Enuresis

15

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15.1 A Vignette of Typical Presentation of the Sleep Disorder

As a paediatrician, you are asked to see a 7-year old boy, Timmy, and his family for his problem of bed-wetting. Timmy enjoyed good past health all along. His parents are worried of his on-going problem of bed-wetting occurring 3–4 times each week. Despite adopting measures for the past 6 months of reducing fluid intake at night and urinating before sleep there has been no improvement.

Timmy usually has 1 episode of bed-wetting every other night and only notices on waking up with his bedsheets being wet. He complained of no urinary frequency, urgency, dysuria or other lower urinary tract symptoms. There were never any urinary incontinence episodes during daytime, and Timmy's bowel openings are normal with no constipation or encopresis. Aside from his night-time urinary incontinence Timmy has no other physical complains.

There were no recent stressors identifiable and Timmy enjoys good relations with his parents and 2 elder siblings. He enjoys school-life and feels no significant stress from his recent examinations. He does not feel any embarrassment from his bedwetting and does not view his bedwetting as a problem, although his parents are obviously concerned. Timmy's physical examination, including a detailed abdominal, genital, and neurological examination, were unremarkable.

On further enquiry, Timmy's father remembered having a similar problem of bedwetting when he was young, which resolved without any treatment in his early childhood. There was no other significant family history identifiable.

15.2 Epidemiology

Enuresis refers to episodes of urinary incontinence during sleep in children aged 5 years or above. A variation of terminologies had been used to describe children with bed-wetting in the past. In 2006, the International Children's Continence Society has developed standardized terminology for lower urinary tract function and malfunction in children [1], with the updated version published in 2016 [2]. To understand the epidemiology of the condition we would first have to understand the terminologies used (Table 15.1).

Enuresis can be classified into monosymptomatic and non-monosymptomatic. For monosymptomatic enuresis, children do not have any other lower urinary tract symptoms. This can be further sub-classified into primary or secondary.

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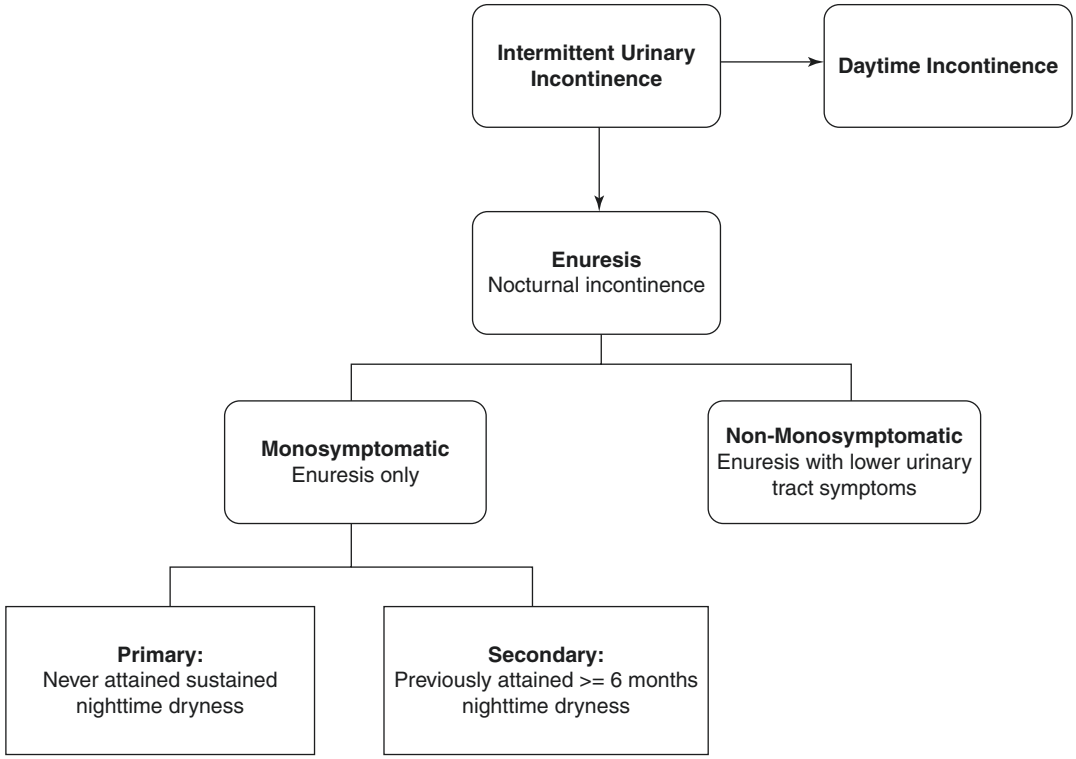
A. M. Li, K. C. Chan (eds.), *Paediatric Sleep Disorders*,
https://doi.org/10.1007/978-981-19-5791-8_15

