NOCTURNAL ENURESIS

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- November 2023

To the CHI Original Nocturnal Enuresis Clinical Guidance- Issued June 2020

Contents

Related Documents

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Abbreviations

ADHD	Attention-Deficit / Hyperactivity Disorder
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CPG	Clinical Practice Guideline
DDVAP	Desmopressin (1-deamino-8-d-arginine vasopressin)
EAU	European Association of Urology
EMA	European Medicines Agency
FDA	Food and Drug Administration
HAS	Haute Autorite de Sante
HTA	Health Technology Assessment
ICCS	International Children's Continence Society
IDF	Insurance Drug Formulary
IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
	Institute for Quality and Efficiency in Health Care
LUT	Lower Urinary Tract
MNE	Monosymptomatic nocturnal enuresis
MSE	Monosymptomatic enuresis
NE	Nocturnal Enuresis
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMNE	Nonmonosymptomatic Nocturnal Enuresis
NMSE	Nonmonosymptomatic Enuresis
OAB	Overactive Bladder
PBAC	Pharmaceutical Benefits Advisory Committee
RCT	Randomized Controlled Trial
SFDA	Saudi Food and Drug Authority

Executive Summary

Bedwetting, scientifically referred to as nocturnal enuresis (NE), is the inadvertent release of urine during sleep. This is a prevalent issue that can affect individuals across various age groups, including children, adolescents, and adults. It becomes a matter of concern when it occurs in individuals older than seven years and when these incidents happen at least twice a week for a consecutive period of three months or more. While NE may have numerous underlying causes, it is generally considered a treatable condition[1].

There are two primary categories of bedwetting[1]:

- **Primary NE**: occurs when an individual has never experienced a dry night for a continuous period of six months or longer.
- **Secondary NE**: occurs when an individual resumes bedwetting after a dry spell of six months or more. Secondary enuresis is often linked to underlying medical or psychological factors.

NE in children has been studied extensively and many of the pathophysiological mechanisms are known, while in nocturia, many mysteries remain. These conditions seem to differ fundamentally; however, similarities can be found in several aspects. Findings in NE in children can therefore be used to elucidate the missing links in knowledge about nocturia in adults[2].

NE is characterized by involuntary nighttime urinary incontinence during sleep, whereas nocturia is defined as the need to wake up one or more times during the night to urinate, with each episode occurring before and after periods of sleep. NE is widely recognized as a genetic disorder, with approximately two-thirds of enuresis patients having an affected first-degree relative[2].

NE and nocturia have the following common characteristics: a genetic factor is suspected, reduced bladder capacity and NP are the main underlying bladder/LUT related conditions, there is a clear link with sleep disorders, physical and mental health are compromised in both conditions, and treatment is often inadequate. The main difference between NE and nocturia seems to be the difference in arousal to bladder stimuli, suggesting that sleep characteristics and the bladder– brain dialogue during sleep are key factors in these conditions. Further research to clarify the remaining gaps is necessary[2].

Waking up with wet pajamas or sheets from pee is the main symptom of bedwetting[1].

The causes of bedwetting can differ depending on age, and there are multiple potential reasons why individuals experience nocturnal enuresis.

In childhood, the primary cause often lies in a lack of bladder control. Typically, children begin mastering bladder control between the ages of 2 and 4. It is common for children to experience bedwetting episodes between the ages of 4 and 6 as they grow and adapt to their bodily changes at their own pace. Most children gain control of their bladders by the age of 7. However, accidents can continue to occur after this age and persist into the teenage years. Additionally, recurrent bedwetting can sometimes signal an underlying medical issue, such as a urinary tract infection, constipation, spina bifida, nerve problems, diabetes, urinary tract blockage, narrow urethra, obstructive sleep apnea, or ADHD[1].

Bed-wetting can affect anyone, but it's twice as common in boys as in girls. Several factors have been linked with an increased risk of childhood bed-wetting, including:

- **Stress and anxiety**: stressful events may trigger bed-wetting. Examples include having a new baby in the family, starting a new school, or sleeping away from home.
- **Family history**: if one or both of a child's parents wet the bed as children, their child has an increased chance of wetting the bed, too. Attention-deficit/hyperactivity disorder (ADHD). Bed-wetting is more common in children who have ADHD[3].

People over the age of 18 can have nocturnal enuresis. Potential causes for adult bedwetting could include[1]:

- Genetics, constipation, hormones, small functional bladder capacity, failure to awaken during the night, psychological or emotional problems: emotional stress caused by traumatic events or disruptions in your normal routine and medical conditions: neurological changes and kidney or bladder abnormalities, sickle cell disease[1].

A healthcare provider diagnoses nocturnal enuresis after a physical exam and taking a complete medical history. Tests, such as a urine test, a blood test, or an imaging test, should be conducted to determine if an underlying medical condition caused bedwetting[1].

The treatment for NE varies depending on the underlying cause and may encompass several approaches[1]:

- Implementing behavioral modifications before or during bedtime, which could involve using an alarm system.
- Addressing or managing any concurrent medical conditions.
- Administering medications that can reduce nighttime urine production.
- Seeking guidance from a mental health professional, psychologist, or therapist to address and manage stress, trauma, or emotional challenges.

Although frustrating, bedwetting without a physical cause does not result in any health risks. Bedwetting can create some issues for the child, including guilt and embarrassment, which can lead to low self-esteem. Loss of opportunities for social activities, such as sleepovers and camp. Rashes on the child's bottom and genital area especially if the child sleeps in wet underwear[3].

NE has a global prevalence ranging from 1.4% to 28% among children aged 6 to 12 years old. In a cross-sectional descriptive study conducted on Saudi children aged 3 to 12 years, hailing from various cities in Saudi Arabia, spanning from October 20th to November 20th, 2019, it was found that 31.2% of these children were identified as experiencing NE. Among those affected, 43.9% exclusively had NE without any other underlying conditions. Notably, there was no statistically significant association between gender and NE, but a significant correlation was observed with the child's age and the presence of a family history of NE. The predominant mode of treatment provided was behavioral modification therapy, followed by pharmacological intervention. It's worth noting that less than half of the cases undergoing treatment exhibited improvement in their condition[4].

CHI issued Nocturnal Enuresis guidelines in June 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations. Below is a description of sections that need updates.

CHI issued Nocturnal Enuresis clinical guidance after thorough review of renowned international and national clinical guidelines in June 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Nocturnal Enuresis clinical guidance and seeks to offer guidance for the effective management of Nocturnal Enuresis. It provides an **update on the Nocturnal Enuresis Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the issuance of updated versions of previously reviewed guidelines** namely Pediatric Urology EAU guidelines 2023.

Moreover, **new guidelines are added to the report**: management and treatment of nocturnal enuresis: an updated standardization document from the International Children's Continence Society (2020); the Japan Pediatric Society management of treatment-resistant nocturnal enuresis (2023); the Enuresis Guideline by Ashford and St. Peter's Hospitals NHS Foundation Trust (2022); and the Canadian Pediatric Society position statement on the evaluation and management of enuresis in the general pediatric setting (2023).

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is advisable to include the SFDA registered drug **Solifenacin, Mirabegron** in the CHI formulary and all the drugs are still registered on the SFDA Drug List of June 2023 so none of them will be removed. In terms of drug information and prescribing edits since June 2020, prescribing edit for Desmopressin changed from PA to ST

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the Nocturnal Enuresis therapeutic management.

Below is a table summarizing the major changes based on the different Nocturnal Enuresis guidelines used to issue this report:

Table 1. General Recommendations for the Management of Nocturnal Enuresis

Management of Nocturnal Enuresis		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Offer desmopressin in proven night-time polyuria.	1, Strong	Pediatric Urology EAU guidelines, 2023
To address excessive nighttime urine production and potential nighttime overactive bladder (OAB), fluid intake should be adjusted and desmopressin alone or in combination with an anticholinergic medication should be considered. Desmopressin, in the form of tablets (200-400 µg) or sublingual desmopressin oral lyophilizate (120-240 µg), can achieve success rates of around 70%. The dosage of 120 µg has been proven effective and safe, although a structured titration may be increased up to 240 µg, as it has also been shown to be effective.	Not graded	Pediatric Urology EAU guidelines, 2023
The prescriber may either start with the full dose and titrate down after a week or so in case of good treatment effect, or use the opposite strategy.	Not graded	ICCS, 2020

Guidelines for continuous use of desmopressin suggest treatment for 3 months at a time, then reassessment with a medication break to determine resolution of enuresis symptoms. Recent strategies involving a structured withdrawal show promise in improving permanent cure rates, with a recommended half-dose given for 2 weeks before discontinuation. If enuresis returns, the effective dose can be used again for 3 months, when reducing titration can be repeated.	Not graded	Canadian Pediatric Society, 2023
The night-time urine production should be registered by weighing the night-time diapers in the morning and adding the first morning voided volume. The night-time urine production should be recorded over (at least) a two-week period to diagnose an eventual differentiation between a high night-time production (more than 130% of the age expected bladder capacity) vs. a night-time OAB.	Not graded	Pediatric Urology EAU guidelines, 2023
Offer alarm treatment in motivated and compliant families.	1, Strong	Pediatric Urology EAU guidelines, 2023
Offer supportive measures in conjunction with other treatment modalities, of which pharmacological and alarm treatment are the two most important	1, Strong	Pediatric Urology EAU guidelines, 2023
Many of the therapy-resistant children will need to be treated for constipation ex *juvantibus* according to the ICCS guidelines and some will need the assistance of a child psychologist or psychiatrist	Evidence level IV	ICCS, 2020
There is also a subgroup that may need surgical treatment for sleep-disordered breathing.	Evidence level III	ICCS, 2020

Anticholinergic Treatment: Provided that there is no residual urine, and that constipation is excluded or successfully treated anticholinergics can be considered as second-line antienuretic therapy, often in combination with desmopressin	Evidence level Ib	ICCS, 2020
Antidepressant Treatment: The tricyclic antidepressant imipramine is an evidence based antienuretic therapy (evidence level Ia) that can be used by specialists as a third-line alternative if desmopressin, the alarm, and anticholinergics have all been unsuccessfully tried and/or are contraindicated.	Evidence level Ia	ICCS, 2020
Nocturnal polyuria that is unresponsive to desmopressin may respond to salt reduction or combined diuretics in the morning and desmopressin in the evening.	Evidence level III	ICCS, 2020
Other treatment options can include tricyclic antidepressants. Tricyclic antidepressants have been used in the treatment of nocturnal enuresis for over 60 years; however, they are now the third choice of pharmacological treatment both domestically and internationally, after DDAVP and anticholinergics, due to their cardiotoxic effects in overdose	Not Graded	Japan Pediatric Society, 2023

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Nocturnal Enuresis clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Nocturnal Enuresis report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the June 2020 CHI Nocturnal Enuresis Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
Section 1.1 Pediatric Urology EAU Guidelines 2018	**Section 1.1.1** Pediatric Urology EAU Guidelines **2023**
Section 1.2 Enuresis in Children: A Case-Based Approach, American Academy of Family Physicians 2014	N/A*

: *No updated versions available

1.1.1 European Association of Urology (EAU) Guidelines on Pediatric Urology (2023)

*Please refer to **Section 1.1** of CHI Nocturnal Enuresis original clinical guidance.*

The 2023 revised edition of European Association of Urology's Guidelines for the treatment of **urological conditions in children** introduced a set of recommendations accompanied by a grading scheme, outlined as follows[5]:

Table 3. EAU Strengths of Recommendations and Levels of Evidence

Grading Scheme for Recommendations	
Strength of recommendation	***Definition***
Strong	Most informed patients would choose the recommended management and that clinicians can structure their interactions with patients accordingly.
Weak	Patients' choices will vary according to their values and preferences, and clinicians must ensure that patients' care is in keeping with their values and preferences
Levels of Evidence	***Definition***
Step 1 (Level 1*)	- Local and current random sample surveys (or censuses) - Systematic review of cross-sectional studies with consistently applied reference standard and blinding. - Systematic review of inception cohort studies - Systematic review of randomized trials or n-of-1 trials - Systematic review of randomized trials, systematic review of nested case-control studies, nof-1 trial with the patient you are raising the question about, or observational study with dramatic effect - Systematic review of randomized trials or n-of-1 trial. - Systematic review of randomized trials
Step 2 (Level 2*)	- Systematic review of surveys that allow matching to local circumstances** - Systematic review of surveys that allow matching to local circumstances** - Inception cohort studies - Randomized trial or observational study with dramatic effect - Individual randomized trial or (exceptionally) observational study with dramatic effect - Individual randomized trial or (exceptionally) observational study with dramatic effect - Randomized trial
Step 3 (Level 3*)	- Local non-random sample** - Non-consecutive studies, or studies without consistently applied reference standards**

