

Childhood enuresis

Epidemiology, pathophysiology and management

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ABSTRACT

The goal of this article is to review childhood enuresis, which is a common behavioral condition reported in millions of children worldwide. An online computer search was made, and the literature up to 1997 was screened in order to include relevant data for this review. The prevalence of childhood enuresis varies across reviewed studies. This was attributed to a variety of sociodemographic and cultural dynamics of societies. Similarly, the pathophysiology of this ubiquitous symptom is determined by multiple risk factors including biological, psychological, social, and cultural, but the developmental/maturational delay influenced by genetics remains the most plausible explanation. Although a variety of pharmacological and non-pharmacological treatment modalities are traced in the literature, there is yet no agreement on a single strategy. A general agreement about behavioral therapy as the first choice of treatment of this minor malady began to emerge. Additionally, tricyclic antidepressants are the most frequently prescribed drugs for the treatment of childhood enuresis. Enuresis is a pediatric public health problem and concerted efforts at all levels, ie, professional, promotional, educational and public should be made to address its multiple domains such as preventive, etiological and curative.

Keywords: Childhood enuresis, epidemiology, risk factors, pathophysiology, public health problem, education.

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Enuresis is reported to be a common health problem worldwide. This symptom is extremely ubiquitous and the frequency of this minor malady obliges it be considered one of the most important pathologies of childhood. This disorder as defined in ICD-10 and DSM-IV is characterized by involuntary or intentional voiding of urine, by day and/or night, that is abnormal in relation to the individual's mental age; and which is not a consequence of a lack of bladder control due to any neurological disorder or to epileptic attacks or to any structural abnormality of the urinary tract. This behavioral problem has been identified in all cultures and may lead to a variety of psychosocial consequences such as emotional stresses and disruptions, frustrations, stigma, guilt, shame, social maladjustment and embarrassment. These psychosocial problems are shared in common by a triad, which includes enuretic children, parents and physicians at large.

On the contrary, it is also not rare that behavioral or emotional disorders may be of prime importance in the etiology of enuresis. There is, however, no straightforward unambiguous way of deciding between these alternatives in the individual case, and the diagnosis should be made on the basis of which type of disturbance-enuresis or emotional disorder-constitutes the chief problem. Despite its complex heterogeneous nature, the majority of enuretic children, ie, more than 80%, could be simply cured.¹ Moreover, childhood enuresis is reported to remit spontaneously and in most of the children it ceases to exist by age 10.

It has been reported that the majority of concerned parents perceive enuresis as a medical problem,² and so tend to seek medical help from a variety of physicians including mental health professionals, pediatricians, urologists, family physicians, and primary health care physicians. Some parents,

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having strong religious beliefs tend to seek help from traditional healers. It will be fascinating to explore the knowledge, attitude and practice of parents and physicians towards childhood enuresis in order to plan its preventive and intervention strategies. Such studies would probably reveal that pediatricians should decide when help by a sub-specialist is needed and importantly the parents should not be expected to be the 'brokers' for various speciality services.³

Classification of childhood enuresis. Enuresis is the involuntary or intentional discharge of urine after the age of bladder control, which ranges from 3-7 years of age. However, enuresis should not be diagnosed in a child under the age of 5 years or with a mental age under 4 years. Childhood enuresis whether functional/psychogenic or organic has been classified into primary and secondary types. Primary enuresis may have been present from birth, which might be an abnormal extension of the normal infantile incontinence. On the other hand, secondary enuresis may have arisen following a period of acquired bladder control. The length of period of continence for making the diagnosis of secondary enuresis ranges between a minimum of 2 months to a maximum of one year or more. Likewise, in both diagnostic formulations and research purposes, the earlier projected frequency of bed-wetting also varied and it was from daily to once a month. Further, enuresis has been classified into nocturnal, diurnal and both. Some researchers have proposed alternative terms like bedwetting during sleep for the nocturnal variety, while pants wetting while awake for the diurnal type.⁴ However, based on certain grounds some researchers have criticized this terminology and proposed that wetting events should be related directly to sleep rather than to the time of sleep.^{5,6}