Table 15.1 International Children's Continence Society Classification of enuresis



Primary monosymptomatic enuresis is defined as enuresis in children who have never achieved a satisfactory period of nighttime dryness. This form of enuresis is the most common and around 80% of children with enuresis can be classified as primary.

Secondary monosymptomatic enuresis is used to describe children who had previously attained a period of dryness for at least 6 months but now presents with night-time incontinence without other lower urinary tract symptoms. Secondary monosymptomatic enuresis is often related to stressful life events, such as the death of a family member or the birth of a sibling, but the exact etiology remains unknown.

Non-monosymptomatic enuresis is defined as children who have enuresis and other lower urinary tract symptoms. These symptoms include: increased (≥8 times/day) or decreased (≤3 times/day) urinary frequency, urinary urgency, and hesitancy, the need for straining for urination, weak/intermittent or spraying urinary stream, pain in the lower urinary tract.

For children with daytime incontinence and nocturnal enuresis, they should be classified as having both conditions of daytime incontinence and enuresis. For children with daytime symptoms of urinary urgency, frequency or incontinence, they can be further defined as having bladder dysfunction. Approximately 20% of all children with enuresis can be classified as suffering from bladder dysfunction. In these children, neurological disorders such as spinal dysraphism and urological causes including urinary tract infection and bladder muscle instability need to be excluded.

Finally, for children with daytime symptoms who also have bowel symptoms of constipation or encopresis they are classified as having bowel and bladder dysfunction. Approximately 15% of children with enuresis have bowel and bladder dysfunction.

As most children with enuresis is classified as primary monosymptomatic enuresis (PME) our discussion will focus on this entity alone.

PME affects around 15% of children aged 5 years of age [3]. It has a genetic predisposition and its prevalence is therefore different amongst regions. In western countries, PME is a common problem as identified by epidemiological studies [4–6]. In the United Kingdom it is found to be affecting 15–20% of 5-year-old children and 1–2% of 15-year-old adolescents [7]. In Asia the incidence reported is variable with a male predominance. An epidemiological study performed in mainland China identified the overall incidence to be 11% amongst all 5 year olds [8], whilst another large epidemiological study performed in Hong Kong showed the incidence of PME to be 16.1% amongst 5 year old children with a male predominance (20.7% boys, 10.8% girls) [9]. In India, the overall incidence for children 6–10 year old. was 7.6% with male predominance [10]. Without treatment, most children with PME experience spontaneous symptom resolution at a rate of approximately 15% per year, and 99% of children with PME are dry by the age of 15 years old [3].

Although PME may not be considered a particularly worrisome medical condition by most physicians, data suggest that children who have prolonged enuresis have lower self-esteem [11]. Families often find the condition troublesome and causing a significant impact on the sleep quality of children and their parents. The social consequences of nocturnal enuresis remain a significant reason for children and families to seek medical attention.