	- Cohort study or control arm of randomized trial* - Non-randomized controlled cohort/follow-up study** - Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)** - Non -randomized controlled cohort/follow-up study**
Step 4 (Level 4*)	- Case-series** - Case-control studies, or "poor or non-independent reference standard** - Case-series or case control studies, or poor-quality prognostic cohort study** - Case-series or case control studies, or poor-quality prognostic cohort study** - Case-series, case-control, or historically controlled studies** - Case-series, case-control, or historically controlled studies**
Step 5 (Level 5)	- Mechanism-based reasoning
* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size. ** As always, a systematic review is generally better than an individual study	

The recommendations listed below are assigned the grades defined in the preceding table:

- Do not treat children less than five years of age in whom spontaneous cure is likely, but inform the family about the involuntary nature, the high incidence of spontaneous resolution and the fact that punishment will not help to improve the condition. (2, Strong)
- Use micturition diaries or questionnaires to exclude day-time symptoms. (2 Strong)
- Perform a urine test to exclude the presence of infection or potential causes such as diabetes insipidus. (2, Strong)

- Offer supportive measures in conjunction with other treatment modalities, of which pharmacological and alarm treatment are the two most important. (1, Strong
- Offer desmopressin in proven night-time polyuria. (1, Strong)
- Offer alarm treatment in motivated and compliant families. (1, Strong)

Supportive treatment measures

- To ensure a good night's sleep for children dealing with NE, it's advisable to restrict the use of electronic devices before bedtime.
- It is recommended that patients with NE and their families be referred for psychological support and that this referral be followed up, especially when NE is accompanied by developmental, attention, or learning difficulties, family issues, parental distress, or potential punishment of the child.
- Parents of children with NE tend to experience higher levels of stress compared to those with non-NE children, and anger appears to be the most common emotional response to NE children. This phenomenon may help explain why NE children are more frequently exposed to childhood traumas such as neglect and abuse.
- Engaging parents of NE children in psychological interventions has been shown to significantly enhance their ability to cope with the challenges they face.

Wetting alarm treatment

- In the latest Cochrane review, despite the studies' limited quality, multiple research papers indicate that utilizing alarm treatment can lead to a reduction in the frequency of nightly bedwetting incidents. Furthermore, alarm treatment demonstrates a higher rate of complete success and a lower chance of recurrence when compared to the absence of any treatment.
- If a relapse occurs after an initially successful treatment, it is advisable to actively explore the possibility of Overactive Bladder (OAB) as a potential cause. The optimal duration of alarm treatment remains uncertain: the International Children’s Continence Society (ICCS) suggests 8-12 weeks, while durations of up to 16-20 weeks have been reported.

Medical Treatment:

- If the child and their family are interested in addressing excessive nighttime urine production and potential nighttime Overactive Bladder (OAB), they should be willing to adjust their fluid intake and consider either desmopressin alone or a combination of desmopressin and an anticholinergic medication.
- Desmopressin, in the form of tablets (200-400 µg) or sublingual desmopressin oral lyophilizate (120-240 µg), can achieve success rates of around 70%.
- A rare side effect to be aware of is water intoxication, which can be prevented by restricting water intake when advised.
- The dosage of 120 µg has been proven effective and safe, although a structured titration may be increased up to 240 µg, as it has also been shown to be effective.
- The use of intranasal formulations is no longer recommended due to an elevated risk of overdose.

Electrical Neuromodulation:

- Numerous systematic reviews and randomized trials have documented potential advantages of electrical neuromodulation for treating NE. However, it's important to note that the quality of the studies included in these reviews was generally low, and various forms of electrical neuromodulation, such as intra-anal stimulation and interferential current stimulation, were considered.
- One randomized controlled trial (RCT) that compared transcutaneous electrical nerve stimulation to a placebo demonstrated no discernible anti-enuretic effect.

Complementary Treatments:

- A Cochrane review found no evidence of benefit for treatments such as hypnosis, psychotherapy, acupuncture, chiropractic care, or herbal remedies in the management of NE.

Figure 1 details the stepwise assessment and management options for NE.

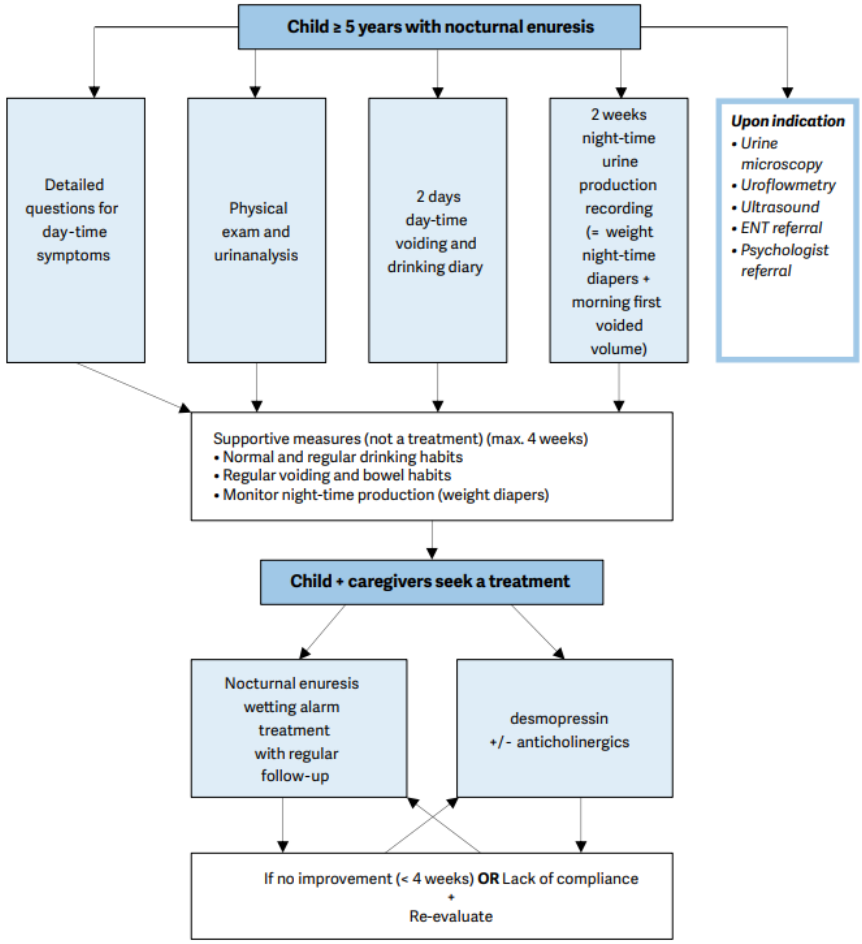

Figure 1. *A Stepwise Assessment and Management Options for Nocturnal Enuresis (Retrieved from the EAU 2023 Guidelines)*

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Nocturnal Enuresis report, along with their recommendations.

Table 4. List of Additional Guidelines

Additional Guidelines
1.2.1 Management and Treatment of Nocturnal Enuresis: An Updated Standardization Document from the **International Children's Continence Society** (**2020**)
1.2.2 **Japan Pediatric Society**: Management of Treatment-Resistant Nocturnal Enuresis (**2023**)
1.2.3 **NHS** Ashford and St. Peter's Hospitals: Enuresis Guideline (**2022**)

1.2.4 **Canadian Pediatric Society**: Position Statement Evaluation and Management of Enuresis in the General Pediatric Setting (2023)

1.2.1 Management and Treatment of Nocturnal Enuresis: An Updated Standardization Document from the International Children's Continence Society (2020)

These guidelines were developed by the International Children's Continence Society (ICCS) and cover both monosymptomatic nocturnal enuresis (MNE) and non-monosymptomatic nocturnal enuresis (NMNE) in one document[6]. The grading scheme of the recommendations is detailed in table 5.

Table 5. ICCS Grading Scheme for Recommendations

Levels of Evidence	Definition
Levels of evidence for studies of intervention	**Ia**: from systematic review and meta-analysis of randomised controlled trials (RCTs) **Ib**: individual RCT(s) (with narrow confidence intervals) **IIa**: systematic review of at least one non-randomised controlled trial or well-designed cohort study **IIb**: individual cohort study or low quality RCTs **IIIa**: systematic review of at least one case-controlled study **IIIb**: individual case-control study **IV**: expert committee reports or opinions and/or clinical experience of authorities, case series (and poor-quality cohort and case-control studies)
Level I: Evidence from a systematic review of all relevant randomized controlled trials.	
Level II: Evidence from a meta-analysis of all relevant randomized controlled trials.	
Level III: Evidence from evidence summaries developed from systematic reviews	
Level IV: Evidence from guidelines developed from systematic reviews	
Level V: Evidence from meta-syntheses of a group of descriptive or qualitative studies	
Level VI: Evidence from evidence summaries of individual studies	
Level VII: Evidence from one properly designed randomized controlled trial	

I. Initial Evaluation

a. Warning signs

The initial evaluation should make the clinician able to react, without delay, to important warning signs (table 6).

Table 6. Warning signs in the Initial Assessment of the Child with Enuresis (Adapted from the ICCS 2020 Guidelines)

Warning Sign	Action
Weight loss, growth retardation and/or nausea	Check creatinine and urine glucose. Physical examination.
Excessive thirst with a need to drink at night	Check urine glucose. Complete a fluid intake list. Consider creatinine and morning urine osmolality. Physical examination.
Voiding difficulties: weak stream, need to strain to void	Check uroflow and residual urine. Physical examination.
Secondary nocturnal enuresis with recent debut	Check urine glucose. Physical examination.
Heavy snoring or sleep apneas	Contact otorhinolaryngologist. Physical examination.

b. History

Medical history is the most important and sometimes the only necessary part of the evaluation of the enuretic child.

The following should be checked: general health, the enuresis, daytime micturition habits, bowel habits, sleep problems, behavioral issues, and previous treatment.

c. Examinations

The physical examination of the enuretic child usually comes out completely normal or gives findings unrelated to the enuresis. Thus, in the absence of warning signs in (table 6), the child could be managed initially without being examined by a physician.

In case of doubt, however, a general physical examination, focusing on general health and signs of occult spinal dysraphism (lower back findings, leg and anal cleft asymmetries, abnormal neurology of the lower limb) is needed.

The voiding chart, as described by the ICCS; In addition to the FVC (Frequency–volume chart which records the time of each micturition and the volume voided for at least 24 h, although 2 or 3 days of recording (not necessarily consecutive) generally provide more useful clinical data), a voiding diary will include fluid intake, pad usage, incontinence episodes and the degree of incontinence. Episodes of urgency and sensation might also be recorded, as might the activities performed during or immediately preceding the involuntary loss of urine. Additional

information obtained from the voiding diary involves severity of incontinence in terms of leakage episodes and pad usage[7].

The voiding chart is recommended in the initial evaluation of all enuretic children, and mandatory if there are any indications from the history that the enuresis is of the no monosymptomatic kind, that is, if there are any daytime LUT (Lower urinary tract) symptoms.

A urine dipstick detecting glucosuria and leukocytes is a necessary part of initial evaluation if enuresis is secondary, if there are any daytime LUT symptoms, or if there are any relevant warning signs.

Blood samples are only indicated if there is glucosuria or general warning signs suggesting polyuric renal failure.

II. Initial treatment

The children need help to become dry before their self-esteem and social interactions become adversely affected. Thus, the "wait and see-attitude" is not adequate in the management of the child who is old enough to be bothered by his/her condition.

a. General advice

Parents who restrict the child's fluid intake in the evenings should be discouraged from this practice unless they see a clear benefit (regarding fluid restriction during desmopressin therapy, see below).

The advice to give extra fluid during daytime to keep the child well hydrated is often given, but the evidence base is scant (evidence level IV).

b. NMNE initial treatment

Nonmonosymptomatic NE (NMNE) is defined as NE with day-time lower urinary tract symptoms, recurrent urinary tract infections (UTIs), and/or bowel dysfunction[8].

The fact that there are concomitant daytime LUT symptoms indicate 1) that uninhibited detrusor contractions are likely to play a role as a pathogenetic factor, which will influence choice of therapy and, 2) comorbidity-somatic or psychiatric-is extra common and may need to be addressed. These children need to complete a voiding chart and the initial evaluation should include a urine dipstick.

Constipation is more common in this group and should be treated on the slightest suspicion (evidence level IV for effect against enuresis).