Sociodemography of childhood enuresis. The estimated prevalence of enuresis is variable and attributed to a variety of factors. The main determinants of variable prevalence are; definition and diagnostic criteria of enuresis, types of enuresis, different age groups under investigation, types of

gender and their differential maturation, types of sample, sociocultural including child rearing practices, toileting and breast feeding and finally observing and studying disciplines. Enuresis is completely universal and found in all countries and races. It is reported that the prevalence of diurnal enuresis preferentially affecting females [5% vs 3%] is less than the nocturnal one, which predominantly affects the male gender.⁷ It is also reported that about 80% of enuretics are nocturnal, 15% of sufferers are both nocturnal and diurnal and 5% of sufferers are diurnal enuretics.⁸ Further, enuresis is found to be more common in the winter than in the summer season. Moreover, about 5% of children wet during latency and 1% to 3% of men such as military recruits develop enuresis at 18-20 years of age.⁸ In graduate students the incidence of enuresis is also reported to be 0.5% to 4%. According to DSM-111R the prevalence of enuresis at ages 5, 10 and 18 for males and females is 7% and 3%, 3% and 2%, and 1% and 0%. Naturalistic studies revealed that most children become continent through adolescence and approximately 1% continue to have incontinence in adulthood. The reported prevalence in various reviewed studies^{5,7,9-15} is shown in Table 1.

Age is a crucial demographic parameter in determining the prevalence of enuresis and it has an inverse correlation with it. The age cut-off points determined for females and males are 5 and 6-7 years. As mentioned before, involuntary voiding of urine before these sex-divergent age groups should not be considered as enuresis. In general, enuresis is 2 times more prevalent in males than in females. Similarly, primary nocturnal enuresis without diurnal wetting is 2 times more common in males than females. Some researchers,¹¹ however, found no sex differences and one study paradoxically reported higher prevalence of enuresis in females.¹⁶ In the same vein, sex-divergent differences disappeared when nocturnal and diurnal wetting were combined.⁷ It is obvious that further research defining enuresis accurately is warranted to clarify this issue. Social class has been reported to affect the prevalence rates of enuresis. Both upper and lower class families

Table 1 - The prevalence of enuresis in reviewed studies.^{7-9,12-18}

Sr. no	Age-years	WF*	PR-N/D**	Sample Source	Country/year
1.	5-13	1 or>/week	14% overall	families	USA, 1986
2.	3-15	several times/w	14% overall	house-hold	Sudan, 1986
3.	7	1 or>/10 days	6%/2%	schools	Finland, 1988
4.	4-12	1/month	13%/1.5%	hsopital-based	India, 1990
5.	6-10	2 or>/week	10% overall	schools	Kuwait, 1990
6.	5	2 or>/week	40%/4%	schools	Jamaica, 1991
7.	7	unrecorded	9% overall	schools	Sweden, 1992
8.	3-12	1/2-w or>/1/3-w or>	10%/18%	community	USA, 1993
9.	6-16	1/month or >	15%/0.3%	schools	KSA, 1994
10.	5-17	frequent, >6/y	33%, 18%, 7% to 1%	National sample	USA, 1996
11.	6	not available	3%>control, 4.5%> control	hospital-based	USA, 1997

*WF - wetting frequency, **PR-prevalence N/D-nocturnal/diurnal

were found to have more enuretic children. There is no consensus whether enuresis is predominantly found in upper socioeconomic families. Similarly there is no information how the family constitution, extended and nuclear, affects the prevalence of enuresis. It is prudent to say that enuretics in childhood and adulthood function as well in ordinary pursuits as does the general population.

