Nocturnal Enuresis Treatments

Number: 0431

POLICY

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers the use of a bedwetting alarm medically necessary durable medical equipment for the treatment of primary nocturnal enuresis when all of the following criteria are met:

1. The member is 7 years of age or older; and
2. The member has experienced bedwetting a minimum of 3 nights a week in the previous month, or at least 1 wetting episode weekly for 1 year; and
3. The member has no daytime wetting; and
4. The member has been examined by a physician, and physical or organic causes for nocturnal enuresis (e.g., renal disease, neurological disease, infection, etc.) have been ruled out.

Aetna considers the use of a bedwetting alarm experimental and investigational when the aforementioned criteria are not met.

Aetna considers desmopressin medically necessary for the treatment of primary nocturnal enuresis in children older than 5 years whose bedwetting has not responded to non-pharmacologic therapies (e.g., fluid and food intake advice, enuresis alarm treatment; or refused or are unlikely to adhere to enuresis alarm treatment).
Aetna considers the following interventions for the treatment of nocturnal enuresis experimental and investigational because their effectiveness for this indication have not been established.

- Acupuncture
- Bladder training (urotherapy)
- Chiropractic management
- Clonidine
- Extracorporeal magnetic innervation therapy
- Homeopathy
- Hypnosis
- Magnetic sacral root stimulation
- Rapid palatal expansion
- Tonsillectomy
- Transcutaneous electrical nerve stimulation
- Tuina (massage) therapy

**Note:** Special training and skilled care or monitoring services to use the enuresis alarm are *not* generally considered medically necessary.

**BACKGROUND**

Primary nocturnal enuresis (NE) refers to involuntary loss of urine during sleep in patients who have never achieved a sustained period of dryness. Secondary NE is enuresis that develops after a patient has achieved a sustained period of bladder control. More than 5% of 7-year old children and 0.5% of adults experience primary nocturnal enuresis. Nocturnal enuresis in children is rarely caused by psychological factors. It is usually the result of a delay in maturation of the somatic mechanisms – reduction of nocturnal urine production, relaxation of the bladder during sleep, and a normal arousal to a full bladder – that prevent bedwetting. There is evidence of genetic predisposition to primary nocturnal enuresis.

Primary NE resolves spontaneously in most children over time. Treatment options include pharmacotherapy, the enuretic alarm, and complex regimens such as dry-bed training. Recently, desmopressin acetate (DDAVP) nasal spray has been found to be useful when
Nocturnal Enuresis Treatments

Treatment of NE with imipramine has fallen into disfavor because of high relapse rate and risk of fatal over-dosing. By far, the most successful treatment is the enuretic alarm; it enjoys the best long-term cure rate and lowest relapse rate of treatment for primary NE. The enuretic alarm is most effective in patients with the highest frequency of NE. Bedwetting alarms provide biofeedback to enhance bladder sensation and overcome sleep arousal difficulties. However, behavioral modification techniques such as enuretic alarm require strong commitment and are rarely successful in patients less than 7 years of age.

Naitoh et al (2005) noted that desmopressin and imipramine combined with an alarm was no more effective than alarm monotherapy. As for alarm monotherapy, other therapeutic modalities should be considered if it has not proved effective after 3 months. In such a situation, combination therapy may be effective as a second choice.

Kang et al (2007) evaluated the effect of extracorporeal magnetic innervation (ExMI) therapy in children with refractory monosymptomatic nocturnal enuresis (MNE). A total of 55 children (21 girls and 34 boys, median age of 8.0 years, range of 5 to 13) who wetted the bed more than twice per week because of MNE that was refractory to treatment with desmopressin, anti-cholinergics, and enuretic alarm were assessed prospectively using a voiding diary before and after ExMI, administered once-weekly for at least 4 weeks with a size-adjusted magnetic chair (each session lasted 20 mins). After all sessions of ExMI, the mean frequency of NE decreased significantly to 2.09 +/- 2.47 in all patients (p = 0.04), and the mean functional bladder capacity increased 1.88 times in all patients (p = 0.00). In total, 63.6 % of patients had a NE frequency of less than 50 % after a mean of 6.62 +/- 4.26 ExMI sessions. The authors concluded that reduced functional bladder capacity might be the main pathophysiological cause in children with MNE refractory to established treatment. Extracorporeal magnetic innervation might have an acute inhibitory effect in children with refractory MNE by increasing functional bladder capacity. However, they stated that long-term follow-up data and controlled study with a sham-stimulation group are needed to determine the durability of this new therapy for refractory MNE.
Libonate et al (2008) stated that acupuncture has been used to treat a variety of childhood problems; however, the safety and effectiveness of pediatric acupuncture remains unclear. These researchers reviewed the existing empirical literature relating to the use of acupuncture for medical conditions in children. A systematic search of the literature revealed that acupuncture has been used in the treatment of 5 main conditions in children: (i) pain, (ii) NE, (iii) post-operative nausea and vomiting, (iv) laryngospasm/stridor, and (v) neurological disorders. Despite a number of methodological issues, including limited sample sizes, lack of randomization, and inappropriate control groups, it is concluded that acupuncture represents a promising intervention for a variety of pediatric health conditions. Moreover, the authors concluded that large-scale randomized controlled trials are needed to further address the safety, effectiveness, and acceptability of acupuncture in children.

