLE I: Characteristics of randomized controlled clinical trials of tolterodine in children with urinary incontinence.

S.No.	Author (year)	Total patients	Treatment groups (no. of subjects)	Age (yr) (mean±SD) or only mean	Primary efficacy endpoint	Duration of study period	ADRs reported	Remarks
1.	Ayan et al., (2007)[10]	72	T (2 mg/ day) + B (31)/B (20)/ P+B (20)	9.09±2.59	DVSS	12 wks	New urinary tract infections were documented in 6 patients in the tolterodine group, 5 of those receiving B and 7 of those receiving P+B. Two patients receiving tolterodine reported headache and 5 reported dry mouth.	Tolterodine was more effective as at the end of 3 month the symptom scores were significantly low (P<0.05) than other two groups
2.	Nijman et al., (2005)[11]	711 (combination of two studies)	T (2 mg/day) (487)/P (224)	8±1.5 incontinent episodes/wk	No. of incontinent episodes/wk	12 wks	In study 1 the most common AE was headache (tolterodine 10% vs placebo 14%). In study 2 the most common AE was urinary tract infection (9%) in the tolterodine group and abdominal pain (8%) in the placebo group. Dry mouth and constipation occurred infrequently. Across both studies 6 tolterodine recipients (1%) and 2 placebo recipients (1%) had serious adverse events, but not considered to be treatment related.	Primary end point was not significantly different, however, secondary analyses demonstrated that tolterodine was well tolerated among 5 to 10-year-old children. Exploratory analyses also showed that children weighing 35 kg or less benefited most from tolterodine treatment. Concluded that weight adjusted regimen required.
3.	Kilic et al., (2006)[12]	60	T (30)/ Oxy (30)[1]	7.97±2.71	Urodynamic parameters	24 wks	The side effects observed were dry mouth, no sweating, hyperpyrexia, constipation, flushing, dizziness, headache and dyspepsia. Side effects were more in oxybutynin group, even in oxybutynin group, eight patients were crossed over to tolterodine because of the severe side-effects of the oxybutynin	Comparable efficacy as measured by bladder capacity, maximum detrusor pressure and compliance; better tolerability of tolterodine as (13 events in 13 patients) compared to the oxybutynin group (27 events in 20 patients; P=0.027)
4.	Deng et al., (2011)[13]	204	T (68)/ Oxy (68)/P (68)[2]	7.1	Urodynamic parameters	4 wks	The incidence of adverse events in the tolterodine-treated group 18 (28%) was significantly lower than that in the oxybutynin-treated group 38 (57%) (P<0.05). Adverse reactions were dry mouth, constipation, abdominal pain, skin redness, rash, dry eyes, inability to urinate, urinary retention, headache, excitement and other adverse reactions.	Effective rate was 25% in the placebo group, 89% in the tolterodine-treated group, and 92% in the oxybutynin-treated group. The two drug groups were having comparable efficacy. Tolterodine has better tolerability as adverse events in the tolterodine-treated group (28%) was significantly lower than that in the oxybutnin-treated group (57%) (P<0.05).

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5.	Austin et al., (2008)[14]	34	T (4 mg/day) (16)/P (18); all subjects were with desmopressin therapy (0.6 mg every night)	10.56±2.28	No. of wet nights	4 wks	There were no adverse events seen during the study period.	Full and partial responses (44% success) were more in tolterodine group as compared to placebo group (31% success). Complete lack of response (0% change) in the placebo group was exhibited in 44% subjects, compared with the long acting tolterodine group (16.5%).
6.	Nevéus and Tullus, (2008)[15]	27#	T (1-2 mg/day) (27)/I (25-50 mg/day) (27)/P (27)	9.4±2.1	No. of wet nights	5 wks	Imipramine group had more side effects (nine children experienced side effects) compared to tolterodine (one subject, p=0.001).	Imipramine more efficacious than tolterodine. Number of wet nights during last 14 days of a 5-week treatment period in placebo, tolterodine and imipramine treatment were 11.0±3.9, 10.4±3.9 and 7.8±5.1, respectively (p<0.001).