Psychosociocultural dynamics of enuresis. Emotional stresses are reported to have diverse adverse effects on the psyche of developing children. Acute psychological trauma in early childhood originating from a variety of situations such as return to disturbed homes, enforced separation from mother, birth of a sibling and resultant rivalry, hospital admission and others may result in delayed bladder control and therefore, continuation of incontinence. In a similar fashion, secondary enuresis might result from stressful events like going to a new school, bullying at school, severely disturbed family dynamics, parental conflicts, emotional divorcement, enforced separation from a family, residential dislocation, child abuse and acute physical illnesses, all these occurring beyond 5 years of age. It has been reported that these stresses cause loss of learned sphincter control, urethral and anal, which leads to enuresis and encopresis, particularly in vulnerable children. As emphasized earlier, enuresis occurring day/night time may also lead to multiple emotional problems both in enuretic children and their parents. However, in controlled studies, enuretic vs nonenuretic, found no psychological differences between them.⁸ It has been suggested that psychological factors might just contribute rather than cause enuresis. An enuretic child, as an instance of maladjustment tends to induce adverse parental reactions, which results in impaired child-parent interactions. Beside this, the families of enuretics are usually characterized by psychopathologies such as poor marital adjustment, reduced social contacts, parental desertion and conflicts, parents' punitive, rejecting and permissive attitudes towards enuretic children.

Recently, researchers have reported increased emotional and behavioral problems in enuretic as compared to nonenuretic children. The extreme scores on the 32-item Behavior Problem Index [BPI > 90th percentile] was independently associated with both infrequent and frequent bed-wetting. In this context infrequent bed-wetters, ie, less than 6 episodes per year, may not warrant medical intervention, this condition should prompt health care providers to explore various behavioral issues in greater depth.¹⁷ Nonetheless, a proportion of enuretic children may behave perfectly and may not have any emotional problems.⁸ Overall, it appears that there might exist a reciprocal relationship between bed-wetting and behavioral problems. The psychodynamic considerations relevant to childhood

enuresis are highlighted in the psychoanalytical literature,⁸ but are unlikely to exclusively explain the symptom of enuresis.

The symptom of enuresis has also been viewed from sociocultural perspectives. The variable statistics of prevalence of enuresis has been understood in terms of culture, beliefs, attitudes and expectations of parents, ethnic groups and finally toilet training and breast feeding. For instance, the prevalence of enuresis was found to be higher in Jamaican, Irish, Indian and Sudanese children than their dark counterparts elsewhere and fair skin Jamaican, Asian, and European children.^{10,12,18} In particular reference to toilet training, it has been suggested that it should start when the child is prepared psychologically as well as physiologically, components merely determined by genetic influences. Toilet training, if not carried out properly, may cause many untoward problems including enuresis and encopresis, which might be of great concern to parents and a frequent source of family discord.¹⁹ The age of toilet training, though not of paramount value, varies across cultures and 1 to 2 years is the most appropriate age. Of greater importance is the way the toilet training is carried out by parents. In the USA since 1900, toilet training took a path between the polar opposites of passive permissiveness and systematic control. This was followed by delayed toilet training since the mid-century. The authors predicted that this trend will change and early training will emerge which may be accompanied by toilet training problems.²⁰ Both researches recommended behavioral management of toilet training, enuresis, encopresis, and the treatment of toilet-refusal behavior. It is noticed that too harsh/punitive or too lax toilet training is associated with multiple problems including enuresis. Sex-divergent prevalence of enuresis has also been explained by societal attitudes, which emphasized that girls are not permitted to be untidy and are trained to greater fastidiousness. Moreover, they easily submit to training strategies. It is summarized that psychosociocultural factors contribute to the development of enuresis and these factors should be considered while managing enuretic children.