15.3 Aetiology

PME is considered a functional type of incontinence rather than secondary to urological, anatomical or psychiatric causes. The pathophysiology of the condition is not well understood but different theories have been postulated. One prominent theory is an abnormal circadian release of antidiuretic hormone (ADH). In normal children, nocturnal urine production is approximately half of the daytime urine production, whilst for children with PME it has been shown that they have decreased nocturnal ADH production [12]. Aside from hormonal differences, anatomical differences with diminished bladder capacities and abnormal urodynamic functions with higher rate of nocturnal bladder instability have also been identified in children with PME [13].

There is definite genetic predisposition to development of PME. Studies have shown that there is a 44% chance of a child to suffer from PME if one of their parent has this condition as a child [14]. The chance is drastically increased to 77% if both parents have the condition [15]. In addition, twin studies support the genetic basis with a high concordance rate of PME in monozygotic twins [16].

Aside from anatomical, physiological differences and a genetic predisposition, psychological factors can also contribute to development of PME. An example is attention-deficit/hyperactivity disorder (ADHD); children with this disorder have a 30% greater chance of PME. Children with PME were also found to have a higher prevalence of motor and speech delay and perceptual dysfunction compared to those without [17]. This supports the another widely accepted hypothesis of neuro-maturational delay as the cause of PME.

In the end, PME is likely the result of an admixture of the aforementioned contributing factors.

Secondary enuresis, on the other-hand, is often related to the occurrence of psychologically stressful life events, such as the birth of a sibling or the death of a close-relative. There are often no organic causes identified to cause secondary enuresis in children.

15.4 Presentation and Diagnosis

15.4.1 History

The key to diagnosis and classification of enuresis is through obtaining a reliable history. History of daytime events and lower urinary tract symptoms can differentiate between monosymptomatic and non-monosymptomatic enuresis. Non-monosymptomatic enuresis requires more

extensive investigations to exclude pathological causes.

For monosymptomatic patients, enquire on whether there had been a history of achieving dryness of at least 6 months in the past to differentiate between primary and secondary enuresis. For children with secondary enuresis, physicians need to further enquire on any recent stressful life events.

For children classified as having PME, a detailed history of the child's urinary, bowel, dietary and sleep habits is crucial to identify any possible lifestyle modifications necessary to help improve the situation. For urinary habits, enquire on the usual voiding pattern and the voiding hygiene of the child, including any straining necessary and any incomplete voiding to suggest non-monosymptomatic enuresis. The stooling habit is also important as enuresis and stooling dysfunction are closely related.

Enquire on the child's eating and drinking habits with details to the content, amount and timing of the fluid intake to identify any potential cause of excessive fluid load for enuresis. Fluid intake shortly before sleep can lead to bladder over-capacity.

A detailed enquiry on sleep habits of the child is necessary. Sleep-disordered breathing such as obstructive sleep apnea can result in impaired arousal causing enuresis. In addition, the child's sleep quality maybe markedly interrupted affecting their daytime social performance, especially when children experience more than one bedwetting episodes per night. On the other hand, children who are deep sleepers are often unaware of their events until the next morning. These children may be more resistant to behavioral modifications therapies which rely on their wakening, such as enuresis alarms.

Finally, the physician needs to review the disorder's emotional impact on the child. PME can be distressing for children and their families. Children are reported with a lower self-esteem. Parents may find the condition challenging to handle especially when there are no obvious improvements with treatment, and there have been reports of a higher chance of physical abuse occurring amongst families with children suffering from PME [11]. Psychological screening and specialist referrals may be necessary.

15.4.2 Physical Examination

Physical examination for children with PME are often normal. However, physicians should still conduct a focused and detailed examination to identify any potential underlying medical conditions resulting in enuresis. Document the growth of the child as obesity is associated with higher incidence of PME and measure blood pressure at rest to identify any features of failure to thrive and hypertension related to chronic renal disease. Perform detailed abdominal examination for any ballotable kidneys, distended urinary bladder and external genitalia abnormalities to indicate an underlying urological abnormality. Hard palpable stool will indicate constipation. Physicians should also perform a detailed lower limb neurological examination and look for abnormalities of the lumbosacral spine to suggest spinal dysraphism/abnormality.