T: Tolterodine; AEs : Adverse events
T/Oxy[1] : Tolterodine 1 mg twice daily (<5 yrs age - 0.1 mg/kg/day); Oxybutynin 0.4 mg/kg/day.
T/Oxy/P[2] : Tolterodine 0.1 mg/kg/day; Oxybutynin 0.5 mg/kg/day.
P : Placebo; B : Behavioral modification; I: Imipramine; Oxy: Oxybutynin.
DVSS : Dysfunctional voiding symptom score.
: All patients were refractory to alarm and desmopressin and continued on desmopressin along with study drugs. It was a crossover study, i.e. each subject received each type of treatment for one cycle.

treated group 38 (57%) (P<0.05). The treatment withdrawals due to adverse events were also significantly low in tolterodine group (3 cases) as compared to oxybutynin group (7 cases). Adverse reactions were dry mouth, constipation, abdominal pain, skin redness, rash, dry eyes, inability to urinate, urinary retention, headache, excitement and other adverse reactions. Three cases of discontinuation of treatment in tolterodine group were due to severe dry mouth, urinary retention, excitement. In oxybutynin group the 7 cases discontinued:, 4 cases of severe dry mouth; urinary retention in one case; inability to urinate, urinary dribbling in one case; excruciating headache in one case (13).

5. Austin et al. in their study on desmopressin non-responders subjects compared desmopressin plus long acting tolterodine with desmopressin plus placebo administered for one month in a total 34 patients. In result there was significant reduction in the mean number of wet nights in the group receiving tolterodine, compared with placebo. None of the groups experienced adverse events during the study period (14).

6. Nevéus and Tullus (2008) in a randomized double blind cross over study done in 27 children of primary nocturnal enuresis unresponsive to alarm and desmopressin compared placebo, tolterodine 1-2 mg, and imipramine 25-50 mg at bedtime for 5 weeks. They found that imipramine was significantly better than both placebo (p=0.001) and tolterodine (p=0.006) in reducing number of wet nights. Nine children on imipramine experienced adverse effects and only one on tolterodine had adverse effects (p=0.001) (15).

Studies other than RCTs done for tolterodine in children with Urinary Incontinence (UI)

1. The study by Yucel et al. evaluated the potential of tolterodine being a replacement treatment for children with non-neurogenic daytime urinary

TABLE II : Characteristics of studies other than randomized trials of tolterodine in children with urinary incontinence.

S. No.	Author (year)	Total patients	Treatment groups (no. of subjects)	Mean age (yr)	Primary efficacy endpoint	Duration of study period	ADRs reported	Remarks
1.	Yucel et al., (2005)[6]	41	T (2-4 mg daily) (30) replacing Oxy; Oxy (0.4-0.8 mg/kg daily) (11)	7.2	Number of wetting episodes	Mean 7.1 months	Tolterodine treated subjects had lower side effects score (2 to 3.1) than oxybutynin treated subjects (7.2 to 16.9) according to following ADRs: mouth dryness, vision disturbances, dizziness or headache, gastrointestinal disturbances, mood swings, and academic success or cognitive abilities. For each ADR scores ranged from none (1) to severe (3).	Tolterodine treated subjects: complete response (24 patients), partial (5 patients) and failed response (1 patient)
2.	Bolduc et al., (2003)[9]	34	T 1 mg (12) and T 2 mg (22) vs. replacing Oxy	8.9	Number of wetting episodes	11.5 months	In the tolterodine crossed-over group, there was decrease by 50-75% of the incidence of side-effects including dry mouth (P<0.001), constipation, blurred vision, mood swings, dizziness, headache, flushing and fatigue. Side-effects were graded as moderate or severe in 89% in the oxybutynin group, compared with 31% in the tolterodine group.	Comparable efficacy; better tolerability; reduction in wetting episodes at 1 year was> 90% in 23 (68%), >50% in five and <50% (or failure) in six patients.
3.	Ayan et al., (2005)[16]	44	T 1 mg daily + B (44)	7	DVSS	12 wks	14 (31%) subjects reported dry mouth and two (4%) reported headache after the first few days of treatment, but the effects were not severe.	Mean (SD) DVSS was14.0 (2.67) and 6.68 (3.67) before and after Treatment (P<0.001). Concluded that it can be used as 1st line therapy.
4.	Babu R (2006) [17]	44	T 2 mg daily (36) vs. 4 mg daily (8)	9.3	DVSS	12 wks	Two patients reported mild side effects in the form of dry mouth and hyperpyrexia.	Mean (SD) DVSS was17.1 (2.8) and 12.0 (2.4) before and afterTreatment (P<0.01). Concluded that single daily dose of long acting tolterodine is effective and has good compliance and minimal side effects.
5.	Hjalmas et al., (2001)[18]	33	T 0.5 mg (11) vs. 1 mg (10) vs. 2 mg (12); all are given twice daily	7.4	Voiding dairy variables[1]	2 wks	20 patients had adverse events (six on 0.5 mg, five on 1 mg and nine on 2 mg). Out of the 13 possibly related events, 10 occurred in the 2 mg group. The most commonly reported adverse event was headache; no serious adverse events were reported.	Reduction in number of incontinence episodes/week in 0.5 mg group: 17%, in 1 mg group: 44%, in 2 mg group: 44%. Concluded that 1 mg BD optimal dose for 5-10 yrs age.