Pathophysiology of enuresis. In about 1% to 10% of cases of enuresis, nonfunctional etiologies have been found. These biological factors are described in the context of geneticity/hereditary, sleep patterns, structural abnormalities both of central nervous system and genitourinary tract and other medical conditions. It is agreed that nocturnal enuretics (80%) as compared to diurnal ones (5%) are less likely to have any associated or causative organic pathologies. Both familial and sporadic cases of enuresis, commonly in first-born children, has been reported in the literature. Enuresis is transmitted as a single recessive gene. Geneticity is reflected in higher percentages reported for enuresis among

parents and siblings of enuretics as compared to their non-enuretic counterparts. Likewise, the incidence of enuresis in offspring increases, ie, from 15% to 44% and 77% when both parents are non-enuretic and one parent and both parents are enuretic.²¹ It is further reported that 75% of enuretic children have a first degree biologic relative who has or had enuresis. Moreover, there is a greater concordance rate for enuresis in monozygotic than dizygotic twins. Hereditary factors are also reported at faults as regards the developmental/maturation lag in enuretic children.

Although enuresis has been reported in any stage of sleep, however, it is most commonly associated with stages 3 and 4 of non-rapid eye movement and occurs mostly during the first 3rd of sleep. Occasionally, nocturnal enuresis is also reported during rapid-eye movement sleep. Therefore, sometimes enuretic children recall dreams. The concept of enuresis being linked with deep sleepers or as an arousal disorder is equivocal. One recent study, however, reported that arousal attempts were successful in 9% of the time in enuretics and 40% of the time in controls. It was concluded that elevated arousal threshold in enuretics may be due to delayed maturation.²² Polysomnographic studies of enuretic children during stage 3 and 4 revealed a series of bladder contractions, mental confusion, increased general body movements, increased muscular tone, penile erection, poor reactivity to external stimuli, retrograde amnesia, tachycardia, compensatory bradycardia, and tachypnea or apnea. At the same time the sleeper's EEG changes to stage 2 or stage 1 reflecting arousal, and the patient occasionally wakes up. Thus enuresis appears to be associated with an active physiological body state. Some researchers have proposed, based on the analysis of EEG and sleep cytometry, a defective coordination between bladder and brain which is situated between the pontine micturition center and the cortex.²³ Additionally, the role of the hypothalamus, which is linked to sleep and water regulation should be clarified in future research recruiting enuretic children⁸ or animal experimental studies.

At a structural level, small functional bladder capacity has been ascribed to cause nocturnal enuresis.²⁴ Similarly an unstable bladder, attributed to delayed maturation of central nervous system may cause nocturnal enuresis in children under 5 years of age. The high prevalence of enuresis in mentally handicapped children (27%) of 7 years of age as compared to normal children (9.5%)¹³ is also related to the maturational lag and the maldevelopment of the central nervous system. Similarly minor insults to the developing brain might be the cause of enuresis in patients with attention-deficit hyperactivity disorder (ADHD).²⁵ Therefore, the physicians who treat children with ADHD and mental subnormality,

should routinely inquire about the presence of enuresis.

Another reported pathophysiological mechanism is dysregulated vasopressin circadian rhythm²³ probably causing reduced nocturnal secretion of antidiuretic hormone.²⁴ Another recent pathophysiological mechanism of enuresis is the alteration of the lipid order, such as phospholipids and triglycerides, in the exterior part of the platelet (PLT) plasma membrane from patients with primary nocturnal enuresis (PNE). The increase in membrane fluidity at the surface level of PLT from subjects with PNE was corrected by decreasing membrane fluidity through the administration of desmopressin.²⁶ Interestingly, some foods containing methylxanthines such as tea, coffee, cocoa, chocolate and other drinks and some drugs may lead to bedwetting by its diuretic actions. It is not known whether some foods might cause enuresis by either irritating the bladder or reducing its functional capacity. Enuresis (12%) and encopresis (10%) may be associated with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS).²⁷ Collectively, in these disorders autoimmunological mechanisms have been evoked in order to explain the pathophysiology of these disorders. The relevant reviewed literature revealed that enuresis may comorbid with other psychiatric conditions such as attention-deficit hyperactivity disorder, PANDAS, obsessive compulsive disorders and tics, encopresis (0.1%), somnambulism, night terrors, Prader-Willi syndrome, and delinquency.