15.4.3 Investigations

In a child with features of non-monosymptomatic nocturnal enuresis, or when the physician is in doubt, investigations should be performed to exclude underlying organic causes. Simple urinalysis can screen for medical conditions of urinary tract infection, diabetes mellitus and diabetes insipidus.

If urinary obstruction is suspected based on history and physical examination, a post-void residual urinary bladder volume measurement and urinary system ultrasound should be obtained. If there is suspicion of spinal anomaly, magnetic resonance imaging of the lumbosacral

spine should be arranged, in addition to urodynamic study to delineate associated neurogenic bladder. In children with recurrent urinary tract infections in addition to enuresis, voiding cystourethrogram and renal isotope testing maybe necessary.

15.5 Management

Treatment of non-monosymptomatic and secondary monosymptomatic nocturnal enuresis is out of the scope of our discussion. We shall focus of management of PME.

Prior to treatment initiation, the necessity and timing for treatment should be discussed as these are dependent on the view of the family and child. Parents with personal history of PME may find it unnecessary to initiate treatment for their child with infrequent episodes. On the-other hand, a 5-year-old-child whose younger sibling had already achieved dryness may find episodes embarrassing with a negative effect on their self-esteem even if they are infrequent. The child's maturity needs also to be taken into consideration, as first-line treatment with behavioral therapy requires the child to be willing to partake responsibility and be highly motivated for change.

Most children with PME will have spontaneous resolution with time. The prevalence decreases from 15% at 5 years to 5% at 10 years, and to 1–2% in ≥15 years. The key is to educate and reassure children and their families of the condition's natural progression. Another key is to set achievable goals. ICCS guidelines categorize response to treatment into initial and long-term response and can act as a reference (Table 15.2). In general, the goals of treatment include: reducing total number of enuretic nights, avoiding enuresis on specific nights, avoidance of event recurrence, and stress reduction for the child and family. Setting goals of treatment should be a joint process and therapeutic goals should match the expectation of the family and child. Some children may not be affected at all by enuretic episodes and hence have little motivation for change. Others may only wish to achieve dryness on special occasions such as during camps with peers to avoid embarrassment.

Table 15.2 Conditions causing enuresis

Conditions	Mechanism
Constipation	Reduced bladder capacity
Urinary tract infection	Reduced bladder capacity Bladder hyperactivity
Diabetes mellitus/ insipidus	Increased urine production
Spinal dysraphism	Neurogenic bladder
Urethral obstruction	Reduced bladder capacity
Stressful life events	Psychological stress

Table 15.3 International Children's Continence Society definition of initial and long term successful response to treatment of enuresis

Initial success	
No response	<50% reduction
Partial response	50–99% reduction
Complete response	100% reduction
Long term success	
Relapse	More than one symptom recurrence per month
Continued success	No relapse in 6 months after interruption of treatment
Complete success	No relapse in 2 years after interruption of treatment

In addition, families should be given the appropriate expectations of treatment. It takes weeks to months before treatment effect is obvious even with medication, and relapse after treatment cessation is common. For some children, a combination of treatment modalities maybe necessary before any significant improvements can be observed (Table 15.3).

15.5.1 Education and General Advice

Education is aimed at normalizing children with PME. The high prevalence of PME and its natural progression and resolution should be emphasized. Neither children nor their families are at

fault, and children should definitely not be punished for bedwetting episodes. This key message should be stressed by the clinician as surveys have identified a high prevalence of punishment, sometimes physical, in children who experience bedwetting [18].

The family is advised to keep track of dry and wet nights with use of a calendar to determine treatment effectiveness. During the day, children are encouraged to regularly and completely empty their bladder around 4–7 times per day, including voiding before sleep. Once asleep, the child should not be awoken intentionally for voiding. Although this method does improve the problem of bed-wetting, it does not condition the child to waking up to the urge sensation of a full bladder.