Reed and colleagues (1994) assessed chiropractic management of primary NE in children in a controlled clinical trial for 10 weeks preceded by and followed by a 2-week non-treatment period. A total of 46 nocturnal enuretic children (31 treatment and 15 control group) from a group of 57 children initially included in the study, participated in the trial. Subjects received high-velocity, short- ever adjustments of the spine consistent with the Palmer Package Techniques; or a sham adjustment using an Activator at a non-tension setting administered to the examiner's underlying contact point. Two fifth-year chiropractic students under the supervision of 2 clinic faculty performed the adjustments. Main outcome measure was frequency of wet nights. The post-treatment mean wet night frequency of 7.6 nights/2 weeks for the treatment group was significantly less than its baseline mean wet night frequency of 9.1 nights/2 weeks (p = 0.05). For the control group, there was practically no change (12.1 to 12.2 nights/2 weeks) in the mean wet night frequency from the baseline to the post-treatment. The mean pre- to post-treatment change in the wet night frequency for the treatment group compared with the control group did not reach statistical significance (p = 0.067). Twenty-five percent of the treatment-group children had 50 % or more reduction in the wet night frequency from baseline to post-treatment while none among the control group had such reduction. The authors concluded that these findings suggested that chiropractic treatment is effective for primary NE. Moreover, they stated that a larger study of longer duration with a 6-month follow-up is needed.

Kreitz and Aker (1994) performed a comprehensive review of the
literature concerning the etiology, diagnosis, and the natural history of primary NE. Contemporary treatment options are discussed in light of the documented annual remission rate of this disorder. Articles reviewed were obtained by conducting a computer-aided search of papers indexed in Medline and the Index to Chiropractic Literature from 1989 to 1993. In addition, the Chiropractic Research Abstracts Collection and bibliographies from pertinent articles were manually searched. Primary NE affects some 200,000 children and their families throughout Canada. Twenty percent of children wet the bed at age 5, 10% at age 10, and only about 1% at age 15. The documented natural history of the disorder reveals that for those affected, 10% to 20% exhibit spontaneous resolution per year. Contemporary treatment options center on 3 factors that play primary roles in the etiology of this condition: (i) functional bladder capacity, (ii) patient conditioning, and (iii) the circadian rhythm of nocturnal secretion of vasopressin. The authors concluded that the success of each therapeutic option must, in part, be attributed to the natural history of enuresis, as well as any educational or placebo aspects of treatment. Conditioning therapy utilizing the urine pad alarm may be the most reasonable initial mode of intervention. Spinal manipulative therapy has been shown to possess an efficacy comparable to the natural history.

van Poecke and Cunliffe (2009) evaluated the effect of a specific type of chiropractic treatment on the wet night frequency of patients between the ages of 3 and 18 years who were treated for primary NE in the chiropractic setting. A total of 33 consecutive patient, dating over a 3-year period, of children 3 to 18 years old who had been treated for primary NE using a form of chiropractic treatment method (NeuroImpulse Protocol) were included. All patient records were analyzed for a baseline wet night frequency and at 3, 6, 9, and 12 months after the commencement of treatment. Data were collected regarding the number of treatment visits over the 12-month period and the presence of constipation and/or positive family history at presentation. Data were analyzed using descriptive statistics, Friedman's test, and Dunn's Multiple Comparison test. Of the 33 patient records analyzed, 22 showed resolution of primary NE during the 12 months after commencement of chiropractic care. The mean number of treatments in the responders group was 2.05 +/- 1.33. Ten responders presented with constipation and a further 8 with a positive family history of primary NE. Resolution of constipation was noted to be essential to the successful response to treatment. A combination of constipation and
positive family history at presentation represented a poor prognostic factor. The authors concluded that there was a 66.6% resolution rate within 1 year in 33 consecutive children and teenagers who experienced primary NE. These findings provided an indication for possible effectiveness of chiropractic treatment in patients with primary NE. The results of this small retrospective study need to be validated by well-designed studies.

The International Children's Continence Society's guideline on the evaluation and treatment of MNE (Neveus et al, 2010) noted that the mainstays of primary therapy are bladder advice, the enuresis alarm and/or desmopressin. Among the recommended second-line therapies are anti-cholinergics and in select cases imipramine. Chiropractic management is not discussed as a therapeutic option for these patients.

A French task force of 6 experts based its work on the guide for literature analysis and recommendations and recommendation grading of the French Haute Autorité de Santé (formalized consensus process methodological guidelines) to evaluate the level of scientific proof (grade of 1 to 4) and the strength of the recommendations (grade A, B, C) of the publications on primary NE. A total of 223 articles from 2003 on were identified, of which only 127 (57%) had an evaluable level of proof. This evaluation was then reviewed by a 19-member rating group. Several recommendations, poorly defined by the literature, had to be proposed by a professional agreement resulting from a consultation between the members of the task force and those of the rating group. For its final validation, the document was submitted to a reading group of 21 members working in a wide range of specialist areas and practices but all involved in primary NE. The definition of primary NE is very specific: intermittent incontinence during sleep, from the age of 5, with no continuous period of continence longer than 6 months, with no other associated symptom, particularly during the day. Its diagnosis is clinical by the exclusion of all other urinary pathologies. Two factors must be identified during the consultation: (i) nocturnal polyuria promoted by excessive fluid intake, and (ii) inverse secretion of vasopressin, snoring and sleep apnea. It is sensitive to desmopressin; small bladder capacity evaluated according to a voiding diary and the International Children's Continence Society formula. It may be associated with diurnal hyperactivity of the detrusor (30%). It is resistant to desmopressin. Problems associated with primary NE are: abnormal arousal threshold, attention deficit hyperactivity disorder (ADHD) (10%), low self-esteem.
The psychological component is not very significant. The authors concluded that primary NE is not psychological in origin. The management of this condition includes: evaluating the intra-familial tolerance and the child’s motivation, evaluating the rate, the volume of urine and wet nights using a diurnal and nocturnal diary; education (sufficient fluid intake at the start of the day, decrease in hyper-osmolar intake in the evening, regular and complete urination); specific treatments: desmopressin for polyuric forms (expected success rate of 60 to 70 %), alarms for forms involving small bladder capacity (expected success rate of 60 to 80 %); alternative treatments and/or treatments combined with the preceding ones, for refractory forms: oxybutinin, tricyclic anti-depressants (risk). Results obtained with hypnosis, psychotherapy, acupuncture, homeopathy or chiropractic are not currently validated (insufficient level of proof).