Finally, there are a variety of organic factors (a comprehensive list of organic conditions associated with enuresis may be obtained from the authors) which may cause mainly diurnal enuresis in about 5% of children.²⁴ These factors have different pathophysiological mechanisms to cause enuresis. For example, in sickle-cell anemia renal damage is caused by intravascular sickling or sickling hemoglobin in renal tubular cells. Patients with this disease ingest increased amounts of fluid and void large quantities of urine of low specific gravity.⁸ From a clinical perspective, these organic factors should be excluded carefully by history, physical examination and a battery of investigations before diagnosing psychogenic enuresis, which represents about 80% of cases.

Management of enuresis. Enuresis is a repetitive and inappropriate symptom and not a disease. It is therefore, difficult to discern a definite cause or an effective treatment. Further, besides organic etiologies, enuresis is caused by psychological, social and cultural factors. On the other hand, enuresis is also a source of decreased self-esteem, embarrassment, anger, punishment, social ostracism by peers and rejection by care takers. Therefore, enuresis should be managed by care, non-punitive and non-shaming approaches.

A cursory look at the history of enuresis with special reference to its management revealed that bed wetting was well known in 1500 BC and a variety of traditional and unscientific treatments including consumption of wood lice and swine's urine, mice pie, corporal punishments like penile clamps, frogs tying to genitalia, applying alkali agents to genitalia, causing blisters on buttocks, beating and using animal parts were used in the past.^{8,21} These unorthodox methods in fact reflected an undercurrent of deterrence to the enuretic children. These modalities might also have been associated with adverse consequences on the psychic development of children. Fortunately these treatments are more or less obsolete now.

Subsequently, pharmacological and non-pharmacological therapies were used for the amelioration of this symptom. The drugs for the treatment of enuresis are mainly tricyclic antidepressants, imipramine and nortriptylin, anticholinergics, propantheline and synthetic vasopressin, desmopressin (Table 2). The various non-pharmacological modalities are placebos, bladder exercise and training, various conditioning, behavioral techniques, psychotherapy, family therapy, hypnotherapy, avoidance of certain foods, restriction of fluid, use of star charts,⁸ and awakening related strategies, ie, sleep interruption.²² With exception to the behavioral techniques, most of the time, the aforesaid modalities are used as adjunctive.

In particular reference to the conditioning of the bladder, the alarm treatments were first reported in 1904, but they were not in routine use until 1930's. The sensors in the bed or underwear, in conjunction with audible warning devices are the most common

types of alarms and are the most beneficial to the enuretic children. The alarm success rate of approximately 75% is independent of the type of alarm and there is a low relapse rate.²⁸ Although no known variable is predictive of outcome, the standard definitions and well-defined populations of enuretic children have a better potential response to enuresis alarms. Buzzer frequencies may be adjusted while dealing with a deep sleeper (105 decibel alarm) or a normal sleeper (80 decibel alarm). The nuisance created by alarms to other members should be as minimal as possible.

Surprisingly, in contrast, a considerable number of adult enuretics might resist behavioral modification techniques. They are characterized by passive-aggressive/dependent behavior, past and family history of sleepwalking, family history of enuresis, inferior dentition and chronic genitourinary tract complaints such as frequency, urgency and nocturia.⁸ Alarm buzzer/bell conditioning should be combined with other positive reinforcements and adjunctive psychotherapy, which is often helpful to correct serious family psychopathology.