Although the evidence base is weak, the consensus is that bothersome daytime LUT symptoms should be treated before the nocturnal enuresis is addressed (evidence level IV).

The child with NMNE should be instructed to 1) establish regular voiding habits with micturition approximately 6 times per day, 2) drink adequately especially in the morning and at lunch, and 3) adopt a good voiding posture with the thighs well supported.

c. MNE initial treatment

Monosymptomatic nocturnal enuresis (MNE) is involuntary voiding of urine during sleep, in children over 5 years of age in the absence of congenital or acquired defects of the urological or central nervous system and without day-time voiding symptoms[8].

There are two established first-line therapies in MNE:

- enuresis alarm (evidence level Ia)
- desmopressin (evidence level Ia)

Regardless of the therapy chosen, the role of the parents is crucial.

<u>Alarm therapy</u>

If alarm therapy is chosen it is imperative that the following practicalities are adhered to:

- The alarm should only be used by well-motivated, well-informed families.
- The device should be thoroughly demonstrated for both child and parents.
- The alarm needs to be used continuously, every night without interruption.
- The parents need to be prepared to wake the child immediately when the signal is heard, since very often during the first weeks of treatment the child itself will not wake up by the signal.
- The healthcare provider should contact the family after 1-3 weeks to give encouragement and solve technical problems during this crucial period.
- If there is no sign of progress after 6 weeks therapy should be stopped
- If there is progress (smaller wet spot, occasional dry nights) then therapy should be continued until 14 consecutive dry nights have been achieved.

Desmopressin

- Desmopressin was developed as an analogue to the antidiuretic human hormone vasopressin, or antidiuretic hormone.
- The chance of response is highest in children with MNE who have nocturnal polyuria and normal daytime void volumes.
- The choice of first-line therapy can be made in two ways (A or B), depending on whether to put most emphasis on the prognostic indicators for desmopressin (A) or the alarm (B).
- Strategy A means that the family has completed a voiding chart including measurements of nocturnal urine production. If this shows that the child has nocturnal polyuria and normal daytime voided volumes then desmopressin is tried first, and if nocturnal urine output is normal and MVV are low the alarm is provided. If both nocturnal polyuria and reduced MVV below 65-70% of EBC Is present combination therapy with desmopressin and alarm can be considered.
- Strategy B means that the family chooses which therapy to use first after being informed about the pros and cons of both alternatives. This means that the families most motivated for the alarm will choose the alarm.
- Regardless of which strategy (A or B) is used, if the first choice of therapy (alarm or desmopressin) did not make the child dry then the other alternative should be offered. If both fail as monotherapy a combination of the two can be considered.

III. Management of therapy-resistant children

a. Evaluation

The child with enuresis who has neither responded to desmopressin nor alarm therapy needs to be examined by a physician, usually a pediatrician or a pediatric urologist.

Questions need to be asked regarding Rome IV criteria for constipation; possible behavior issues need to be enquired about and the family will be asked to describe how the unsuccessful therapies were given. Often it will be found that the alarm was incorrectly used.

The child needs to be physically examined, with focus on signs of spinal dysraphism as described above.

Therapy-resistant children should undergo noninvasive urodynamic investigation with flowmetry and residual urine measurement. The reason for this is that the

finding of pathological curves or post-void residual urine on repeated measurements means that:

- anatomic obstruction or neurogenic bladder needs to be excluded and
- anticholinergic treatment is contraindicated.

Many of the therapy-resistant children will need to be treated for constipation ex *juvantibus* (evidence level IV) according to the ICCS guidelines and some will need the assistance of a child psychologist or psychiatrist (evidence level IV).

There is also a subgroup that may need surgical treatment for sleep-disordered breathing (evidence level III).

b. Anticholinergic treatment

Provided that there is no residual urine, and that constipation is excluded or successfully treated, anticholinergics can be considered as second-line antienuretic therapy, often in combination with desmopressin (evidence level Ib).

There are several anticholinergic drugs available, but it needs to be emphasized that only **oxybutynin** is available for label use in children.

The reasons that other alternatives were mentioned in this review are that 1) the side-effect profile is more favorable in the off-label alternatives and 2) other alternatives can be expected to become available for label prescription in the near future.

Medication is taken in the evening **1 hour before bedtime** and should be started with a dose in the lower interval mentioned in below table:

Table 7. Proposed Dosage of Anticholinergics in Nocturnal Enuresis (Adapted from the ICCS 2020 Guidelines)

Drug	Proposed dosage[a]
Oxybutynin	2.5 – 5 mg
Tolterodine[b]	2 – 4 mg
Fesoterodine[b]	4 – 8 mg
Solifenacin[b]	5 – 10 mg
[a] All doses are oral tablets given 1 h before bedtime. [b] Not yet approved for label use in children.	

Oxybutinin and fesoterodine are not currently SFDA-registered.

- Therapy should be evaluated after 1-2 months. If then there is an insufficient reduction of wet nights, but no side-effects desmopressin may be added (in standard dosage) and anticholinergic dose increased.

  (Insufficient evidence to provide recommendations whether to increase anticholinergic dosage or add desmopressin first, so this will have to be decided on an individual basis)

- Another strategy is to start with **combination therapy with desmopressin**, and then try and discontinue desmopressin. If a satisfactory situation is reached and the child is dry at night, then the family should be instructed to make regular attempts to gradually discontinue medication approximately every third month.
- The noradrenergic drug **mirabegron** has recently proved to be an efficient and safe addition or alternative to anticholinergics in adults with detrusor overactivity. Future research will determine its possible role in children with enuresis.

c. Antidepressant treatment

- The tricyclic antidepressant **imipramine** is an evidence based antienuretic therapy (evidence level Ia) that can be used by specialists as a third-line alternative if desmopressin, the alarm, and anticholinergics have all been unsuccessfully tried and/or are contraindicated.
- The drug should not be given without prior long-time electrocardiographic evaluation if there is any history of unclear syncope or palpitations in the child or a positive family history of sudden cardiac death. Obviously, the recommended dosage should never be exceeded, and the family needs to ensure that the pills are kept securely locked.
- Imipramine should be given approximately 1 hour before bedtime. The dosage is 25-50 mg, the larger dose given to children older than 9 years of age or if the lower dose is ineffective and free of side-effects. Therapeutic response is evaluated after 1 month, and desmopressin may be added if the effect is incomplete.

As with anticholinergics, an alternative strategy is to start with **desmopressin combination therapy**. If treatment is successful, then it is imperative that regular drug-free periods are interspersed to decrease the risk for tolerance. One suggested strategy is that a drug holiday of 2 weeks is given every third month, but this may have to be individualized. Whenever discontinuing imipramine therapy, this should be done gradually, with dosage halved for 1e2 weeks, to decrease the risk for side-effects on discontinuation.

d. New attempts with the enuresis alarm

It is a sensible strategy to encourage children to make fresh attempts with alarm therapy **every 2 years** or so. Before a new attempt, it is recommended that the family complete a voiding chart including measurements of nocturnal urine production. If there is nocturnal polyuria the addition of desmopressin even if it did not work as monotherapy may increase the likelihood of alarm response.

In children who have previously responded to enuresis alarm therapy but then have relapsed, there is some evidence that "overlearning" methods could improve the chance of cure during the next alarm attempt. One such strategy is to instruct the child, after 14 consecutive dry nights have been achieved, to drink 1-2 extra glasses of water every evening (desmopressin is then contraindicated, of course)

e. Extra therapy-resistant children

First, and most importantly, a first-line therapy that did not work previously may function after an interval of a few years.

Second, nocturnal polyuria that is unresponsive to desmopressin may respond to **salt reduction** or **combined diuretics in the morning and desmopressin in the evening** (evidence level III)

Third, specialists in the field may opt for **individualized combination therapies** including components such as desmopressin, the enuresis alarm, anticholinergics, mirabegron, or antidepressants. Also, alternatives to imipramine such as **atomoxetine** or **reboxetine** have been shown to have antienuretic effects (evidence level Ib)

1.2.2 Japan Pediatric Society: Management of Treatment-Resistant Nocturnal Enuresis (2023)

The main recommendations published by the Japan Pediatric Society (JPS) on the management of treatment-resistant nocturnal enuresis are listed below[9]. Recommendations are not graded.

Nocturnal enuresis is defined by the International Children's Continence Society (ICCS) as "nocturnal urination of one or more times per month for three months in children 5 years and older. The classification of nocturnal enuresis is detailed in table 8.

Table 8. Classification of Nocturnal Enuresis (Adapted from the JPS 2023 Guidelines)

Classification	Definition	Percentage
Primary nocturnal enuresis	The child has not yet achieved nighttime dryness over a period of at least six consecutive months	75 – 90
Secondary nocturnal enuresis	The child has achieved nighttime dryness over a period of at least six consecutive months and they start to wet the bed regularly again	10 – 25
Monosymptomatic nocturnal enuresis	Nocturnal enuresis children without any other lower urinary tract symptoms and without a history of bladder dysfunction	75
Non-monosymptomatic nocturnal enuresis	The presence of diurnal voiding symptoms in a child with nocturnal enuresis	25

I. Desmopressin therapy

Desmopressin (1-deamino-8-d-arginine vasopressin: DDAVP), along with alarm therapy, is clearly indicated as the first choice for active treatment in the ICCS treatment guidelines and Japanese guidelines for nocturnal enuresis.

Management of patients with desmopressin treatment resistance

- Although DDAVP is highly effective in the treatment of nocturnal enuresis in children, it is also recognized that some patients do not respond even to 240μg of DDAVP.
- For such DDAVP treatment-resistant patients, some patients may respond effectively by checking their medication regimen and correcting any incorrect medication taken before changing the treatment regimen.

II. Alarm therapy

Alarm therapy for nocturnal enuresis is the first-line treatment in the ICCS nocturnal enuresis guidelines and Japanese nocturnal enuresis guidelines along with DDAVP.

Management of patients with alarm therapy resistance

Although alarm therapy, as well as DDAVP, is considered the first-line treatment for nocturnal enuresis in the ICCS treatment guidelines and Japanese guidelines for the treatment of nocturnal enuresis, there are patients for whom alarm therapy is not suitable:

(1) patients who experience wet nights less than once or twice a week

(2) if the parent or guardian has mental difficulty managing the patient's nocturnal enuresis treatment

(3) if the parents or guardians are angry with, reluctant to treat, or blame the nocturnal enuresis patient

(4) if the patients and parents have low motivation to undergo alarm therapy

(5) if the patient presents with multiple episodes of urinary incontinence per night. It is necessary to reconfirm that the patient does not fall into any of those categories.

Even when nocturnal enuresis treatment is ineffective with a wired alarm, switching to a wireless alarm may increase the success rate.

Recently, the therapeutic efficacy of **vibegron**, a novel β3-adrenergic receptor stimulator for overactive bladder, has been reported for the treatment of nocturnal enuresis.

- The duration of treatment (from the first visit to the cessation of all treatment, including lifestyle guidance) was compared between the two groups of 16 pediatric patients with drug-resistant nocturnal enuresis who achieved remission with vibegron (vibegron group; 12 boys) and 15 who achieved remission with drugs other than vibegron (non-vibegron group; 12 boys)
- The results showed that the treatment of drug-resistant nocturnal enuresis with vibegron was significantly more effective in shortening the duration of treatment compared with the group that did not receive vibegron.

III. Management of patient's refractory to desmopressin and alarm therapy

- If the patient continues to be refractory to desmopressin therapy despite confirmation and guidance on the above points, consider adding an anticholinergic agent, because low bladder capacity may be the cause of nocturnal enuresis, even if daytime urinary incontinence is not present.
- In addition, unlike **oxybutynin**, newer generation anticholinergic agents such as **tolterodine**, **solifenacin**, and **imidafenacin** (imidafenacin available in Asia only) are less fat soluble and less likely to cross the blood–brain barrier, resulting in less frequent central nervous system side effects.
- Other treatment options can include **tricyclic antidepressants**. Tricyclic antidepressants have been used in the treatment of nocturnal enuresis for over 60 years; however, they are now the third choice of pharmacological treatment both domestically and internationally, after DDAVP and anticholinergics, due to their cardiotoxic effects in overdose.

- Otherwise, refractory nocturnal enuresis should be checked for comorbidities. Attention-deficit/hyperactivity disorder (ADHD) is common in childhood, as is nocturnal enuresis, and it is known that ADHD patients often have comorbid nocturnal enuresis.
- Sleep-disordered breathing is another known comorbidity of nocturnal enuresis. The primary cause of sleep-disordered breathing in children is obstructive apnea caused by adenoids and enlarged palatine tonsils.
- Surgical treatment may be considered if sleep-disordered breathing due to adenoids or enlarged palatine tonsils is present and refractory nocturnal enuresis is comorbid.