As simply restricting the total daily fluids may not be effective, families can be advised to set limit to fluid intake after evening to around 20% of the child's total daily intake. Children should especially avoid drinking within 2 h from bedtime. Caffeinated drinks and drinks with high-sugar content should also be avoided. The exact effectiveness of these modifications to fluid intake remains debatable [19, 20] and may not be helpful for all children, they should be discontinued if deemed ineffective after an initial trial.

Identifying, treating and avoiding constipation is also important as it will propagate and worsen enuresis. In the setting of reduced fluid intake, maintaining a high-fiber diet is essential.

15.5.2 Motivational Therapy

Motivational therapies are effective especially for children aged 5–7 years with infrequent bedwetting episodes. They are behavioral interventions based on reward systems such as star charts, and their effectiveness in promoting dryness have been proven in achieving fewer bedwetting episodes per week and greater chance of attaining 14 consecutive dry nights [21]. The rewards can be gradually incremented to maintain adherence and to maintain longer periods of dryness.

In case the enuresis is persistent despite the above measures, active management with either behavioral or pharmacological measures can be considered.

15.5.3 Behavioral

15.5.3.1 Alarm Treatment

Alarm therapy is based on conditioning and teaches children to wake for urination. It is especially effective for children who do not have nocturnal polyuria and in children with adequate family support. Different types of alarms exist but all work on the basis of waking the child when the alarms come into contact with urine, with different intensities of stimulation such as oscillation or sound. There is no evidence favoring one alarm over another, but they should not be used for children who could not be awoken by sound or vibration. All enuresis alarms consist of a sensor and an arousal device, and their use require the child to have comprehension of how to activate, deactivate and reset the alarm.

Enuresis alarms must be used every night. The child is instructed to place the sensor in a dry bed pad or in the undergarments each night before sleep. If the alarm goes off, the child should turn off the alarm, get up from bed and finish voiding in the toilet. They should then replace the sensor in a dry bed pad or undergarment and reset the alarm. Although this process is not complex to adults, some children may find this responsibility challenging to carry out. The child's maturity and comprehension of how to setup the alarm is therefore crucial to treatment success.

Enuresis alarms require motivation and commitment of the child and family as treatment success is not immediately obvious. Their use should be reviewed only after continual use for 12–16 weeks. Effectiveness can be in form of fewer episodes each night, smaller wet patches, and more nights with dryness. If deemed effective, alarms should be used continually for at least achieving 2 weeks of dry nights before discontinuing. Successful treatment with alarm therapy has been reported to be up to 75% [22]. If enuresis recurs after treatment cessation ($\geq$2 wet nights per month), alarm therapy can be reiniti-

ated and usually can result in rapid response. Alternative treatments may be necessary if continual use for more than 12 weeks have shown no response.

15.5.4 Pharmacological

15.5.4.1 Desmopressin

Desmopressin is a synthetic analogue of arginine vasopressin. Based on the observation of abnormal circadian rhythm of vasopressin release in children with PME, especially those with nocturnal polyuria, restoring the hormonal balance can aid in reduction of urine production and promote dry-nights. Desmopressin is available as tablet form or a nasal spray with an effect lasting for up to 12 h. The oral tablet form is recommended as nasal spray is associated with hyponatraemic seizures. Oral medication should be administered 1 h before sleep with dose titrated to best effect. Important side effects to mention include dilutional hyponatraemia, water intoxication, headache, anorexia and visual problems. The effectiveness of desmopressin for treatment of PNE is reported up to 60–70%, although some have shown a relapse rate as high as 50–90% especially with sudden discontinuation [23–25]. Fluid intake should be restricted from 1 h before to 8 h after administration to prevent dilutional hyponatraemia. Routine measurements of plasma sodium or urine osmolarity are unnecessary.

Treatment response is expected within 1–2 weeks. If deemed responsive with fewer bedwetting episodes each night, smaller wet patches and more dry nights, desmopressin should be continued for at least 3 months before discontinuation. Discontinuation should be via gradual tapering rather than abrupt complete cessation to avoid recurrence.