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6.	Goessl et al., (2000)[19]	22	T 0.1 mg/kg/ day as 1st line (12) vs replacing Oxy (10)	5.7	Urodynamic Parameters[2]	12 wks	Only 1 patient experienced a transient and moderately adverse effect	Efficacy was assessed increase in by maximum bladder capacity, detrusor compliance and reduction in detrusor pressure. Concluded that tolterodine and oxybutynin were having comparable efficacy and tolterodine had better tolerability.
7.	Mahanta et al., (2008)[20]	25	T 2 mg/day ER vs IR (Cross over study)	7.5	Urodynamic Parameters, VAS, Subjective assessment	3 wks	A few patients reported diarrhea with ER tolterodine.	Decrease in detrusor leak pressures and improvement in compliance were not significantly different between the groups. However, IR has increased bladder capacity than ER ($P<0.0001$). Concluded as ER and IR were of comparable efficacy
8.	Nijman et al., (2007)[21]	318	T 2 mg/day ER	7.6	No efficacy endpoint. Primary endpoint was incidence and severity of adverse events	12 months	49% of patients reported≥1 adverse event. The most frequent AEs were urinary tract infection (7%), nasopharyngitis (5%), headache (5%), and abdominal pain (4%)	Tolterodine ER was well tolerated with a favorable long-term safety profile.
9.	Rombis et al., (2005)[22]	35	T or Oxy (15), T+D or Oxy+D (20)	9	Number of wetting episodes	3 to 6 months follow up	Not reported	Almost complete response i.e. stopping of wetting.
10.	Munding et al., (2001)[23]	30	T 2 mg/day (1), T 4 mg/day (27) and T 8 mg/ day (2)	8.7	Number of wetting episodes	Mean 5.2 months (retro-spective study)	Four patients (13.3%) reported side effects. There were no reports of hyperpyrexia, flushing or intolerance to sunshine and outdoor temperature.	10 (33%) cured i.e. greater than 90% reduction in wetting episodes, 12 (40%) improved i.e. greater than 50% reduction and 8 (27%) failed i.e. less than 50% reduction. Concluded that tolterodine can be used safely to decrease wetting episodes in children.
11.	Reinberg et al., (2003)[24]	86 girls and 46 boys in 3 groups (IR, ER and long acting tolterodine)	Started at 2 mg T and 5 mg Oxy and titrated according to response.	9, 10.4 and 9.1 in the three groups respectively	Voiding diary variables	Dose was titrated until complete diurnal urinary continence or bothersome anticholinergic side effects developed	No statistically significant differences in peripheral or central nervous system anticholinergic side effects among the 3 treatment groups.	Extended release oxybutynin chloride was more effective than either immediate or long acting tolterodine for control of daytime urinary incontinence and urinary frequency ($P<0.05$). Similarly, long acting tolterodine was more effective than immediate release tolterodine.