Kalorin and colleagues (2010) noted that sleep disordered breathing caused by tonsillar hypertrophy has been implicated as a cause of primary and secondary NE in children. In a prospective, controlled trial, these investigators studied the pre-operative and post-operative rates of nocturnal and daytime incontinence in a group of children with tonsillar hypertrophy undergoing tonsillectomy compared to a matched control group undergoing surgery unrelated to the airway or urinary tract. A total of 326 toilet trained children 3 to 15 years old were included, with 257 in the tonsillectomy group and 69 in the control group. Severity of tonsillar hypertrophy was graded pre-operatively on a scale of 1 to 4. A voiding questionnaire regarding number of bedwetting and daytime incontinence episodes per week, voids per day, bowel movements per week, secondary or primary enuresis and family history was completed by parents pre-operatively, and at 3 and 6 months post-operatively. Pre-operatively, the respective rates of NE and daytime incontinence were 33 % and 17 % in the tonsillectomy group (p = 0.89), and 35 % and 14 % in the control group (p = 0.3). The respective cure rates for bedwetting at 3 and 6 months post-operatively were 40 % and 50 % in the tonsillectomy group (p = 0.60), and 35 % and 48 % in the control group (p = 0.61).

Similarly, no difference was seen in improvement or cure of daytime incontinence at 3 and 6 months post-operatively. The authors concluded that there was no association between tonsillar hypertrophy and urinary incontinence before or after tonsillectomy; tonsillectomy does not improve bedwetting.
Jeyakumar et al (2012) evaluated the prevalence of nocturnal enuresis in children diagnosed with sleep disordered breathing (SDB) and the effect of adenotonsillectomy (T&A) on nocturnal enuresis. Systematic review of the literature was performed using PubMed and Ovid. A systematic analysis of the literature was performed from 1980 to 2010 to identify children who had SDB and enuresis. A subset of children with enuresis who underwent T&A for SDB were also studied. A total of 14 studies were reviewed. A total of 3,550 children had SDB, of which one-third (n = 1,113) had a diagnosis of enuresis. Age range was 18 months to 19 years. A total of 7 studies (n = 1,360) had data on patients who underwent T&A for SDB with follow-up data on enuresis. The mean sample size was 194, with a median follow-up of 6 months and age range of 2 to 18 years. Pre-operative prevalence of enuresis was 31 % (426/1,360). A total of 587 children were followed after T&A. The post-operative prevalence of enuresis was 16 % (95/587; p < 0.0002, 2-tailed). Most studies did not make a distinction between primary and secondary enuresis. The age range of the subjects (18 months to 19 years) likely included some patients with developmentally acceptable enuresis. The authors concluded that SDB in children is associated with nocturnal enuresis. Adenotonsillectomy is associated with a significant improvement in enuresis in children with SDB. Moreover, they stated that there is a need for randomized controlled trials (RCTs) to examine the role of T&A in children with SDB and enuresis.

In a Cochrane review, Huang et al (2011) evaluated the effects of complementary interventions and others such as surgery or diet on NE in children, and compared them with other interventions. These investigators searched PubMed (1950 to June 2010), EMBASE (1980 to June 2010), the Traditional Chinese Medical Literature Analysis and Retrieval System (TCMLARS) (1984 to June 2010), Chinese Biomedical Literature Database (CBM) (1975 to June 2010), China National Knowledge Infrastructure (CNKI) (1979 to June 2010), VIP database (1989 to June 2010), and the reference lists of relevant articles, all last searched June 26, 2010. No language restriction was used. All randomized or quasi-randomized trials of complementary and other miscellaneous interventions for NE in children were included except those focused solely on daytime wetting. Comparison interventions could include no treatment, placebo or sham treatment, alarms, simple behavioral treatment, desmopressin, imipramine and miscellaneous other drugs and interventions. Two reviewers independently assessed the quality of the eligible trials, and extracted data. In 24 RCTs, a total of
2,334 children were studied, of whom 1,283 received a complementary intervention. The quality of the trials was poor: 5 trials were quasi-randomized, 5 showed differences at baseline and 17 lacked follow-up data. The outcome was better after hypnosis than imipramine in 1 trial (relative risk (RR) for failure or relapse after stopping treatment 0.42, 95% confidence interval (CI): 0.23 to 0.78). Psychotherapy appeared to be better in terms of fewer children failing or relapsing than both alarm (RR 0.28, 95% CI: 0.09 to 0.85) and rewards (RR 0.29, 95% CI: 0.09 to 0.90), but this depended on data from only 1 trial. Medicinal herbs had better results than desmopressin in 1 trial (RR for failure or relapse after stopping treatment 0.35, 95% CI: 0.14 to 0.85). Acupuncture had better results than sham control acupuncture (RR for failure or relapse after stopping treatment 0.67, 95% CI: 0.48 to 0.94) in a further trial. Active chiropractic adjustment had better results than sham adjustment (RR for failure to improve 0.76, 95% CI: 0.60 to 0.95). However, each of these findings came from small single trials, and must be verified in further trials. The findings for diet and faradization were unreliable, and there were no trials including homeopathy or surgery. The authors concluded that there was weak evidence to support the use of hypnosis, psychotherapy, acupuncture, chiropractic and medicinal herbs but it was provided in each case by single small trials, some of dubious methodological rigour. They stated that robust RCTs are needed with efficacy, cost-effectiveness and adverse effects clearly reported.