1.2.3 NHS Ashford and St. Peter's Hospitals: Enuresis Guideline (2022)

The recommendations mentioned are listed below[10]:

I. Management of MNE

Under 5 years: Reassurance

5 years of age and over:

Try general measures first.

- Initial advice-demystify, reassure (most children become asymptomatic over time), educate. Motivation is a significant factor for success. Explain to the child that bedwetting is not his/her fault. It is important for the child not to restrict social activities because of bedwetting.
- Adjust fluid intake to the correct age-appropriate amount (see appendix 2)
- Regular voiding during daytime and bladder training: timed voiding (voiding every 2-3 hours while awake), avoidance of holding maneuvers, optimal voiding posture.
- Avoid bladder irritants (tea, coffee, fruit squash, fizzy drinks)
- Avoid drinking 1-2 hours before bedtime.
- Advice the child to empty his/her bladder just before he/she goes to bed.
- Star charts/ reward systems may have a place in the management of enuresis.
- Early referral to enuresis one-stop clinic for support
- Treat Constipation/UTI (Urinary Tract Infection)
- Manage bedwetting; i) mattress protectors, duvet protectors, pillow protectors, sleeping bag liners ii) lifting to toilet during the night does not help long term but can be a useful short-term management strategy.

If general measures prove unsuccessful (about 4 weeks should be allowed for the measures to take effect), subsequent treatment should be attempted.

a. First line

Enuresis alarm

- It is one of the best and most widely used therapies for enuresis/bedwetting
- The alarm sends off a sound signal when the child wets the bed, it gradually teaches him/her to recognize the body's own signals.
- Assess response at about 4 weeks (or in the next clinic review). Continue if there are early signs of response (until a minimum of 2 weeks of uninterrupted dry nights have been achieved)
- If there is no good response after 3-4 months, move to second line.

b. Second line

Enuresis alarm and desmopressin

- Desmopressin is an anti-diuretic that reduces the urine made by the kidneys by increasing water re-absorption.
- It should be taken at bedtime.
- Restrict fluid 1 hour before until 8 hours after taking desmopressin, this is to reduce risk of water intoxication and hyponatremia.
- Dose can be increased if there is an inadequate response to the starting dose (start at 200mcg for Desmotabs or 120mcg for DesmoMelt)
- Continue for 3-4 months. Repeated courses may be used (in children and young people who are not completely dry after 1-2 weeks of the initial dose, consider increasing dose to 400mcg for Desmotabs or 240mcg for DesmoMelt)

Desmopressin alone

- If using the alarm is no longer acceptable to the child or carer.

c. Third line

Add-in anticholinergics (e.g., oxybutynin or tolterodine)

These are detrusor-relaxing drugs which act as adjuvant therapy.

II. Management of NMNE – nighttime and daytime wetting

Aim to treat daytime wetting first then address nighttime wetting. Use the measures as stated daytime incontinence and nocturnal enuresis management.

One may need to prescribe anticholinergic and desmopressin.

1.2.4 Canadian Pediatric Society: Position Statement Evaluation and Management of Enuresis in the General Pediatric Setting (2023)

The recommendations published by the Canadian Pediatric Society on the evaluation and management of enuresis in the general pediatric setting are not graded[11].

Management

- In primary monosymptomatic enuresis, the mainstay of management is education and reassurance that no treatment is necessary.

Behavioral and motivational counselling

- For children and families experiencing ongoing distress after education and reassurance, behavioral and motivational counselling may help children and adolescents awaiting natural resolution.

  Behavioral strategies include ***Optimal voiding practices, Fluid intake, Diet and nutrition, Positive reinforcement,***

Active therapies

Alarm therapy

- Nightly enuresis is more resistant to alarm therapy, while infrequent enuresis (less than once per week) does not allow sufficient opportunity for appropriate training. At least two episodes per week should be the baseline for alarm use to be effective.
- Alarm therapy may be more effective in children with a normal or small bladder capacity than in those with nocturnal polyuria.
- Treatment response can take time. Early signs of success include waking to the alarm without parental assistance, smaller volume enuretic voids, being able to urinate in the toilet after waking instead of emptying the bladder during sleep, and fewer enuresis episodes per night.
- At the end of treatment, after consecutive dry nights and when the alarm is discontinued, higher evening fluid intake might help improve bladder conditioning.

- Clinical follow-up should occur after the first 2 weeks of alarm therapy to provide support and identify early signs of success. Additional follow-up should depend on child and family needs. The usual treatment course is 12 to 16 weeks, though some children require longer.
- Treatment should continue until the child has at least 14 consecutive days of dryness and should be discontinued if there is no noticeable improvement after 6 weeks. Recent evidence suggests that relapse rates may be improved if the standard of 14 consecutive dry nights is extended.

Desmopressin

- Intermittent use of desmopressin is recommended when families do not wish to use an alarm but do wish to help children control enuresis periodically or for special occasions (i.e., sleepovers, summer camp).
- Daily desmopressin use, with the aim of completely controlling enuresis, may be considered for select cases, but only after discussing potential benefits and limitations with the child and family.
- Side effects from desmopressin are uncommon. However, the risks associated with water intoxication should be disclosed to all families contemplating this therapy. Water intoxication can be prevented by strictly restricting liquid intake to one sip with teeth-brushing, then limiting fluids to no more than 200 mL for at least 8 h (i.e., from 1 h before receiving medication until the next morning).
- Guidelines for continuous use of desmopressin suggest treatment for 3 months at a time, then reassessment with a medication break to determine resolution of enuresis symptoms.
- Evidence is emerging for the benefits of combining treatments for enuresis. Trials that have combined alarm use and desmopressin have reported some favorable results, especially for children with nocturnal polyuria who do not respond to alarm therapy alone.

Anticholinergics

- Anticholinergic (antispasmodic) medications should only be used in rare cases and require the supervision of an expert (a pediatric urologist and/or nephrologist) familiar with the risks and adverse events associated with anticholinergics.
- There may be a role for combination treatment in children with LUTS or an enuresis pattern characteristic of small bladder capacity or overactive bladder (small, frequent night-time voids), who have not responded to other therapies.

- Tolterodine or Solifenacin may be associated with fewer side effects compared to Oxybutynin.

Tricyclics

- They should only be used in exceptional cases and under the close supervision of a clinician expert in the use of these drugs.

Other treatments

- Children who do not respond to education and reassurance, behavioral modifications, the bedwetting alarm, and/or desmopressin, and who are experiencing significant psychological distress should be referred to an expert in enuresis for consideration of further investigations and treatments.
- Families should be advised that the evidence base supporting these therapeutic options is limited, and research to determine their effectiveness is ongoing.

Mirabegron

- Mirabegron is a selective agonist of the beta-3 adrenergic receptor present in the bladder wall. Mirabegron is used to treat overactive bladder (OAB) and acts by relaxing the detrusor muscle, similar to anticholinergic medications.
- Mirabegron does not cause constipation or other common anticholinergic-associated side effects and may be useful for children with NMSE and OAB who also have constipation or who experience negative side effects from anticholinergic medications.
- Rare cases of hypertension have been reported. If treatment with Mirabegron is considered, a referral to a pediatric urologist is recommended.
- Monitoring of blood pressure and post-void residual volumes is recommended before starting therapy and during follow-up.

Neuromodulation

- In very rare circumstances, and only in cases of extreme psychological distress, neuromodulation can be considered for older children and adolescents with refractory primary MSE.
- Transcutaneous electrical neurostimulation (TENS) provides electrical stimulation to the sacral nerves responsible for bladder control. Early evidence suggests that this therapy can be safe and efficacious for treating refractory enuresis in children.

Section 2.0 Drug Therapy in Nocturnal Enuresis

This section comprises three subsections: the first contains the newly recommended drugs, the second covers drug modifications, and the third outlines the drugs that have been withdrawn from the market.

2.1 Additions

After June 2020, there have been no Nocturnal Enuresis drugs that have received FDA or EMA approval. Nevertheless, an anticholinergic agent, **Solifenacin**, was registered in the SFDA list and submitted to the CHI for evaluation. Hence, relevant information pertaining to this drug can be found below.

2.1.1 Solifenacin

This section includes pertinent information regarding the use of Solifenacin in Nocturnal Enuresis[12].

Table 9. Solifenacin Drug Information

SCIENTIFIC NAME **Solifenacin**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	No
Indication (ICD-10)	N39.44
Drug Class	Anticholinergic Agent
Drug Sub-class	-
ATC Code	G04BD08
Pharmacological Class (ASHP)	Antimuscarinics
DRUG INFORMATION	
Dosage Form	Film-coated tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	Initial: 5 mg once daily; if tolerated, may increase to 10 mg once daily.
Maximum Daily Dose Adults*	10 mg once daily

Dose (pediatrics) **Maximum Daily Dose Pediatrics***	Children ≥2 years and Adolescents: Oral suspension (1 mg/mL): 9 to 15 kg: Oral: Initial dose: 2 mg once daily; may titrate every 3 weeks to lowest effective dose. Maximum daily dose: 4 mg/day. >15 to 30 kg: Oral: Initial dose: 3 mg once daily; may titrate every 3 weeks to lowest effective dose. Maximum daily dose: 5 mg/day. >30 to 45 kg: Oral: Initial dose: 3 mg once daily; may titrate every 3 weeks to lowest effective dose. Maximum daily dose: 6 mg/day. >45 to 60 kg: Initial dose: Oral: 4 mg once daily; may titrate every 3 weeks to lowest effective dose. Maximum daily dose: 8 mg/day. >60 kg: Initial dose: Oral: 5 mg once daily; may titrate every 3 weeks to lowest effective dose. Maximum daily dose: 10 mg/day.
Adjustment	***For Altered Kidney Function:*** Children ≥2 years and Adolescents: Oral: • CrCl ≥30 mL/minute/1.73 m2: No dosage adjustment necessary. • CrCl <30 mL/minute/1.73 m2: ➢ 9 to 15 kg: Maximum daily dose: 2 mg/day. ➢ >15 to 45 kg: Maximum daily dose: 3 mg/day. ➢ >45 to 60 kg: Maximum daily dose: 4 mg/day. ➢ >60 kg: Maximum daily dose: 5 mg/day ***For Hepatic Impairment:*** Children ≥2 years and Adolescents: Oral: • Mild impairment: There are no dosage adjustments provided in manufacturer's labeling. • Moderate impairment:

	9 to 15 kg: Maximum daily dose: 2 mg/day. >15 to 45 kg: Maximum daily dose: 3 mg/day. >45 to 60 kg: Maximum daily dose: 4 mg/day. >60 kg: Maximum daily dose: 5 mg/day. • Severe impairment: Use is not recommended.
Prescribing edits*	AGE, ST, PA
AGE (Age Edit): Treatment of neurogenic detrusor overactivity in pediatric patients ≥ 2 years of age.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): Solifenacin should be given at a dose of 5 mg once daily; if tolerated, may increase to 10 mg once daily to treat neurogenic detrusor overactivity in pediatric patients ≥2 years of age who failed first-line therapies. PA is needed as it is not yet approved for the treatment of NE and this is an **off-label** use.	
QL (Quantity Limit N/A	
ST (Step Therapy): Second-line therapy in patients refractory to first-line treatment as a monotherapy or combined to other therapies	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** · Gastrointestinal: Constipation (5% to 13%, dose-dependent) · Xerostomia (11% to 28%, dose-dependent; children and adolescents: 3%) **Most serious:** · Angioedema · CNS Effects · Heat prostration · Hypersensitivity reactions:
Drug Interactions	**Category X** XAclidinium XCimetropium

	X Eluxadoline **X** Fexinidazole **X** Fusidic Acid (Systemic) **X** Glycopyrrolate (Oral Inhalation) **X** Glycopyrronium (Topical) **X** Ipratropium (Oral Inhalation) **X** Levosulpiride **X** Oxatomide **X** Potassium Chloride *Depends on Dosage Form* **X** Potassium Citrate *Depends on Dosage Form* **X** Pramlintide **X** Revefenacin **X** Tiotropium **X** Umeclidinium **Category D** **D** Adagrasib **D** Atazanavir **D** Ceritinib **D** Clarithromycin **D** CloZAPine **D** Cobicistat **D** Darunavir **D** Idelalisib **D** Indinavir **D** Itraconazole *Depends on Hepatic Function and Renal Function* **D** Ketoconazole (Systemic) **D** Levoketoconazole **D** Lonafarnib **D** Lopinavir **D** MiFEPRIStone **D** Nefazodone **D** Nelfinavir **D** Nirmatrelvir and Ritonavir **D** Ombitasvir, Paritaprevir, and Ritonavir