T : Tolterodine; Oxy : Oxybutynin; B: Behavioral modification; D: Desmopressin, AEs : Adverse events, DVSS: Dysfunctional voiding symptom score
[1] : frequency and incontinent episodes
[2] : maximum bladder capacity, mean detrusor compliance, maximum detrusor pressure
ER : Extended release; IR: Instant release
VAS : Visual analogue scale

incontinence secondary to overactive bladder who had previously failed to improve with oral oxybutynin treatment. Forty-one children (mean age 7.2 years, range 5 to 14 years) were enrolled, out of which 30 switched to tolterodine and 11 continued receiving oxybutynin. After a mean of 7.1 months (range 6 to 9 months) of tolterodine use, a complete response (i.e. no episodes of enuresis and no symptoms of urinary urgency or frequency) was reported in 24 patients and partial improvement in 5 (17%). In 1 patient, treatment failed completely. All tolterodine users were compliant with treatment (6).

2. In the study by Bolduc et al., children with dysfunctional voiding and on oxybutynin treatment were shifted to tolterodine 1 mg (12 patients) and 2 mg (22 patients). Efficacy was assessed by questionnaire for lower urinary tract dysfunction as defined by the International Children's Continence Society as cured-greater than 90% reduction in wetting episodes, improved-greater than 50% reduction or failed-less than 50% reduction. After a median duration of 11.5 months (range 5 months to 16 months) the efficacy was comparable between oxybutynin and tolterodine. Tolterodine is well tolerated in children than oxybutynin. The incidence of side-effects including dry mouth ($P<0.001$), constipation, blurred vision, mood swings, dizziness, headache, flushing and fatigue was decreased by 50–75% when patients were crossed-over to tolterodine (9).

3. In a study conducted by Ayan et al., in 2005, the effect of antimuscarinic treatment with tolterodine combined with behavioral modification in children with non-neurogenic voiding dysfunction but no obvious anatomical or neurogenic cause was assessed. Treatment with tolterodine (1 mg twice daily) was started in all patients. Therapy was assessed with dysfunctional voiding symptoms score (DVSS) at the start and after 3 months. Headache & dry mouth were noted in some patients. The study concluded that tolterodine 1 mg along with behavioral modification can be used as a first line therapy in children with UI (16).

4. In 2006, the study by Babu analyzed the efficacy of tolterodine in children with non-neurogenic voiding dysfunction (17). Of 44 patients (mean age 9.3 yrs; M:F=25:19), 36 received long acting tolterodine tartrate at a dose of 2 mg OD and 8 patients at a dose of 4mg OD. Therapy was assessed with DVSS before and after the treatment. The results concluded that single dose of long acting tolterodine is effective in children with voiding dysfunction (17).

5. Hjalmas et al., conducted a study to determine the safety, efficacy and pharmacokinetics of tolterodine in children with an overactive bladder. Thirty-three children (20 boys and 13 girls, aged 5-10 years) with an overactive bladder and symptoms of urgency, frequency and/or urge incontinence were treated with oral tolterodine 0.5 mg (n=11), 1 mg (n=10) or 2 mg (n=12) twice daily for 14 days. Change in residual urinary volume, frequency and incontinence episodes were evaluated in each group for a period of 2 wks. Headache was the most commonly reported adverse event and there were no general safety concerns. The results supported the use of 1 mg twice daily as the optimal dose of tolterodine for treating children aged 5-10 years with an overactive bladder (18).

6. A comparative study by Goessl et al., investigated the urodynamic effects and tolerability of the new antimuscarinic drug tolterodine in children with detrusor hyperreflexia. Twenty-two children (12 boys and 10 girls; age range 3 months to 15 years) with detrusor hyperreflexia were enrolled. Group1 (n=12) was given tolterodine tartrate as a first-line therapy and Group 2 (n=10) received tolterodine replacing oxybutynin for a period of 12 wks. Treatment was assessed with urodynamic parameters such as maximum bladder capacity, mean detrusor compliance and maximum detrusor pressure. The study showed that tolterodine has comparable efficacy and better tolerability than oxybutynin (19).