Desmopressin Therapy

Paruszkiewicz (2013) reviewed International Children's Continence Society guidelines on the recommended diagnostic evaluation and therapy for children with NE. Enuresis is characterized as monosymptomatic nocturnal enuresis (MNE) if there are no additional voiding problems. Children with other daytime symptoms (daytime incontinence, urgency, frequency) and NE are said to have non-monosymptomatic nocturnal enuresis (NMNE). A careful medical history, including bladder diary, physical examination, urinalysis, an ultrasound of the urinary tract system will usually provide sufficient information for the physician to arrive at a diagnosis. Urodynamic, radiologic and endoscopic evaluations are not necessary in children with MNE. Two first line treatment options of MNE are currently recommended: (i) non-pharmacologic treatment, and (ii) pharmacologic treatment (desmopressin). Non-pharmacologic treatment of enuresis includes motivational therapy, bladder-training exercises, fluid and food intake advice as well as enuresis alarm. Before using alarm treatment or
desmopressin, simple therapeutic interventions should be considered.

Children with nocturnal polyuria and normal bladder capacity will be more sensitive to desmopressin.

Dibianco et al (2014) provided a review of NE, including its epidemiology, etiology, pathophysiology, evaluation, and current management. These researchers also provided further insight on the treatment of this condition from the experience derived from patients cared for at their tertiary-care institution. Nocturnal enuresis affects approximately 15% of all children at 5-year old, affecting boys more frequently than girls. These investigators examined the condition in detail, highlighting specific goals of the initial evaluation and treatment. They contrasted the commonly implemented treatment recommendations, available from the literature with strategies they have found valuable from their extensive experience in treating patients with this disorder. Using current urologic reference textbooks, book chapters, Medline, journal articles and reviews describing the many aspects of NE were reviewed in order to describe NE and the current practices at their institution. Although, this was not a systematic literature review, it included relevant available research, institutional experience and urological expert opinion and current practices at a tertiary state health facility. The authors have established a treatment algorithm at their institution, which they have found successful in the majority of their patients. This consists of starting patients on urotherapy, then offering both the enuresis alarm device and medication therapy (desmopressin) as first-line treatments.

An UpToDate review on "Nocturnal enuresis in children: Management" (Tu and Baskin, 2015) states that "Desmopressin (a synthetic vasopressin analog) is a first-line treatment for enuresis in children older than five years whose bedwetting has not responded to advice about fluid intake, toileting, or an appropriate reward system. It is an alternative to enuresis alarms for children and families who seek rapid or short-term improvement of enuresis; have failed, refused, or are unlikely to adhere to enuresis alarm treatment; and for whom an enuresis alarm is unsuitable. .... A review of complementary approaches such as hypnosis, psychotherapy, and acupuncture found limited evidence from small trials with methodologic limitations to support the use of such modalities for the treatment of nocturnal enuresis".

Desmopressin for the Treatment of Nocturia in Multiple Sclerosis
On behalf of the Neuro-Urology Promotion Committee of the International Continence Society (ICS), Phe and colleagues (2019) evaluated the available evidence on the safety and efficacy of desmopressin for treating nocturia in patients with MS. This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Studies were identified by electronic search of Cochrane register, Embase, Medline, Scopus (last search March 3, 2018) and by screening of reference lists and reviews. After screening of 7015 abstracts, 8 prospective, and 1 retrospective studies were included enrolling a total of 178 patients. The mean patient age ranged between 43 and 51 years. A significant decrease in the number of micturitions per night was reported in 5 studies. An increase in the maximum hours of uninterrupted sleep was only found in 2 studies. A significant reduction of the volume of nocturnal incontinence was described in 1 study. The patient satisfaction rates ranged from 56% to 82%. The rate of adverse events (AEs) was between 0% and 57.9%. The rate of hyponatremia ranged from 0% to 23.5% and other commonly reported AEs were headache, nausea, fluid retention, rhinitis/epistaxis, malaise, and swollen ankles. Risk of bias and confounding was relevant in all studies. The authors concluded that preliminary data suggested that desmopressin might be effective for treating nocturia in patients with MS. However, AEs were relatively common, the overall quality of evidence was low and the number of studied patients was very limited. These researchers stated that further studies with newer formulations of desmopressin are needed.

Acupuncture

In a systematic review and meta-analysis of RCTs, Lv and colleagues (2015) evaluated the effectiveness of acupuncture for nocturnal enuresis. A comprehensive literature search of 8 databases was performed up to June 2014; RCTs which compared acupuncture and placebo treatment or pharmacotherapy were identified. A meta-analysis was conducted. This review included 21 RCTs and a total of 1,590 subjects. The overall methodological qualities were low. The results of meta-analysis showed that acupuncture was more effective when compared with placebo or pharmacotherapy. Adverse events associated with acupuncture were not documented. The authors concluded that based on the findings of this study, they suggested that acupuncture could be effective in improving nocturnal enuresis in children. However, they stated that these benefits of acupuncture might be over-stated due to low methodological qualities;
rigorous high quality RCTs are urgently needed.