	DOmbitasvir, Paritaprevir, Ritonavir, and Dasabuvir **D**Posaconazole **D**Ritonavir **D**Saquinavir **D**Secretin **D**Tucatinib **D**Voriconazole
Special Population	**Older Adult Considerations** In patients with CrCl <30 mL/minute, doses >5 mg/day are not recommended. Similar safety and effectiveness were observed in elderly and younger patients. Given the ability of solifenacin to antagonize central and peripheral muscarinic receptors, it has the potential to cause constipation, dry eyes, dry mouth, confusion, and urinary retention. For these reasons, it should be used with caution in the elderly. Efficacy with solifenacin is limited, with resolution of urge urinary incontinence occurring in only 107 for every 1,000 women treated. There is a theoretical pharmacodynamic drug-drug interaction between medications with antimuscarinic/anticholinergic effects and cholinesterase inhibitors, therefore, cognitive, functional, and behavioral worsening should be monitored upon the addition of a bladder antimuscarinic, such as solifenacin.
Pregnancy	Adverse events were observed in some animal reproduction studies.
Lactation	• It is not known if solifenacin is present in breast milk. • According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to

	the infant, and the benefits of treatment to the mother.
Contraindications	• Hypersensitivity (eg, anaphylaxis, angioedema) to solifenacin or any component of the formulation; urinary retention (tablet only); gastric retention; uncontrolled narrow-angle glaucoma. • Canadian labeling: Additional contraindication (not in the US labeling): Dialysis
Monitoring Requirements	Mini Mental State exam (MMSE) (periodically); creatinine clearance; hepatic function; postvoid residual urine volume (at baseline and as clinically indicated thereafter)
Precautions	***Disease-related concerns:*** • Alzheimer disease: Preliminary data suggest that long-term use of anticholinergics may potentially adversely affect the clinical course of Alzheimer disease in patients receiving cholinesterase inhibitors (Lu 2003; Sink 2008). • Bladder outlet obstruction: Use not recommended in patients with significant bladder outlet obstruction (eg, BPH) being treated for overactive bladder; may increase the risk of urinary retention. • Gastrointestinal disease: Use with caution in patients with decreased GI motility (severe constipation, ulcerative colitis) or GI obstructive disorders (pyloric stenosis); may increase the risk of gastric retention. Instruct patients to report severe abdominal pain or constipation that lasts longer than 3 days. • Glaucoma: Use with caution in patients with controlled (treated) narrow-angle glaucoma; use is contraindicated in uncontrolled narrow-angle glaucoma.

	• Hepatic impairment: Use with caution in patients with moderate hepatic impairment (Child-Pugh class B); dosage adjustment required; use is not recommended in patients with severe hepatic impairment (Child-Pugh class C). • QT prolongation: Use with caution in patients with a known history of QT prolongation or other risk factors for QT prolongation (eg, concomitant use of medications known to prolong QT interval, electrolyte abnormalities). The risk for QT prolongation is dose related. • Renal impairment: Use with caution in patients with renal impairment; dosage adjustment is required for severe renal impairment (CrCl <30 mL/minute). ***Dosage forms specific issues:*** • Propylene glycol: Some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated hyperosmolality, lactic acidosis, seizures, and respiratory depression.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of nocturnal enuresis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable.

Table 10. Solifenacin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Solifenacin	NICE[13]	N/A
	CADTH[14]	**May 20, 2009:** The CADTH Canadian Expert Drug Advisory Committee (CEDAC) recommends that Solifenacin be listed for patients who cannot tolerate or have insufficient response to an adequate trial of immediate-release oxybutynin, and in a similar manner as drug plans list tolterodine.
	HAS[15]	**Feb 05, 2016:** Therapeutic Indication: Symptomatic treatment of urge urinary incontinence and/or pollakiuria and urinary urgency that can be observed in patients suffering from overactive bladder.
	IQWIG[16]	N/A
	PBS[17]	N/A

Conclusion Statement – Solifenacin

Solifenacin received favorable recommendations for use for patients with overactive bladder but no HTA recommendations for its use in children with Nocturnal Enuresis.

For the treatment of NE in children, adding an anticholinergic agent may be considered if a patient remains unresponsive to desmopressin therapy. Newer generation anticholinergic agents such as tolterodine and **solifenacin**, which are less fat-soluble and less likely to penetrate the blood-brain barrier, may be preferred due to their reduced central nervous system side effects compared to oxybutynin. As a new generation of M-receptor blockers, solifenacin is commonly used in the treatment of overactive bladder. Low dose solifenacin in pediatric PNE has shown that it can effectively improve the curative effect and reduce recurrence[18].

In a prospective double-blind randomized placebo-controlled study published in Urologia Journal[19] where the objective was to evaluate the efficacy and safety of the combination of solifenacin, and imipramine compared with placebo in the treatment of desmopressin refractory MNE; One hundred children aged 6 years or more with primary MNE unresponsive to desmopressin treatment were included. The children were randomly divided into two equal groups. Group A received imipramine 25mg and solifenacin 5–10mg oral tablets and group B received placebo once 1 h before bedtime for 3 months. The primary end point was to investigate the efficacy of the combined treatment of solifenacin, and imipramine and the

secondary end point was the safety of the drugs. No significant side effects related to the drugs were reported.

The results showed that the mean post treatment wet nights per month was significantly lesser in the treatment group than placebo group ($p<0.001$) and cure rate was significantly higher in treatment group than placebo group ($p<0.001$). The relapse rate was statistically significantly lower in the treatment group than placebo group ($p=0.032$).

As a conclusion, the combination treatment of solifenacin and imipramine is a useful and safe treatment for nocturnal enuresis after failure of everything else.

2.1.2 Mirabegron

This section includes pertinent information regarding the use of Mirabegron (in Nocturnal Enuresis[12].

Table 11. Mirabegron Drug Information

SCIENTIFIC NAME **Mirabegron**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	No
Indication (ICD-10)	N39.44
Drug Class	Beta3 Agonist
Drug Sub-class	-
ATC Code	G04BD12
Pharmacological Class (ASHP)	Beta-3 adrenergic agonists
DRUG INFORMATION	
Dosage Form	Prolonged-release film-coated tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	Note: May be used as monotherapy or in combination with an antimuscarinic agent. Oral: Initial: 25 mg once daily. May increase to 50 mg once daily after 4 to 8 weeks based on response and tolerability.
Maximum Daily Dose Adults*	50 mg

Dose (pediatrics) **Maximum Daily Dose Pediatrics***	Children ≥3 years and Adolescents: Note: Appropriate dosage form dependent on patient weight. 11 to <22 kg: Oral: Granules: Initial: 24 mg once daily; after 4 to 8 weeks of therapy, may increase dose if needed up to a maximum daily dose: 48 mg/day once daily. 22 to <35 kg: Oral: Granules: Initial: 32 mg once daily; after 4 to 8 weeks of therapy, may increase dose if needed up to a maximum daily dose: 64 mg/day once daily. ≥35 kg: Oral: Granules: Initial: 48 mg once daily; after 4 to 8 weeks of therapy, may increase dose if needed up to a maximum daily dose: 80 mg/day once daily. Tablets: Initial: 25 mg once daily; after 4 to 8 weeks of therapy, may increase dose if needed up to a maximum daily dose: 50 mg/day once daily.
Adjustment	***For Altered Kidney Function:*** Children ≥3 years and Adolescents: Oral: • eGFR 30 to 89 mL/minute/1.73 m^2: No dosage adjustment necessary (regardless of patient weight or dosage form). • eGFR 15 to 29 mL/minute/1.73 m^2: 11 to <22 kg: Granules: Do not exceed 24 mg once daily. 22 to <35 kg: Granules: Do not exceed 32 mg once daily. ≥35 kg: ➢ Granules: Do not exceed 48 mg once daily. ➢ Tablets: Do not exceed 25 mg once daily. eGFR <15 mL/minute/1.73 m^2: Not recommended (has not been studied). • Hemodialysis: Not recommended (has not been studied). ***For Hepatic Impairment:*** Children ≥3 years and Adolescents: Oral:

	• Mild impairment (Child-Pugh class A): No dosage adjustment necessary (regardless of weight or dosage form). • Moderate impairment (Child-Pugh class B): 11 to <22 kg: Granules: Do not exceed 24 mg once daily. 22 to <35 kg: Granules: Do not exceed 32 mg once daily. ≥35 kg: ➢ Granules: Do not exceed 48 mg once daily. ➢ Tablets: Do not exceed 25 mg once daily. • Severe impairment (Child-Pugh class C): Not recommended (has not been studied).
Prescribing edits*	AGE, ST, PA, CU
AGE (Age Edit): Treatment of neurogenic detrusor overactivity in pediatric patients ≥3 years of age (granules) and weighing ≥ 35 kg (tablets).	
CU (Concurrent Use Edit): Adjuvant treatment in children with refractory neurogenic bladder dysfunction.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): Mirabegron should be given at a dose based on the weight to treat neurogenic detrusor overactivity in children ≥3 years and Adolescents as adjuvant treatment in children with refractory neurogenic bladder dysfunction PA is needed as it is not yet approved for the treatment of NE, and this is an off-label use.	
QL (Quantity Limit): N/A	
ST (Step Therapy): Adjuvant treatment in children with refractory neurogenic bladder dysfunction	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** · >10%: Cardiovascular: Hypertension (8% to 11%) **Most serious:**

	• Angioedema
Drug Interactions	**Category X** **X**DOXOrubicin (Conventional) **X**Mequitazine **X**Thioridazine **Category D** **D**Digoxin **D**Eliglustat *Depends on Additional drug/group and Genotype* **D**Tamoxifen
Special Population	**Older Adult Considerations** No overall differences in safety or effectiveness were observed between patients over 65 and those younger than 65 years. Adjust dose for severe renal impairment. This agent may be used in patients who do not tolerate the anticholinergic effects of other overactive bladder (OAB) treatments.
Pregnancy	Adverse effects have been observed in some animal reproduction studies.
Lactation	It is not known if mirabegron is present in breast milk. According to the manufacturer, the decision to continue or discontinue breastfeeding during therapy should take into account the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	• Hypersensitivity to mirabegron or any component of the formulation • Canadian labeling: Additional contraindications (not in US labeling): Severe uncontrolled hypertension (systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg); pregnancy
Monitoring Requirements	Monitor BP at baseline and then periodically during therapy (especially in patients with preexisting hypertension, even if controlled);

	postvoid residual urine volume at baseline and as clinically indicated thereafter (AUA [Lerner 2021]); signs and symptoms of urinary retention.
Precautions	***Disease-related concerns:*** • Hepatic impairment: Use with caution in patients with mild to moderate hepatic impairment; dosage adjustment is required in patients with moderate hepatic impairment. Use is not recommended in severe hepatic impairment. • Hypertension: Use with caution if used in patients with controlled and less severe hypertension; use is not recommended in patients with uncontrolled hypertension. • Renal impairment: Use with caution in patients with renal impairment; dosage adjustment is required in patients with severe renal impairment. Use is not recommended in ESRD. ***Dosage forms specific issues:*** • Product interchangeability: ER granules and ER tablets are not interchangeable; do not combine products to achieve a total dose. Select appropriate product based on patient's indication and weight; ER granules are not approved for adult use (recommended dose not determined).
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of nocturnal enuresis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency

in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable.

Table 12. Mirabegron HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Mirabegron	NICE[13]	Mirabegron is recommended as an option for treating the symptoms of overactive bladder only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective or have unacceptable side effects.
	CADTH[14]	**October 15, 2014:** The CADTH Canadian Expert Drug Advisory Committee (CEDAC) recommends that Mirabegron be listed for the treatment of overactive bladder (OAB) with symptoms of urgency, urgency incontinence, and urinary frequency, if the following clinical criteria and conditions are met: Clinical Criteria: • Intolerance or inadequate response to an adequate trial of an anticholinergic therapy. Conditions: • List in a manner similar to other pharmacological treatments for use after oxybutynin. • Not to be used in combination with other pharmacological treatments for OAB.
	HAS[15]	**March 29, 2018:** Insufficient clinical benefit to justify its inclusion on the list of reimbursable products for overactive bladder syndrome due to a poorly established efficacy/adverse effects ratio.
	IQWIG[16]	**Sep 01, 2014:** Mirabegron for overactive bladder: added benefit not proven.
	PBS[17]	N/A

Conclusion Statement – Mirabegron

No HTA recommendations about the use of Mirabegron in children for nocturnal enuresis. Mirabegron has promising results for nocturnal enuresis symptoms in children. Mirabegron may be useful for children with NMSE. Mirabegron can be used as an adjuvant treatment for extremely therapy-resistant cases as part of personalized combination therapies involving components such as desmopressin, the enuresis alarm, anticholinergics, or antidepressants. Mirabegron is used to treat overactive bladder (OAB) and acts by relaxing the detrusor muscle, similar to anticholinergic medications. Mirabegron does not cause constipation or other common anticholinergic-associated side effects. Rare cases of hypertension have been reported. If treatment with Mirabegron is considered, a referral to a pediatric urologist is recommended. Ongoing research will determine the effectiveness of Mirabegron in children with nocturnal enuresis.