15.5.4.2 Tricyclic Antidepressants

Tricyclic medications inhibit the reuptake of serotonin and noradrenaline from synaptic alpha receptors of the central nervous system. The most commonly used tricyclic antidepressant for control of enuresis is Imipramine. Its specific action in inhibiting enuresis remains unknown but may act through inhibiting the detrusor muscle with its antispasmodic and anticholinergic effect. There have also been reports of an increase in ADH level with Imipramine use thus reducing urine production. Imipramine is administered orally 1 hour before bedtime. The starting dose is 10–25 mg with average effective dose of 25 mg. The maximum dose is 50 mg for children aged 6–12 years old and 75 mg for children ≥12 years old. Its effectiveness is expected after 1 month of treatment. If deemed successful, the dose should be tapered to lowest effective dose.

A wide variation in medication effectiveness has been reported, ranging from 64–80%. However, recurrence of symptoms with discontinuation is common and only 25% of patients remain dry in the long term. Side effects are uncommon but can be serious. Approximately 5% of children develop neurological symptoms including sleep disturbance and nervousness. Serious side effects can result from Imipramine overdose and fatalities from arrhythmias and cardio-toxicities resulting in myocardial depression have been reported. Families should be notified of these significant risks.

15.5.4.3 Anti-Cholinergics

Anticholinergic agents such as Oxybutinin have long been used in the treatment of nocturnal enuresis. They work by relaxation of the urinary bladder's smooth muscle and by increasing bladder capacity. They may not be effective in treating children with PME [26, 27] but may help children with bladder dysfunction who have reduced functional bladder capacity and detrusor instability with symptoms of urgency, frequency or with daytime wetting. They may also improve treatment effectiveness when used in combination with desmopressin. Common side effects include dryness of mouth, headache and blurred vision. Constipation can potentially result and can further precipitate enuresis, families should be advised for adequate fiber intake as preventive measure (Table 15.4).

Table 15.4 Medications for Primary Monosymptomatic Enuresis

Medication	Classification	Starting dose	Maximum dose	Side effects
Desmopressin	Synthetic vasopressin analogue	Tablet: 0.2 mg 1 h before bedtime Gradual titration by 0.2 mg/day every 3 days as needed Sublingual (DDAVP Melt): 120 μg 1 h before bedtime Gradual titration by 120 μg/day every 3 days as needed to a maximum dose of 360 μg/day	Tablet: 0.6 mg/day Sublingual: 360 μg/day	Hyponatraemia, headache, anorexia, visual problems
Imipramine	Tricyclic antidepressant	Oral: 10–25 mg 1 h before bedtime. Gradual titration after 1 week by 25 mg/day to maximum daily dose	6–12 years old: 2.5 mg/kg/day or 50 mg/day (whichever is lesser) ≥12 years old: 75 mg/day	Cardiac: Palpitations, arrhythmia, myocardial depression, cardiac failure, hypertension, myocardial infarction Neurological: Agitation, anxiety, ataxia, confusion, delusions, disorientation, dizziness, hallucination, headache, insomnia, nightmares, restlessness, seizure Haematological:Agranulocytosis, thrombocytopenia Others: Nausea, vomiting Increase risk of suicidal thinking and behavior in children, adolescents and young adults with psychiatric disorders (US Boxed Warning)
Oxybutynin	Anticholinergic	Oral: Immediate release:5 mg twice daily Oral: Extended release: 5 mg once daily Increase dose weekly by 5 mg	Immediate release: 5 mg 4 times daily Extended release: 20 mg/day	Palpitations, tachycardia, Dry mouth, constipation Blurred vision Drowsiness, Dizziness Agitation, Confusion Hallucintations

15.5.5 Choice of Active Treatment

If the trial of general measures and motivational therapy have not resulted in significant improvement, active treatment can be initiated. In general, first-line treatment of PME can either be with an enuresis alarm or with desmopressin.

The choice of therapy would be dependent on the preference of the family and the goals they wish to achieve.