Bladder Training

Cederblad et al (2015) noted that there are 2 first-line, evidence-based treatments available for nocturnal enuresis: (i) desmopressin and (ii) the enuresis alarm. Prior to use of these therapies, international experts usually recommend that the children also be given basic bladder training during the daytime. The rationale behind this recommendation is that daytime bladder training or urotherapy, is a mainstay in the treatment of daytime incontinence caused by detrusor over-activity. However, there is no firm evidence that daytime bladder training is useful against nocturnal enuresis. In a prospective RCT, these investigators examined if basic bladder advice has any effect against nocturnal enuresis. The evaluated intervention was bladder advice, given in accordance with ICCS guidelines and focused on regular voiding, sound voiding posture, and sufficient fluid intake. A total of 40 children aged 6 years or more with previously untreated enuresis, but no daytime incontinence, were randomized (20 in each group) to receive either first basic bladder advice for 1 month and then alarm therapy (group A) or just the alarm therapy (group B). Based on power calculations, the minimum number of children required in each treatment arm was 15. The basic bladder advice did not reduce the enuresis frequency in group A (p = 0.089) and the end result after alarm therapy did not differ between the 2 groups (p = 0.74). Only 4 children in group A had a partial or full response to bladder training, and 2 of these children relapsed immediately during alarm therapy. This was the first study to evaluate, in a prospective, randomized manner, the value of daytime basic bladder training as a treatment of enuresis. It was found that the treatment neither resulted in a significant reduction in the number of wet nights, nor did it improve the success of subsequent alarm therapy. The authors concluded that the recommendation that all children with enuresis be given bladder training as a first-line therapy can no longer be supported. Instead, they recommended that treatment of these children start with the enuresis alarm or desmopressin without delay.

Magnetic Sacral Root Stimulation

Khedr et al (2015) evaluated the long-term effectiveness of repetitive sacral root magnetic stimulation (rSMS) in patients with MNE. A total of 44 patients were randomized to receive either sham or real rSMS (15 Hz with a total of 1,500 pulses/session) for 10 sessions. Evaluation was
performed before treatment, immediately after the fifth and 10th treatment session, and 1 month later, using frequency of enuresis/week, visual analogue scale (VAS) and quality of life as outcome measures. Resting and active motor thresholds of gastrocnemius muscles were measured before and after the end of sessions. Both treatment and control groups were comparable for baseline measures of frequency of enuresis, and VAS. The mean number of wet nights/week was significantly reduced in patients who received real rSMS. This improvement was maintained 1 month after the end of treatment. Patients receiving real rSMS also reported an improvement in VAS ratings and quality of life. A significant reduction of resting motor threshold was recorded after rSMS in the real group while no such changes were observed in the sham group. The authors concluded that these findings suggested that rSMS has potential as an adjuvant treatment for MNE and deserves further study.

In a systematic review and meta-analysis, Pan and colleagues (2018) examined the value of magnetic stimulation (MS) in patients with pelvic floor dysfunction (PFD). The Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement was followed. These investigators searched 5 databases for articles published until November 2017. Included studies investigated the effects of MS on PFD. Meta-analysis of RCTs was performed using a random effects model, and narrative analysis was undertaken where meta-analysis was not possible. A total of 20 studies including 1,019 patients were eligible for inclusion whose level of evidence for the included studies was low. Meta-analysis of 4 trials comparing MS with sham intervention showed that MS was not associated with significant improvement in ICIQ-SF score (-0.52, 95% CI: -1.05 to 0.01; p = 0.06, I² = 16%), quality of life (QOL) score (-0.27, 95% CI: -0.57 to 0.04; p = 0.09, I² = 0%), number of leakages (-0.16, 95% CI: -0.62 to 0.29; p = 0.48, I² = 52%), and pad test (-1.36, 95% CI: -2.64 to -0.08; p = 0.04, I² = 94%). Narrative review showed that there were no convincing evidences that MS was effective for chronic pelvic floor pain, detrusor overactivity, overactive bladder, and the included RCTs had controversial results. These researchers also noted that MS may have some benefits for nocturnal enuresis and erectile dysfunction according to the trials. The authors concluded that there is no convinced evidence to support the benefits of using MS in the management of PFD. They stated that the applicability of MS in the treatment of PFD remains uncertain; larger, well-designed trials with longer follow-up durations, adopted relevant and comparable outcomes are needed to provide a definitive conclusion.
Rapid Palatal Expansion

In a systematic review and meta-analysis, Poorsattar-Bejeh et al (2015) examined the effectiveness of rapid palatal expansion for the treatment of nocturnal enuresis among children. A sensitive search of electronic databases of PubMed (since 1966), SCOPUS (containing EMBASE, since 1980), Cochrane Central Register of Controlled Trials, CINAHL and EBSCO until January 2014 was performed. A set of regular terms was used for searching in data banks except for PubMed, for which medical subject headings (MeSH) keywords were used. Children aged at least 6 years old at the time of recruitment of either gender who underwent rapid palatal expansion and had attempted any type of pharmacotherapy prior to orthodontic intervention were included. A total of 6 non-randomized clinical trials were found relevant, of which 5 studies had no control group. Overall, 80 children were investigated with the mean age of 118 (28.12) months (range of 74 to 185). The median time to become completely dry was 2.87 months [95% CI: 2.07 to 2.93]. After 1 year, the average rate of becoming complete dry was 31%. The presence of posterior cross-bite [RR: 0.31, 95% CI: 0.12 to 0.79] and signs of upper respiratory obstruction during sleep (RR: 5.1, 95% CI: 1.44 to 18.04) significantly decreased and increased the chance of improvement, respectively. Meanwhile, the other predictors did not significantly predict the outcome after simultaneous adjustment in Cox regression model. The authors concluded that rapid palatal expansion may be considered when other treatment modalities have failed. They noted that the 31% rate of cure is promising when compared to the spontaneous cure rate; although high-level evidence from the rigorous RCTs is scarce (Level of evidence: C). These findings need to be validated by well-designed studies.