2.2 Modifications

Modifications have been made since June 2020.

The prescribing edit for desmopressin was changed from "Prior Authorization (PA)" to "Step Therapy (ST)": failure of combination of behavioral and alarm therapy.

2.3 Delisting

All the medications are still SFDA registered[20], therefore, none of the medications is to be delisted the following drugs from CHI formulary. Please refer to **Drugs in the disease - section 2** of CHI Nocturnal Enuresis original clinical guidance.

2.4 Other Drugs

Vibegron

- Recently, the therapeutic efficacy of vibegron, a novel β3-adrenergic receptor stimulator for overactive bladder, has been reported for the treatment of nocturnal enuresis[21].
    - The duration of treatment (from the first visit to the cessation of all treatment, including lifestyle guidance) was compared between the two groups of 16 pediatric patients with drug-resistant nocturnal enuresis who achieved remission with vibegron (vibegron group; 12 boys) and 15 who achieved remission with drugs other than vibegron (non-vibegron group; 12 boys)[21].
    - The results showed that the treatment of drug-resistant nocturnal enuresis with vibegron was significantly more effective in shortening

the duration of treatment compared with the group that did not receive vibegron[21].

- According to a retrospective cohort study of children with therapy-resistant enuresis conducted using data for July to December 2019. Enuresis frequency was recorded during 30 days before and after additional vibegron administration with prior treatment. The study assessed the treatment effectiveness based on enuresis frequencies between before and after treatment with Vibegron 50 mg. The results showed a statistically significant reduction in enuresis frequency ($p < 0.001$) and a significant increase in voiding volume in the early morning was found ($p < 0.05$). No drug-related severe adverse event was found. Short-term treatment with vibegron is safe and effective for children with refractory enuresis[22].

Section 3.0 Key Recommendations Synthesis

- Providing extra fluids during the daytime to maintain proper hydration is a commonly suggested practice, but there is limited supporting evidence (evidence level IV)[23].

NMNE (Nonmonosymptomatic nocturnal enuresis) initial treatment

- In the initial treatment of Nonmonosymptomatic Nocturnal Enuresis (NMNE), it is important to address constipation when there is even a slight suspicion, although the evidence for its effectiveness against enuresis is weak (evidence level IV)[23].
- While the evidence is not strong, there is a consensus that troublesome daytime Lower Urinary Tract (LUT) symptoms should be addressed before tackling nocturnal enuresis (evidence level IV)[23].

MNE (Monosymptomatic nocturnal enuresis) initial treatment

- For the initial treatment of Monosymptomatic Nocturnal Enuresis (MNE), there are two established first-line options: using an enuresis alarm (evidence level Ia) or desmopressin (evidence level Ia). Regardless of the chosen therapy, parental involvement is crucial[23].

Management of therapy-resistant children

- Children resistant to therapy may require treatment for constipation based on the ICCS guidelines (evidence level IV), and some may benefit from the assistance of a child psychologist or psychiatrist (evidence level IV)[23].
- There is also a subgroup that might need surgical intervention for sleep-related breathing issues (evidence level III)[23].

Anticholinergic treatment:

- Anticholinergic treatment can be considered as a second-line therapy for enuresis if there is no residual urine and constipation has been ruled out or successfully treated. This is often used in combination with desmopressin (evidence level Ib)[23].

Antidepressant treatment:

- Imipramine, a tricyclic antidepressant, is a supported third-line option for enuresis when desmopressin, the alarm, and anticholinergics have all proven ineffective or are contraindicated (evidence level Ia)[23].

Extra therapy-resistant children:

- For children who are resistant to desmopressin and experience nocturnal polyuria, salt reduction or a combination of morning diuretics and evening desmopressin may be effective (evidence level III)[23].
- Specialists may opt for personalized combination therapies involving components such as desmopressin, the enuresis alarm, anticholinergics, mirabegron, or antidepressants in the case of extremely therapy-resistant children. Alternatives to imipramine, like atomoxetine or reboxetine, have also shown enuretic effects (evidence level Ib)[23].

Alarm Therapy

- Alarm therapy is recommended as the primary treatment in the ICCS nocturnal enuresis guidelines and Japanese nocturnal enuresis guidelines, alongside DDAVP[21].
- If a patient remains unresponsive to desmopressin therapy despite following the above recommendations, adding an anticholinergic agent may be considered. This is because low bladder capacity could be the underlying cause of nocturnal enuresis, even if daytime urinary incontinence is not present[21].
- Additionally, newer generation anticholinergic agents such as tolterodine and solifenacin, which are less fat-soluble and less likely to penetrate the blood-brain barrier, may be preferred due to their reduced central nervous system side effects compared to oxybutynin[21].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Nocturnal Enuresis report** and aims to provide recommendations to aid in the management of Nocturnal Enuresis. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Nocturnal Enuresis. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

1. Bedwetting - Cleveland Clinic . Accessed September 13, 2023. https://my.clevelandclinic.org/health/diseases/15075-bedwetting
2. Goessaert AS, Everaert K, Hoebeke P, Kapila A, Vande Walle J. Nocturnal enuresis and nocturia, differences and similarities — Lessons to learn? *Acta Clinica Belgica: International Journal of Clinical and Laboratory Medicine*. 2015;70(2):81-86. doi:10.1179/2295333714Y.0000000055
3. Bedwetting - Mayo Clinic. Accessed September 13, 2023. https://my.clevelandclinic.org/health/diseases/15075-bedwetting
4. Alhifthy EH, Habib L, Abu Al-Makarem A, et al. Prevalence of Nocturnal Enuresis among Saudi Children Population. *Cureus*. Published online January 15, 2020. doi:10.7759/cureus.6662
5. Burgu B, Castagnetti M, Dogan H, et al. *Paediatric Urology EAU Guidelines On*.; 2023.
6. Nevéus T, Fonseca E, Franco I, et al. Management and treatment of nocturnal enuresis—an updated standardization document from the International Children's Continence Society. *J Pediatr Urol*. 2020;16(1):10-19. doi:10.1016/j.jpurol.2019.12.020
7. Bladder Diary / Frequency Volume Chart. Accessed September 26, 2023. https://www.ics.org/committees/standardisation/terminologydiscussions/bladderdiary
8. Bogaert G, Stein R, Undre S, et al. Practical recommendations of the EAU-ESPU guidelines committee for monosymptomatic enuresis—Bedwetting. *Neurourol Urodyn*. 2020;39(2):489-497. doi:10.1002/nau.24239
9. Tsuji S, Kaneko K. Management of treatment-resistant nocturnal enuresis. *Pediatr Int*. 2023;65(1):e15573. doi:10.1111/ped.15573

10. *PAEDIATRIC DEPARTMENT Section 1 Organisational Policy*.

11. Position Statement: Evaluation and management of enuresis in the general paediatric setting. Published October 2023. Accessed September 26, 2023. https://cps.ca/en/documents/position/evaluation-and-management-of-enuresis-in-the-general-paediatric-setting

12. Lexicomp. Published 2023. Accessed June 6, 2023. https://online-lexi-com.ezproxy.lau.edu.lb:2443/lco/action/home

13. 1. National Institute for Health and Care Excellence (NICE) Guidance website. .

14. Canadian Agency for Drugs and Technologies in Health (CADTH) website.

15. 3. Haute Autorite de Sante (HAS) website.

16. 4. Institute for Quality and Efficiency in Healthcare (IQWIG) website. 4. Institute for Quality and Efficiency in Healthcare (IQWIG) website. .

17. Pharmaceutical Benefits Advisory Committee (PBAC) website.

18. Y WU. *Effects of M2 Polarization of Microglia on Inflammatory Injury in Cerebral Haemorrhage*. www.ijpsonline.com

19. Samir M, Mahmoud MA, Elawady H. Can the combined treatment of solifenacin and imipramine has a role in desmopressin refractory monosymptomatic nocturnal enuresis? A prospective double-blind randomized placebo-controlled study. *Urologia Journal*. 2021;88(4):369-373. doi:10.1177/0391560321993587

20. SFDA Drug List J. SFDA Drug List . Published 2023. Accessed June 20, 2023. https://www.sfda.gov.sa/en/drugs-list

21. Tsuji S, Kaneko K. Management of treatment-resistant nocturnal enuresis. *Pediatr Int*. 2023;65(1):e15573. doi:10.1111/ped.15573

22. Uchihara Y, Yamashita S, Watanabe H, Hata D, Hata A. Effects of short-term treatment with vibegron for refractory nocturnal enuresis. *Pediatrics International*. 2023;65(1). doi:10.1111/ped.15464

23. Nevéus T, Fonseca E, Franco I, et al. Management and treatment of nocturnal enuresis—an updated standardization document from the International Children's Continence Society. *J Pediatr Urol*. 2020;16(1):10-19. doi:10.1016/j.jpurol.2019.12.020

Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Nocturnal Enuresis Scope

Nocturnal Enuresis Scope

Section	Rationale/Updates
Section 1.1 Pediatric Urology EAU guidelines 2018	Section 1.1.1 Pediatric Urology EAU (European Association of Urology) guidelines 2023[5] The strength of each recommendation is represented by the words 'strong' or 'weak' [12]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength of a recommendation reflects the extent to which we can be confident that desirable effects of an intervention outweigh undesirable effects GRADE classifies recommendations as strong or weak Strong recommendations mean that most informed patients would choose the recommended management and that clinicians can structure their interactions with patients accordingly Weak recommendations mean that patients' choices will vary according to their values and preferences, and clinicians must ensure that patients' care is in keeping with their values and preferences Strength of recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, quality of evidence, variability in values and preferences, and resource use. Level of evidence Imipramine: achieves only a moderate response rate of 50% and has a high relapse rate. Furthermore, cardiotoxicity and death from overdose are described, its use should therefore be discouraged as the first line therapy (Level: 1). Removed Algorithm <u>Recommendations</u> • Do not treat children less than five years of age in whom spontaneous cure is likely, but inform the family about the involuntary nature, the high incidence of spontaneous resolution and the fact that punishment will not help to improve the condition. (2, Strong) • Use micturition diaries or questionnaires to exclude day-time symptoms. (2 Strong) • Perform a urine test to exclude the presence of infection or potential causes such as diabetes insipidus. (2, Strong)

	• Offer supportive measures in conjunction with other treatment modalities, of which pharmacological and alarm treatment are the two most important. (1, Strong) • Offer desmopressin in proven night-time polyuria. (1, Strong) • Offer alarm treatment in motivated and compliant families. (1, Strong) <u>Supportive treatment measures</u> • To assure good sleep quality, specifically in children with NE, it is also recommended to limit the use of electronic devices before bedtime. • Referral for psychological support should be advised and followed-up for patients with NE and their families, especially if the NE comorbid factor is developmental, attention or learning difficulties, family problems, parental distress and possible punishment of the child are observed. • Parental stress levels are higher compared to parents of non-NE children and anger is found to be the most common parental reaction towards NE children, this would explain why childhood traumas such as neglect and abuse are more often seen in children with NE. • Psychological interventions with parents of NE children were shown to significantly improve their coping mechanisms. <u>Wetting alarm treatment</u> • In the most recent Cochrane review (even though the quality of the included studies was low), several studies have shown that alarm treatment will reduce the number of wet nights a week. An alarm treatment has a higher complete response rate and a lower relapse rate compared to no treatment at all. • In the event of relapse after initial success, one should actively investigate for OAB (Overactive Bladder). The recommended length of therapy with the alarm treatment continues to be uncertain, varying from 8-12 weeks (ICCS: International Children's Continence Society) to 16-20 weeks. <u>Medical treatment</u> • If the child and the family would like to act on the high night-time urine production and eventual nighttime OAB, they should be able and willing to adjust their drinking habits and take either desmopressin or a combination of desmopressin and an anticholinergic drug. • Success rates of 70% can be obtained with Desmopressin, either as tablets (200-400 µg), or as sublingual Desmopressin oral lyophilisate (120-240 µg). • A rare side-effect is water intoxication which can be prevented by adequate water intake. • The dosage of 120 ug has been shown to be effective and safe. A structured titration increases up to 240 ug has been shown to be effective. • A nasal spray is no longer recommended due to the increased risk of overdose. <u>Electrical neuromodulation</u>