In the setting of a need for short term treatment effectiveness (for overnight camps to prevent embarrassment), when the family requires a more rapid treatment (when the family is expressing great difficulty in coping with the burden of bedwetting), or when the child has nocturnal polyuria (nocturnal urine production more than 130% of expected bladder capacity for age), Desmopressin is more suitable. It is more rapidly effective than enuresis alarms and requires less parental involvement and self-motivation. The child and family should however be aware that Desmopressin has a higher relapse when compared to enuresis alarms when treatment is stopped.

In families where short-term improvement is not a priority, enuresis alarm is the better option. Although its effectiveness is not as apparent initially, it has a more sustained effect with less chance of recurrence compared to Desmopressin. Prior to initiation, the child should be assessed to determine their motivation for change. They should also be ensured to have an adequate understanding of how the alarm works, properly taught the alarm setup and the routine in case of alarm going off in order to ensure effect and adherence.

15.5.6 Refractory Enuresis

Refractory enuresis is defined as less than 50% improvement in baseline frequency of enuresis.

Adequate trial of treatment is defined as a period of at least 3 months of enuresis alarm with good utilization methods and compliance, or an adequate dose Desmopressin at of 0.4 mg regular tablets or 0.24 mg of oral melt tablets.

Physicians should exclude possible reasons leading to a lack of treatment response. History and physical examination should be reviewed to exclude potential underlying medical conditions as trivial as constipation which may result in treatment failure. When in doubt, appropriate investigations such as ultrasonography or urodynamic studies need to be utilized. The child and family needs to describe and demonstrate the correct use of medications or enuresis alarm to identify any inconsistency and misunderstandings. In addition, physicians should pay attention to the social dynamics of the family and the emotional impact the condition has caused the child to review and identify possible psychological contributions to treatment failure.

After comprehensive exclusion of secondary causes, management of refractory monosymptomatic nocturnal enuresis may include switching over from one therapy to another, or additional therapy with combination of alarm treatment and desmopressin.

A trial of tricyclic antidepressant with Imipramine can also be initiated. This option should however be considered only after failure of first-line and combinational therapies given the potentially serious side effect of cardiotoxicity, physicians and parents need to weight the risks and benefits of treatment. Parents should be advised to safely store this medication in order to prevent accidental ingestion and overdose, especially when there are younger siblings in the family. Clinical response of Imipramine should be assessed after 3 months of continual use and should be discontinued if deemed unhelpful. If treatment is effective, the dose should be titrated down to the lowest effect dose. Imipramine should be regularly discontinued every 3 months for at least 2 weeks to reduce risk of medication tolerance.

Anti-cholinergics may not be particularly beneficial for patients with PME. They are, however, proven effective in controlling enuresis in children with urinary urgency and detrusor instability. Conjunctional use of an anti-cholinergic with Desmopressin can be tried in these children with small randomized controlled studies supporting this combinational treatment [28].

15.6 Summary of Key Take-Home Messages and Research Gaps

Nocturnal enuresis is a common sleep related disorder. In dealing with children with enuresis, one should first classify the specific subtype based on presence and absence of lower urinary tract symptoms and whether the child had previously attained night-time urinary continence for at least 6 months.

Although the exact pathophysiology for primary monosymptomatic enuresis remains unknown, it is likely a result of an admixture of underlying hormonal and anatomical factors, genetic predisposition and neuro-psychological maturity.

Most children with enuresis can be classified as PME with expected spontaneous resolution over time. Although considered benign, PME can bring about significant psychological burden on children and their families; active treatment may

be necessary to aid the child's self-esteem and to ease the family's stress.

If PME persists despite general measures of nocturnal fluid restriction, maintaining a good urinary and bowel habit and motivational therapies, active treatment can be initiated after identifying attainable goals of therapy with families. First line active treatment can be either with enuresis alarms or with desmopressin.

An adequate amount of time would need to be given to observe treatment effect. If deemed refractory, combinational therapy can be considered. Tricyclic antidepressants with Imipramine use is one of the treatment options but its use should be carefully discussed with patient and family due to potentially serious side effects.

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