Chiropractic Management

Instebo and Lystad (2016) described the chiropractic management of an 8-year old girl with non-organic, primary nocturnal enuresis. This case entailed an 8-year old female patient presented to a chiropractic clinic with persistent night-time bed-wetting. The patient experienced enuresis, on average, 7 nights per week. The patient presented with no other co-morbidities or complaints, such as low back or pelvic pain. Chiropractic treatment included high-velocity, low-amplitude manipulation of the left sacroiliac joint (SIJ) over 3 visits was carried out. Follow-up at 3 months revealed only 3 subsequent episodes of nocturnal enuresis. The authors concluded that this patient reported the resolution of non-organic, primary
nocturnal enuresis after receiving a series of side-posture chiropractic manipulations of the left sacroiliac joint. Moreover, they stated that because the effectiveness of chiropractic care for nocturnal enuresis has not been established, it is important to acknowledge that this treatment approach can at best be described as experimental. In such circumstances, ethical practice demands that patients, or in the case of minors, their parents or legal guardians, are adequately informed before proceeding with experimental chiropractic care.

These researchers stated that future RCTs investigating the effectiveness of chiropractic care for non-organic enuresis need better trial design to minimize the risk of bias. For instance, steps should be taken to ensure adequate generation and implementation of the random allocation sequence. Although it can be difficult to adequately conceal the group allocation to participants and treatment providers, outcome assessors and personnel responsible for data analysis should nevertheless be adequately blinded. Furthermore, an intention-to-treat analysis should be performed to ensure that the randomization is not broken and selection bias inadvertently introduced. Lastly, an a priori power analysis should be conducted to ensure that a trial includes the minimum sample size required to be likely to detect a clinically meaningful effect. In addition to improved methodological quality, future trials may also consider reducing the heterogeneity of the study population and standardizing the intervention. For instance, it may be worthwhile examining a subpopulation of patients with enuresis such as those that present with SIJ dysfunction. With such homogenous study populations, the intervention could also more easily be standardized (e.g., limited to SIJ manipulation). Decisions regarding specific subpopulations and standardized interventions should be guided by clearly articulated and biologically plausible hypotheses for how the intervention might work.

These investigators noted that it is important to remember that causality cannot be established in case reports. That is, although chiropractic care preceded the resolution of the patient’s enuresis, this does not mean that the intervention caused the resolution. Moreover, although the patient remained dry at 3 months post-discharge, it is possible that the patient relapsed later without seeking further chiropractic care. The critical review of the literature was limited by the lack of good quality clinical trials. The findings herein should be interpreted in light of these limitations. This case report described the resolution of non-organic, primary nocturnal enuresis in an 8-year old girl receiving side-posture HVLA manipulation of the left SIJ. A review of the current best evidence demonstrated that there is insufficient or inconclusive evidence for the
effectiveness of chiropractic intervention for nocturnal enuresis.

In a systematic review, Parnell Prevost and associates (2019) examined the use of manual therapy for clinical conditions in the pediatric population, evaluated the methodological quality of the studies found, and synthesized findings based on health condition. They also evaluated the reporting of AEs within the included studies and compared their conclusions to those of the United Kingdom Update report. A total of 6 databases were searched using the following inclusion criteria: children under the age of 18 years; treatment using manual therapy; any type of healthcare profession; published between 2001 and March 31, 2018; and English. Case reports were excluded from this review. Reference tracking was performed on 6 published relevant systematic reviews to find any missed article. Each study that met the inclusion criteria was screened by 2 authors to determine its suitability for inclusion, extract data, and evaluate quality of study. Of the 3,563 articles identified, 165 full articles were screened, and 50 studies met the inclusion criteria; 26 articles were included in prior reviews with 24 new studies identified; 18 studies were judged to be of high quality. Conditions evaluated were: ADHD, autism, asthma, cerebral palsy (CP), clubfoot, constipation, cranial asymmetry, cuboid syndrome, headache, infantile colic, low back pain (LBP), obstructive sleep apnea (OSA), otitis media, pediatric dysfunctional voiding, pediatric nocturnal enuresis, postural asymmetry, pre-term infants, pulled elbow, scoliosis, sub-optimal infant breastfeeding, temporo-mandibular dysfunction (TMD), torticollis, and upper cervical dysfunction. Musculoskeletal conditions, including and LBP and headache, were evaluated in 7 studies; 20 studies reported AEs, which were transient and mild-to-moderate in severity. The authors concluded that 50 studies examined the clinical effects of manual therapies for a wide variety of pediatric conditions. Moderate-positive overall assessment was found for 3 conditions: LBP, pulled elbow, and premature infants. Inconclusive unfavorable outcomes were found for 2 conditions: scoliosis (osteopathic manipulative therapy) and torticollis (manual therapy). All other condition’s overall assessments were either inconclusive favorable or unclear including nocturnal enuresis (chiropractic manipulative therapy); AEs were uncommonly reported. These researchers stated that more robust clinical trials in this area of healthcare are needed.