	• Several systematic reviews and randomized trials have documented potential benefits of electrical neural stimulation for NE. However, the quality of the included studies was low and different types of electrical neural stimulation, such as intra-anal stimulation and interferential current stimulation have been included. • The one RCT that compares transcutaneous electrical nerve stimulation to placebo demonstrates no antienuretic effect. <u>Complementary treatments:</u> • A Cochrane review showed no benefit for treatments such as hypnosis, psychotherapy, acupuncture, chiropractic, and medicinal herbs for the treatment of NE.
N/A	Section 1.2.1 Journal of pediatric urology. Management and treatment of nocturnal enuresis an updated standardization document from the International Children's Continence Society 2020[23] <u>Initial evaluation:</u> <u>Warning signs:</u> The initial evaluation should make the clinician able to react, without delay, to the following important warning signs: **Table 1** Warning signs in the initial assessment of the child with enuresis. Warning sign — Action Weight loss, growth retardation and/or nausea — Check creatinine and urine glucose. Physical examination. Excessive thirst with a need to drink at night — Check urine glucose. Complete a fluid intake list. Consider creatinine and morning urine osmolality. Physical examination. Voiding difficulties—weak stream, need to strain to void — Check uroflow and residual urine. Physical examination. Secondary nocturnal enuresis with recent debut — Check urine glucose. Physical examination. Heavy snoring or sleep apneas — Contact otorhinolaryngologist. Physical examination. <u>History</u> Medical history is the most important and sometimes the only necessary part of the evaluation of the enuretic child. The following should be checked: General health, the enuresis, daytime micturition habits, bowel habits, sleep problems, behavioral issues, and previous treatment. <u>Examinations</u> • The physical examination of the enuretic child usually comes out completely normal or gives findings unrelated to the enuresis. Thus, in the absence of warning signs in history (see above) the child could be managed initially without being examined by a physician. • In case of doubt, however, a general physical examination, focusing on general health and signs of occult spinal dysraphism (lower back findings, leg and anal cleft asymmetries, abnormal neurology of the lower limb) is needed. • The voiding chart, as described by the ICCS is recommended in the initial evaluation of all enuretic children, and mandatory if there are any indications

	from the history that the enuresis is of the no monosymptomatic kind, that is, if there are any daytime LUT (Lower urinary tract) symptoms. • A urine dipstick detecting glucosuria and leukocytes-is a necessary part of initial evaluation if enuresis is secondary, • Blood samples are only indicated if there is glucosuria or general warning signs suggesting polyuric renal failure. <u>Initial treatment</u> • The children need help to become dry before their self-esteem and social interactions become adversely affected. Thus, the "wait and see-attitude" is not adequate in the management of the child who is old enough to be bothered by his/her condition. <u>General advice</u> • Parents who restrict the child's fluid intake in the evenings should be dissuaded from this practice unless they see a clear benefit (regarding fluid restriction during desmopressin therapy, see below). • The advice to give extra fluid during daytime to keep him/her well hydrated is often given, but the evidence base is scant (evidence level IV). <u>NMNE (Nonmonosymptomatic nocturnal enuresis) initial treatment</u> • The fact that there are concomitant daytime LUT symptoms indicate 1) that uninhibited detrusor contractions are likely to play a role as a pathogenetic factor, which will influence choice of therapy and, 2) comorbidity-somatic or psychiatric-is extra common and may need to be addressed. These children need to complete a voiding chart and the initial evaluation should include a urine dipstick. • Constipation is more common in this group and should be treated on the slightest suspicion (evidence level IV for effect against enuresis). • Although the evidence base is weak, the consensus is that bothersome daytime LUT symptoms should be treated before the nocturnal enuresis is addressed (evidence level IV). • The child with NMNE should be instructed to 1) establish regular voiding habits with micturition approximately 6 times per day, 2) drink adequately especially in the morning and at lunch, and 3) adopt a good voiding posture with the thighs well supported. <u>MNE (Monosymptomatic nocturnal enuresis) initial treatment</u> • There are two established first-line therapies in MNE: the enuresis alarm (evidence level Ia) and desmopressin (evidence level Ia). Regardless of the therapy chosen, the role of the parents is crucial. Alarm Therapy:

	➢ If alarm therapy is chosen it is imperative that the following practicalities are adhered to: - The alarm should only be used by well-motivated, well-informed families. - The device should be thoroughly demonstrated for both child and parents. - The alarm needs to be used continuously, every night without interruption. - The parents need to be prepared to wake the child immediately when the signal is heard, since very often during the first weeks of treatment the child itself will not wake up by the signal. - The healthcare provider should contact the family after 1-3 weeks to give encouragement and solve technical problems during this crucial period. - If there is no sign of progress after 6 weeks therapy should be stopped - If there is progress (smaller wet spot, occasional dry nights) then therapy should be continued until 14 consecutive dry nights have been achieved. Desmopressin: ➢ Desmopressin was developed as an analogue to the antidiuretic human hormone vasopressin, or antidiuretic hormone. ➢ The chance of response is highest in children with MNE who have nocturnal polyuria and normal daytime voided volumes. ➢ The choice of first-line therapy can be made in two ways (A or B), depending on whether to put most emphasis on the prognostic indicators for desmopressin (A) or the alarm (B). ➢ Strategy A means that the family has completed a voiding chart including measurements of nocturnal urine production. If this shows that the child has nocturnal polyuria and normal daytime voided volumes then desmopressin is tried first, and if nocturnal urine output is normal and MVV are low the alarm is provided. If both nocturnal polyuria and reduced MVV below 65-70% of EBC Is present combination therapy with desmopressin and alarm can be considered. ➢ Strategy B means that the family chooses which therapy to use first after being informed about the pros and cons of both alternatives. This means that the families most motivated for the alarm will choose the alarm. ➢ Regardless of which strategy (A or B) is used, if the first choice of therapy (alarm or desmopressin) did not make the child dry then the other alternative should be offered. If both fails as monotherapy a combination of the two can be considered <u>Management of therapy-resistant children</u> Evaluation: • The child with enuresis who has neither responded to desmopressin nor alarm therapy needs to be examined by a physician, usually a pediatrician or a pediatric urologist.

	• Questions need to be asked regarding Rome IV criteria for constipation; possible behavior issues need to be enquired about and the family will be asked to describe how the unsuccessful therapies were given. Often it will be found that the alarm was incorrectly used. • The child needs to be physically examined, with focus on signs of spinal dysraphism as described above. • Therapy-resistant children should undergo noninvasive urodynamic investigation with flowmetry and residual urine measurement: ➢ The reason for this is that the finding of pathological curves or post-void residual urine on repeated measurements means that: a) anatomic obstruction or neurogenic bladder needs to be excluded and b) anticholinergic treatment is contraindicated. • Many of the therapy-resistant children will need to be treated for constipation ex juvantibus (evidence level IV) according to the ICCS guidelines and some will need the assistance of a child psychologist or psychiatrist (evidence level IV). • There is also a subgroup that may need surgical treatment for sleep-disordered breathing (evidence level III). Anticholinergic treatment: • Provided that there is no residual urine, and that constipation is excluded or successfully treated anticholinergics can be considered as second-line antienuretic therapy, often in combination with desmopressin (evidence level Ib). • There are several anticholinergic drugs available, but it needs to be emphasized that only oxybutynin is available for label use in children. • The reasons that other alternatives were mentioned in this review are that 1) the side-effect profile is more favorable in the off-label alternatives and 2) other alternatives can be expected to become available for label prescription in the near future. • Medication is taken in the evening 1 h before bedtime and should be started with a dose in the lower interval mentioned in below table:

Table 2 Proposed dosage of anticholinergics in nocturnal enuresis.

Drug	Proposed dosage[a]
Oxybutynin	2.5—5 mg
Tolterodine[b]	2—4 mg
Fesoterodine[b]	4—8 mg
Solifenacin[b]	5—10 mg

[a] All doses are oral tablets given 1 h before bedtime.
[b] Not yet approved for label use in children.

- Therapy should be evaluated after 1-2 months. If then there is an insufficient reduction of wet nights, but no side-effects desmopressin may be added (in standard dosage) and anticholinergic dose increased.
  (Insufficient evidence to provide recommendations whether to increase anticholinergic dosage or add desmopressin first, so this will have to be decided on an individual basis)
- Another strategy is to start with combination therapy and then try and discontinue desmopressin. If a satisfactory situation is reached and the child is dry at night, then the family should be instructed to make regular attempts to gradually discontinue medication approximately every third month.
- The noradrenergic drug mirabegron has recently proved to be an efficient and safe addition or alternative to anticholinergics in adults with detrusor overactivity. Future research will determine its possible role in children with enuresis.

Antidepressant treatment:

- The tricyclic antidepressant imipramine is an evidence based antienuretic therapy (evidence level Ia) that can be used by specialists as a third-line alternative if desmopressin, the alarm, and anticholinergics have all been unsuccessfully tried and/or are contraindicated.
- The drug should not be given without prior long-time electrocardiographic evaluation if there is any history of unclear syncope or palpitations in the child or a positive family history of sudden cardiac death. Obviously, the recommended dosage should never be exceeded, and the family needs to ensure that the pills are kept securely locked.
- Imipramine should be given approximately 1 h before bedtime. The dosage is 25-50 mg, the larger dose given to children older than 9 years of age or if the lower dose is ineffective and free of side-effects. Therapeutic response is evaluated after 1 month, and desmopressin may be added if the effect is incomplete.
- As with anticholinergics, an alternative strategy is to start with desmopressin combination therapy. If treatment is successful, then it is imperative that regular drug-free periods are interspersed to decrease the risk for tolerance. One suggested strategy is that a drug holiday of 2 weeks is given every third month,

	but this may have to be individualized. Whenever discontinuing imipramine therapy, this should be done gradually, with dosage halved for 1e2 weeks, to decrease the risk for side-effects on discontinuation. New attempts with the enuresis alarm: • It is a sensible strategy to encourage children to make fresh attempts with alarm therapy every 2 years or so. Before making a new alarm attempt, it is recommended that the family complete a voiding chart including measurements of nocturnal urine production. If there is nocturnal polyuria the addition of desmopressin even if it did not work as monotherapy may increase the likelihood of alarm response • In children who have previously responded to enuresis alarm therapy but then have relapsed, there is some evidence that "overlearning" methods could improve the chance of cure during the next alarm attempt. One such strategy is to instruct the child, after 14 consecutive dry nights have been achieved, to drink 1e2 extra glasses of water every evening (desmopressin is then contraindicated, of course) Extra therapy-resistant children: • First, and most importantly, a first-line therapy that did not work previously may function after an interval of a few years. • Second, nocturnal polyuria that is unresponsive to desmopressin may respond to salt reduction or combined diuretics in the morning and desmopressin in the evening (evidence level III) • Third, specialists in the field may opt for individualized combination therapies including components such as desmopressin, the enuresis alarm, anticholinergics, mirabegron, or antidepressants. Also, alternatives to imipramine such as atomoxetine or reboxetine have been shown to have antienuretic effects (evidence level Ib) SFDA: - Solifenacin (found on IQVIA) - Mirabegron
N/A	Section 1.2.2 Pediatrics International. Management of treatment-resistant nocturnal enuresis. Shoji Tsuji, Kazunari Kaneko. First published: 10 July 2023 https://doi.org/10.1111/ped.15573 (waiting to get article) • Nocturnal enuresis is defined by the International Children's Continence Society (ICCS) as "nocturnal urination of one or more times per month for three months in children 5years and older.

- The classification of nocturnal enuresis is shown in the table below:

	Classification definition	Percentage
Primary nocturnal enuresis	The child has not yet achieved nighttime dryness over a period of at least six consecutive months.	75–90
Secondary nocturnal enuresis	The child has achieved nighttime dryness over a period of at least six consecutive months and they start to wet the bed regularly again.	10–25
Monosymptomatic nocturnal enuresis	Nocturnal enuresis children without any other lower urinary tract symptoms[a] and without a history of bladder dysfunction.	75
Non-monosymptomatic nocturnal enuresis	The presence of diurnal voiding symptoms in a child with nocturnal enuresis.	25

[a]Daytime lower urinary tract symptoms:[18] daytime incontinence; urgency (sudden, unexpected, and imperative urge to void); voiding difficulties (poor stream, hesitancy, need to strain to void); abnormally low or high daytime voiding frequency (voiding <4 or >7 times per day).