7. Another study compared the efficacy of tolterodine 2 mg extended release (ER) and Instant release (IR) preparations in 25 children for a period of 3 wks. Assessment was made

TABLE III : Adverse drug reactions and withdrawals in randomized clinical trials and other studies.

S.No.	Author	Total withdrawals	
Randomized controlled trials		*Control*	*Treatment*
1.	Ayan et al., (2007)[10]	Nil in P	One (edema in hands and feet within 3 days of start of treatment)
2.	Nijman et al., (2005)[11]	Nil in P	Nil
3.	Kilic et al.,(2006)[12]	Nil in Oxy	Nil
4.	Deng et al., (2011)[13]	Nil in P, seven in Oxy	Three (3 cases withdrew in tolterodine group due to dry mouth, urinary retention and excitement; whereas 7 cases withdrew in oxybutynin group due to severe dry mouth, urinary retention, inability to urinate and urinary dribbling, and excruciating headache)
5.	Austin et al., (2008)[14]	Nil	Nil
6.	Nevéus and Tullus, (2008)[15]	Nil	Nil
Other studies			
7.	Yucel et al., (2005)[6]	Not applicable	Nil
8.	Bolduc et al., (2003)[9]		Eight (dry mouth in three, blurred vision in three and mood swings in two)
9.	Ayan et al., (2005) [16]		Nil
10.	Babu R(2006)[17]		Nil
11.	Hjalmas et al., (2001)[18]		Two (tachycardia, visual accommodation problems with 2 mg dose)
12.	Goessl et al., (2000)[19]		Nil
13.	Mahanta et al., (2008)[20]		Nil
14.	Nijman et al., (2007)[21]		Ten (nature of these AEs were not shown in the study)
15.	Rombis et al., (2005)[22]		Not reported
16.	Munding et al., (2001)[23]		One (diarrhea)
17.	Reinberg et al., (2003)[24]		Not reported

ADR table (1: headache; 2: dry mouth; 3: constipation; 4: hyperpyrexia; 5: nausea, vomiting, diarrhea; 6: flushing; 7: no sweating)
P: Placebo; Oxy: Oxybutynin, AEs : Adverse events

with urodynamic parameters, visual analogue scale & subjective assessment. There were no adverse effects. The study showed comparable efficacy of ER & IR Tolterodine (20).

8. In the open label extension phase of a double blind study by Nijman et al. in 2007, 318 children (aged 5-11 yr) with urgency urinary incontinence. One of the inclusion criteria in this study was "Completion of the 12-wk double-blind study was required for participation in the open-label extension." All the subjects in this study were administered tolterodine ER (2 mg once daily) for 12 months. The primary end points were the incidence and severity of adverse events. The result depicted that tolterodine was well tolerated. Forty-nine percent of patients reported one or more adverse events during the study. Among the adverse events the most frequently seen were urinary tract infection (7%), nasopharyngitis (5%), headache (5%), and abdominal pain (4%). Ten patients (3%) withdrew because of AEs but the nature of these AEs were not shown in the study (21).

9. In the study by Rombis et al., 142 healthy children, aged between 6.5 and 18 years with complain of bedwetting were administered different treatments. Out of them fifteen children with detrusor instability received oxybutynin or tolterodine. Twenty children with diurnal and nocturnal enuresis were given desmopressin and oxybutynin or desmopressin and tolterodine. The follow up period ranged from 3 to 6 months. In these subjects with oxybutynin and tolterodine treatment almost complete response (stopped wetting) to treatment was obtained (22).

10. In a retrospective study by Munding et al., the safety and efficacy of tolterodine in children with dysfunctional voiding were evaluated in 30 patients. The mean age of children was 8.7 yrs and tolterodine was administered at a dose of 1 to 4 mg twice daily. According to the criteria of International Children's Continence Society, final treatment outcomes on medication were as 10 (33%) cured i.e. greater than 90% reduction in wetting episodes, 12 (40%) improved i.e. greater than 50% reduction and 8 (27%) failed

i.e. less than 50% reduction. Four patients (13.3%) reported side effects and only 1 discontinued the medication due to diarrhea (23).