Driehuis and colleagues (2019) noted that studies on the safety and effectiveness of specific spinal manual therapy (SMT) techniques in
children, which distinguished between age groups, are lacking. These investigators carried out a systematic review of the evidence for effectiveness and harms of specific SMT techniques for infants (less than 1 year), children and adolescents (1 to 18 years). PubMed, Index to Chiropractic Literature, Embase, CINAHL and Cochrane Library were searched up to December 2017. Controlled studies, describing primary SMT treatment in infants and children/adolescents were included to determine effectiveness. Controlled and observational studies and case reports were included to examine harms. One author screened titles and abstracts and 2 authors independently screened the full text of potentially eligible studies for inclusion; 2 authors assessed risk of bias of included studies and quality of the body of evidence using the GRADE methodology. Data were described according to PRISMA guidelines and CONSORT and TIDieR check-lists. If appropriate, random-effects meta-analysis was performed. Of the 1,236 identified studies, 26 studies were eligible. Infants and children/adolescents were treated for various non-musculoskeletal indications, hypothesized to be related to spinal joint dysfunction. Studies examining the same population, indication and treatment comparison were scarce. Due to very low quality evidence, it was uncertain whether gentle, low-velocity mobilizations reduced complaints in infants with colic or torticollis, and whether high-velocity, low-amplitude (HVLA) manipulations reduced complaints in children/adolescents with autism, asthma, nocturnal enuresis, headache or idiopathic scoliosis. A total of 5 case reports described severe harms after HVLA manipulations in 4 infants and 1 child. Mild, transient harms were reported after gentle spinal mobilizations in infants and children, and could be interpreted as side effect of treatment. The authors concluded that based on GRADE methodology, they found the evidence was of very low quality; this prevented these researchers from drawing conclusions regarding the effectiveness of specific SMT techniques in infants, children and adolescents. Outcomes in the included studies were mostly parent or patient-reported; studies did not report on intermediate outcomes to examine the effectiveness of SMT techniques in relation to the hypothesized spinal dysfunction. Severe harms were relatively scarce, poorly described and likely to be associated with underlying missed pathology. Gentle, low-velocity spinal mobilizations appeared to be a safe treatment technique in infants, children and adolescents. These researchers encouraged future research to describe the safety and effectiveness of specific SMT techniques instead of SMT as a general treatment approach.
Furthermore, an UpToDate review on "Nocturnal enuresis in children: Management" (Tu and Baskin, 2020) does not mention chiropractic manipulation / manual therapy as a management/therapeutic option.

Clonidine

Ohtomo (2017) stated that although the evidence-based treatment for the nocturnal enuresis has established, nearly 1/3 of the patients are still enuretic with desmopressin, anti-cholinergic treatment and alarm. The fourth option, imipramine, could be applied for them, however, its use has been limited because of the risk of cardio-toxicity when over-dosed. Clonidine, an alpha2 adrenoceptor agonist, also having noradrenergic effects like imipramine was chosen for the new option for refractory enuresis therapy. A total of 148 patients (6 to 14 years of age; mean of 9.1) with refractory enuresis under desmopressin, anti-cholinergic treatment and alarm were enrolled. Clonidine at a dose of 4 μg/kg/day (maximally 75 μg/day) orally 30 minutes before bed-time were added and its effects were evaluated after 4 weeks. They were comprised of 100 boys and 48 girls, of whom 23 patients with mono-symptomatic nocturnal enuresis (MNE) and 125 with non-NME (NMNE); 83 patients (56.1 %) achieved partial response (PR) or complete response (CR) with the additional clonidine. No significant AEs were noted. The authors concluded that clonidine could be an aid for refractory enuretic patients although further investigation in a RCT is needed.

Adenotonsillectomy

In a systematic review, Lehmann and colleagues (2018) determine the effectiveness of adenotonsillectomy (T&A) in treating children aged 2 to 19 years with primary nocturnal enuresis (PNE). This was a systematic review using a comprehensive electronic search strategy that included PubMed, Embase, CINAHL, Cochrane Library, conference proceedings, and the gray literature up to July 2015. These investigators included all studies of children aged 2 to 19 years with PNE and sleep-disordered breathing (SDB) who underwent T&A. The primary outcome was resolution of PNE following surgery. Observational studies and randomized trials were reviewed. Risk of bias assessment and meta-analyses of included studies were performed. These researchers screened 3,254 citations; following title and abstract screening, 42 studies
were selected for full-text screening by 2 independent reviewers. They included 18 studies (890 patients) in the final analysis. All studies were observational and only 1 included a control group. Meta-analysis of proportions of all (18) studies revealed a pooled complete resolution rate of 51% (43 to 60%), with significant heterogeneity among studies ($I^2 = 82.2\%$). Partial resolution was seen in 20% (14 to 27%), with similar heterogeneity to the complete resolution group. Sensitivity analysis including only studies with a low risk of bias and with patients greater than or equal to 5 years ($n = 244$ patients) yielded a complete resolution rate of 43% (36 to 49%) with minimal heterogeneity ($I^2 = 0\%$). The authors concluded that in this systematic review, T&A resulted in improvement of nocturnal enuresis in more than 60% of patients, with complete resolution rates in excess of 50%. Findings were persistent on meta-analysis focused only on studies including older patients (greater than or equal to 5 years) and those with short follow-up after surgery (less than or equal to 3 months), which implied a higher cure rate than would be expected based on natural history alone. The limitations of this review included the lack of controlled trials, the overall quality of the evidence reviewed and the heterogeneity between included studies. They stated that the role for systematic investigation and treatment of sleep disorders in patients with PNE should be scrutinized further, since a near 50% complete resolution rate for PNE may be expected with T&A in some settings. Moreover, they noted that caution should be exerted when interpreting these results since the quality of the evidence reviewed overall was poor; additional controlled trials are needed to characterize this association and guide further therapeutic options for patients with PNE and SDB.