<u>DESMOPRESSIN THERAPY</u>

- Desmopressin (1-deamino-8-d-arginine vasopressin: DDAVP), along with alarm therapy, is clearly indicated as the first choice for active treatment in the ICCS treatment guidelines and Japanese guidelines for nocturnal enuresis.
  - **HOW TO MANAGE PATIENTS W ITH DESMOPRESSIN TREATMENT RESISTANCE**
- Although DDAVP is highly effective in the treatment of nocturnal enuresis in children, it is also recognized that some patients do not respond even to 240μg of DDAVP OD.
- For such DDAVP treatment-resistant patients, some patients may respond effectively by checking their medication regimen and correcting any incorrect medication taking before changing the treatment regimen. In other words, it is necessary to confirm whether DDAVP is taken orally just before bedtime, and whether it is taken orally without water, because DDAVP that is prescribed.
- In Japan, Desmopressin is in the form of OD tablets. Constipation and passive smoking have been reported to decrease the effectiveness of DDAVP treatment, so, if necessary, treat constipation and remind guardians to cease smoking.

<u>ALARM THERAPY</u>

- Alarm therapy for nocturnal enuresis is the first-line treatment in the ICCS nocturnal enuresis guidelines18 and Japanese nocturnal enuresis guidelines along with DDAVP.
  - **HOW TO MANAGE PATIENTS WITH ALARM THERAPY RESISTANCE**
- Although alarm therapy, as well as DDAVP, is considered the first-line treatment for nocturnal enuresis in the ICCS treatment guidelines and Japanese guidelines for the treatment of nocturnal enuresis, there are patients for whom alarm therapy is not suitable.

  (1) Patients who experience wet nights less than once or twice a week

  (2) if the parent or guardian has mental difficulty managing the patient's nocturnal enuresis treatment

	(3) if the parents or guardians are angry with, reluctant to treat, or blame the nocturnal enuresis patient (4) if the patients and parents have low motivation to undergo alarm therapy (5) if the patient presents with multiple episodes of urinary incontinence per night. It is necessary to reconfirm that the patient does not fall into any of those categories. • Even when nocturnal enuresis treatment is ineffective with a wired alarm, switching to a wireless alarm may increase the success rate. ➢ **HOW TO MANAGE PATIENTS' REFRACTORY TO DESMOPRESSIN AND ALARM THERAPY** • If the patient continues to be refractory to desmopressin therapy despite confirmation and guidance on the above points, consider adding an anticholinergic agent, because low bladder capacity may be the cause of nocturnal enuresis, even if daytime urinary incontinence is not present. • Currently, there are no anticholinergic drugs in Japan that have been officially approved for pediatric use; however, oxybutynin and propiverine are two drugs that have been adopted in many countries. • In addition, unlike **oxybutynin**, newer generation anticholinergic agents such as **tolterodine**, **solifenacin**, and **imidafenacin** are less fat soluble and less likely to cross the blood–brain barrier, resulting in less frequent central nervous system side effect. • It should be noted that anticholinergics in Japan are not approved for the treatment of nocturnal enuresis, and pediatric doses have not been established for the treatment of overactive bladder. • Other treatment options can include **tricyclic antidepressants**. Tricyclic antidepressants have been used in the treatment of nocturnal enuresis for over 60 years; however, they are now the third choice of pharmacological treatment both domestically and internationally, after DDAVP and anticholinergics, due to their cardiotoxic effects in overdose. • Otherwise, refractory nocturnal enuresis should be checked for comorbidities. Attention-deficit/hyperactivity disorder (ADHD) is common in childhood, as is nocturnal enuresis, and it is known that ADHD patients often have comorbid nocturnal enuresis. • Sleep-disordered breathing is another known comorbidity of nocturnal enuresis. The primary cause of sleep-disordered breathing in children is obstructive apnea caused by adenoids and enlarged palatine tonsils. • Surgical treatment may be considered if sleep-disordered breathing due to adenoids or enlarged palatine tonsils is present and refractory nocturnal enuresis is comorbid.

N/A	Section 1.2.3 NHS Enuresis Guideline – Ashford and St. Peter's Hospitals NHS Foundation Trust 2022[10] MANAGEMENT OF MONOSYMPTOMATIC NOCTURNAL ENURESIS **Under 5 years**: Reassurance **5 years of age and over**: Try general measures first • Initial advice-demystify, reassure (most children become asymptomatic over time), educate. Motivation is a significant factor for success. Explain to the child that bedwetting is not his/her fault. It is important for the child not to restrict social activities because of bedwetting. • Adjust fluid intake to the correct age-appropriate amount (see appendix 2) • Regular voiding during daytime and bladder training: timed voiding (voiding every 2-3 hours while awake), avoidance of holding manoeuvres, optimal voiding posture. • Avoid bladder irritants (tea, coffee, fruit squash, fizzy drinks) • Avoid drinking 1-2 hours before bedtime. • Advice the child to empty his/her bladder just before he/she goes to bed. • Star charts/ reward systems may have a place in the management of enuresis. • Early referral to enuresis one-stop clinic for support • Treat Constipation/UTI • Manage bedwetting; i) mattress protectors, duvet protectors, pillow protectors, • sleeping bag liners ii) lifting to toilet during the night does not help long term but can be a useful short-term management strategy. If general measures prove unsuccessful, progress to subsequent treatment (see next section). Please give above measures about 4 weeks to take effect i.e., if in next clinic review, no change then move to the next line of treatment. **First line:** Enuresis Alarm - It is one of the best and most widely used therapies for enuresis/bedwetting - This could be purchased privately, and they are relatively inexpensive - The alarm sends off a sound signal when the child wets the bed, it gradually teaches him/her to recognize the body's own signals

	- Assess response at about 4 weeks (or in the next clinic review). Continue if there are early signs of response (until a minimum of 2 weeks of uninterrupted dry nights have been achieved) - If no good response after 3-4 months, move to second line (see below) <u>Second line:</u> - Enuresis alarm and desmopressin ➢ Desmopressin is an anti-diuretic that reduces the urine made by the kidneys by increasing water re-absorption ➢ It should be taken at bedtime. ➢ Restrict fluid 1 hour before until 8 hours after taking desmopressin, this is to reduce risk of water intoxication and hyponatraemia. ➢ Dose can be increased if there is an inadequate response to the starting dose (start at 200mcg for Desmotabs or 120mcg for DesmoMelt) ➢ Continue for 3-4 months. Repeated courses may be used (in children and young people who are not completely dry after 1-2 weeks of the initial dose, consider increasing dose to 400mcg for Desmotabs or 240mcg for DesmoMelt) - Desmopressin alone: if using the alarm is no longer acceptable to the child or carer <u>Third line:</u> - Add in anticholinergics (e.g., oxybutynin or tolterodine). These are detrusor-relaxing drugs which act as adjuvant therapy. If no improvement despite above or non-compliance, refer to Paediatric Urology at St Georges hospital or Bladder and bowel service at Evelina Children's hospital. <u>MANAGEMENT OF NON-MONOSYMPTOMATIC NOCTURNAL ENURESIS (NMNE)-NIGHTTIME AND DAYTIME WETTING</u> ➢ Aim to treat daytime wetting first then address nighttime wetting. Use the measures as stated daytime incontinence and nocturnal enuresis management. ➢ One may need to prescribe anticholinergic and desmopressin.

Appendix C. MeSH Terms PubMed

C.1 PubMed Search for Nocturnal Enuresis:

Query	Filters	Search Details	Results
Search: ((((((Nocturnal Enuresis[MeSH Terms]) OR (Nocturnal Enuresis[Title/Abstract])) OR (Enuresis, Nocturnal[Title/Abstract])) OR (Nighttime Urinary Incontinence[Title/Abstract])) OR (Incontinence, Nighttime Urinary[Title/Abstract])) OR (Urinary Incontinence, Nighttime[Title/Abstract])) OR (Bedwetting[Title/Abstract]) Filters: Guideline, in the last 5 years	Guideline, in the last 5 years	("nocturnal enuresis"[MeSH Terms] OR "nocturnal enuresis"[Title/Abstract] OR "enuresis nocturnal"[Title/Abstract] OR "nighttime urinary incontinence"[Title/Abstract] OR "incontinence nighttime urinary"[Title/Abstract] OR "urinary incontinence nighttime"[Title/Abstract] OR "Bedwetting"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	2

incontinence"[Title/Abstract] OR "incontinence nighttime urinary"[Title/Abstract] OR "urinary incontinence nighttime"[Title/Abstract] OR "Bedwetting"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))			

Appendix D. Treatment Algorithm

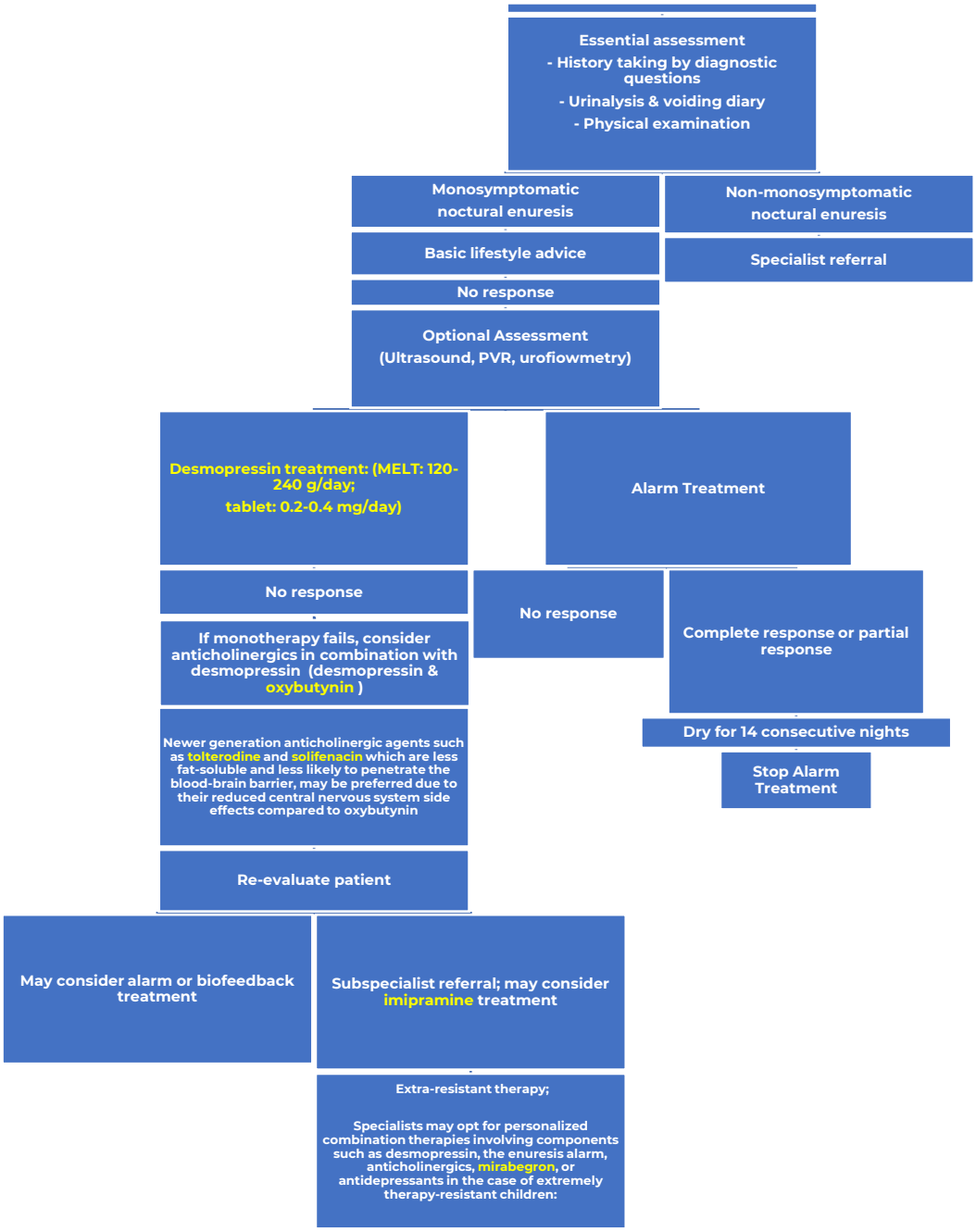

Figure 2. *Recommendations for the Assessment and Treatment of Children with Nocturnal Enuresis*