11. In an open label parallel group study by Reinberg et al., 86 girls and 46 boys with a history of diurnal urinary incontinence were arbitrarily assigned to extended release oxybutynin, immediate release tolterodine or long acting tolterodine. The result showed that extended release oxybutynin chloride was more effective than either immediate or long acting tolterodine for control of daytime urinary incontinence and urinary frequency ($P<0.05$). Similarly, long acting tolterodine was more effective than immediate release tolterodine. There were no statistically significant differences among the 3 treatment groups regarding the presence of peripheral or central nervous system anticholinergic side effects (24).

The efficacy of tolterodine compared to placebo and behavioral therapy was demonstrated in two different studies (10, 16). The dose of tolterodine used in different settings ranged from 0.5 to 8 mg per day and the duration of studies ranged from 2 weeks to 12 months. Both extended and immediate release preparations of tolterodine were shown to have comparable efficacy in the study by Mahanta et al. (20). Besides, tolterodine proved to have comparable efficacy with better tolerability than oxybutynin (12, 13, 19). Adverse effects of tolterodine included headache, dry mouth, constipation, hyperpyrexia, nausea, vomiting, diarrhea, flushing, excitement and no sweating (Table I and II). In an open label trial by Hjalmas et al. (18), 2 patients withdrew due to tachycardia and visual accommodation problems with 2 mg dose while 1 patient in a controlled trial by Ayan et al. (10) withdrew due to edema in hands and feet within 3 days of start of treatment. The head to head comparative study of tolterodine and oxybutynin has shown that adverse effects (28% vs. 57%, respectively) and treatment withdrawal (3 vs. 7, respectively) are more in oxybutynin group compared to tolterodine group (13). However, the non-randomized trials with long term tolterodine administration like 11 to 12 months has also caused a higher number of patient withdrawal (9, 21) (Table III).

Discussion

Tolterodine possesses superior efficacy to behavioral therapy alone for the treatment of pediatric urinary incontinence thereby proving its effectiveness in this condition (10). This finding is further strengthened by demonstration of its efficacy in both randomized controlled trials and other studies as shown in the present study. Tolterodine along with behavioral therapy has been recommended as first line therapy in a previous study (16). Its efficacy in children is similar to oxybutynin, the most commonly used anticholinergic for overactive bladder (12, 13).

Regarding the dosage regimen of tolterodine, 1 mg twice daily dose in children greater than 5 years of age was found useful in both non-randomized (18) and randomized settings (10) while in another non-randomized study (16) 1 mg once daily dose was also efficacious. Nijman et al. (11) however recommend a weight adjusted dosing regimen for older and heavier children on the basis of their observation of efficacy and safety of tolterodine in children 5 to 10 years of age and weighing 35 kg or less. Both immediate and extended release preparations of tolterodine show comparable efficacy (20), however in another study by Reinberg et al. long acting tolterodine was shown to be more efficacious than immediate release tolterodine (24). The adverse effects with tolterodine were almost identical in randomized clinical trials and other studies, which included headache, dry mouth, constipation, hyperpyrexia, nausea, vomiting, diarrhea, flushing and no sweating. There were only few withdrawals from tolterodine treatment in all studies (10, 13, 18), though long term studies (11-12 months) has a little higher number of patient withdrawal (9, 21). Tolterodine has lower incidence of adverse effects leading to better compliance, while upto 10% children discontinue oxybutynin treatment due to adverse effects (25). Thus risk benefit analysis goes in favor of tolterodine as compared to oxybutynin as demonstrated in randomized clinical trial settings and other studies (12, 13, 19).

The limitation of the study is that it has focused on tolterodine and the standard treatment i.e. oxybutynin. As of now multiple anticholinergics are available for

treatment of overactive bladder. So it will be a great benefit to have an analysis of all of these anticholinergics in a single platform. It can be concluded from the above discussion that tolterodine is efficacious in treatment of urinary incontinence in children. Moreover, its efficacy is comparable to oxybutynin, the most commonly prescribed anticholinergic in this condition, while having better tolerability. Hence, it can be considered as first line therapy for the treatment of urinary incontinence in children.

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