Transcutaneous Electrical Nerve Stimulation

Ferroni and associates (2017) evaluated the effect of a novel at-home approach to electrical foot stimulation of peripheral tibial nerve branches on the frequency of nocturnal enuresis episodes in children. Children aged 5 to 18 having 2 or more bedwetting episodes per week for at least 3 consecutive months were eligible. The study was a total of 6 weeks. Participants completed a baseline nighttime voiding diary during the first 2 weeks. This was followed by 2 weeks of transcutaneous electrical nerve stimulation (TENS) of the foot for 60 minutes each night. During the stimulation period, and the following 2 weeks post-stimulation,
participants completed the nighttime voiding diary. A total of 22 patients with a mean age of 11.4 years (range of 7 to 16) completed the study. Overall, there was a significant reduction in mean total wet nights from $9.0 \pm 4.0$ to $6.8 \pm 4.8$ during the stimulation period ($p < 0.01$) and a sustained significant reduction to $7.2 \pm 5.0$ wet nights during the post-stimulation period ($p = 0.02$); 16 patients (72.7 %) showed improvement of at least 1 less wet night during stimulation, demonstrating a significant improvement from a mean of $7.9 \pm 3.7$ to $4.8 \pm 3.5$ wet nights during the 2-week stimulation ($p < 0.01$) and maintained an improved mean of $5.1 \pm 4.0$ wet nights during the post-stimulation period ($p < 0.01$). There were no AEs experienced by any child. The authors concluded that TENS of the foot was a well-tolerated, non-invasive, at-home treatment that may reduce the number of wet nights in children with nocturnal enuresis.

In a randomized, double-blind, placebo-controlled study, Jorgensen and colleagues (2017) examined the effect of TENS in children with mono-symptomatic nocturnal enuresis without nocturnal polyuria. Children with mono-symptomatic nocturnal enuresis (3 or more wet nights per week) and no nocturnal polyuria were randomized to treatment with active or sham TENS involving 1-hour sessions twice-daily for 10 weeks in a double-blind design. Of the 52 children with mono-symptomatic nocturnal enuresis included in the study 47 completed treatment (mean age of $9.5 \pm 2.1$ years, 38 boys). None of the children experienced a full response with complete remission of enuresis. Treatment with TENS did not lead to significant changes in number of wet nights, nocturnal urine production on wet or dry nights, maximum voided volume with and without first morning voided volume, or voiding frequency when comparing parameters before and after treatment. The authors concluded that the findings of this study demonstrated no anti-enuretic effect of TENS in children with mono-symptomatic nocturnal enuresis without nocturnal polyuria. Nocturnal urine production and bladder capacity remained unchanged during and after treatment with TENS.

**Tuina (Massage) Therapy**

Liu and colleagues (2020) stated that primary mono-symptomatic nocturnal enuresis is a common disease of pre-school and school-age children and may cause adverse effects on the healthy growth. Pediatric
Tuina (massage) has been widely used in the treatment of monosymptomatic nocturnal enuresis in China. The study is being conducted to summarize the current evidence on the safety and effectiveness of Pediatric Tuina (massage) therapy for the treatment of primary monosymptomatic nocturnal enuresis in children. The following electronic databases will be searched from establishment to December 2019: Cochrane Library, Medline, Embase, Web of Science, World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), China National Knowledge Infrastructure (CNKI), Wan-fang database, Chinese Scientific Journal Database (VIP), Chinese Biomedical Literature Databases (CBM), and other databases, without any language restrictions; RCTs regarding this theme will be retrieved. Independent reviewers will conduct literature retrieval, duplication removal, screening, quality evaluation, data analyses by EndNote (X9), and Review Manager (5.3). Meta-analysis, subgroup analysis, and/or descriptive analysis will be carried out based on the included data form. High-quality synthesis and/or descriptive analysis of current evidence will be provided from improvement of nocturia frequency, improvement of sleep wakefulness disorder, as well as total efficiency. The authors concluded that this review will provide evidence of whether Pediatric Tuina (massage) therapy is a safe and effective treatment for primary monosymptomatic nocturnal enuresis in children. These investigators stated that the results of this trial will aid physicians to better-understand Tuina therapy and will provide valuable evidence for future research in this area. Moreover, they stated that to provide convincing evidence and better guidance for clinical practice, all actions of this review will be carried out according to the Cochrane Handbook.

**CPT Codes/ HCPCS Codes/ICD-10 Codes**
Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by “+”

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>CPT codes not covered for indications listed in the CPB</td>
</tr>
<tr>
<td></td>
<td>Bladder training (urotherapy), Magnetic sacral root stimulation, Rapid palatal expansion - no specific code</td>
</tr>
<tr>
<td>42820</td>
<td>Tonsillectomy and adenoidectomy; younger than age 12</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>42821</td>
<td>age 12 and over</td>
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<td>42825</td>
<td>Tonsillectomy, primary or secondary; younger than age 12</td>
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<td>97810 - 97814</td>
<td>Acupuncture</td>
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<tr>
<td>98940 - 98943</td>
<td>Chiropractic manipulative treatment</td>
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</tbody>
</table>

HCPCS codes covered if selection criteria are met

- J2597: Injection, desmopressin acetate, per 1 mcg
- S8270: Enuresis alarm, using auditory buzzer and/or vibration device

HCPCS codes not covered for Indications listed in the CPB

- E0720: Transcutaneous electrical nerve stimulation (TENS) device, 2 lead, localized stimulation
- E0730: Transcutaneous electrical nerve stimulation (TENS) device, 4 or more leads, for multiple nerve stimulation
- J0735: Injection, clonidine HCl, 1 mg

ICD-10 codes covered if selection criteria are met

- N39.44: Nocturnal enuresis

The above policy is based on the following references:

7. Caldwell PH, Codarini M, Stewart F, et al. Alarm interventions...


53. Ohtomo Y. Clonidine may have a beneficial effect in refractory nocturnal enuresis. Pediatr Int. 2017;59(6):711-713.

Desmopressin Therapy

5. Phe V, Schneider MP, Peyronnet B, et al. Desmopressin for

6. Tu ND, Baskin LS. Nocturnal enuresis in children: Management. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2015.
AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0431 Nocturnal Enuresis Treatments

There are no amendments for Medicaid.

revised 06/28/2021