It is extremely important to critically review the role of tricyclics in the management of enuresis. In clinical practice, the majority of enuretic children are treated with tricyclic antidepressants due to multiple reasons including simplicity of use, convenience and rapidity of action. Its mechanisms of action are an anti-cholinergic effect, an anxiolytic and an antidepressant action to decrease emotional component, and a possible drug effect on sleep. However the immediate anti-enuretic effect contradicts the suggested antidepressant action as one of the mechanisms of this drug. Children with secondary enuresis respond better to imipramine which is comparatively less effective than the buzzer. Following abrupt withdrawal of imipramine, the symptom of enuresis relapses and at the same time emergence of discomfortable withdrawal symptoms including gastrointestinal symptoms and bizarre behavior. Secondly, preschool enuretic children should not be given antidepressants. They are also associated with a variety of adverse effects, most important of which are weight gain, tremors, seizures, cardiovascular accidents, erythematous maculopapular rashes, paralytic ileus, central toxicity and accidental poisoning. Imipramine, 25-75mg/day should be tried for at least one month, but to be discontinued if there is no response. Tricyclics should not be used more than 3 months at a time in enuretic children. If there is a relapse, a further course can be tried after an interval of months. Most of these side effects may be avoided by selecting drugs which have minimum side effects, in particular specific serotonin reuptake inhibitors. Likewise, the other drugs should be used cautiously in the pediatric population. Desmopressin has been recommended for the treatment of enuretic children. This drug is

Table 2 - Psychopharmacology of enuresis.

Drugs	Doses	Mechanisms
1. Anticholinergics - tincture of belladonna - Ephedrine sulfate	15 to 30 drops/day 25mg/hs	increased bladder retention
2. Sympathomimetics - dextroamphetamine sulfate	5mg/day	combating deep sleep
3. Barbiturates - Phenobarbital	15mg/hs	for sedation
4. Antihistaminics - diphenhydramine	50mg/hs	relaxation & antiallergic
5. Diuretics - caffeine	4-6gr/day	day time diuresis
6. Antidiuretic - pitressin tartrate in oil	0.2ml i.m 8 P.M	stop urine output at night
7. Antidepressants** - imipramine	25-75 mg/day	anticholinergic, anxiolytic
**Among all drugs antidepressants are the treatment of choice and should be combined with other modes of behavioural/social therapies for better results.		

associated with a variety of adverse effects including water intoxication leading to hyponatremia, seizure and coma.²⁹ According to these authors, enuretic children should not drink more than 80 ounces of fluids on any evening that desmopressin is administered. In one randomized controlled trial using oxybutynin, pseudoephedrine and indomethacin, it was found that nocturnal enuretic children showed a significant increase in the number of dry nights without experiencing any side effects when they received pseudoephedrine. Authors recommended that pseudoephedrine can be an alternative in the treatment of primary nocturnal enuresis.³⁰ More studies are needed to further establish the efficacy of pseudoephedrine, or to replicate findings of this research. In the latest move, some researchers have discussed the management implications of enuresis in managed care and compared the economics of tricyclic antidepressants, desmopressin and behavioral models.³¹ It is concluded that the drug treatment should be restored only when the behavioral management²⁴ has failed to treat the enuresis.

Conclusions and future research implications. After an extensive and critical review of childhood enuresis, the following conclusions are made; Childhood enuresis is considered a public health problem with variable prevalence rates across various cultures and all concerned physicians should approach any case of enuresis with care and modesty; the psychosocial factors and family dynamics should be explored in all cases of enuresis; although a minority of enuretic children have organic etiologies, it is mandatory that every case of enuresis is investigated thoroughly in particular the genitourinary system and central nervous system in order to exclude any organic pathologies. Psychological tests including projective and intelligence will assist in diagnostic speculations concerning the presence of organic pathology or to verify the diagnosis of mental subnormality; the treating physicians should ensure whether they are dealing with primary or secondary enuresis of nocturnal, diurnal or both; an enuretic without organic defect is likely to have complete emptying of the bladder while day time dribblers usually have genitourinary obstruction or malfunction; it is also equally important to note the sleeping habits and patterns of enuretic children in order to plan the behavioral conditioning treatments which agreeably are the treatment of choice for them; in addition to alarm treatment, adjunctive family counseling is of considerable value to the parents and the enuretic children; psychodynamic therapy is rarely required for the treatment of enuresis; corporal punishment of enuretic children is not at all acceptable and must be discouraged by all concerned health personnel; the psychopharmacological treatments are easy to administer but at the same time are associated with multiple side-effects and comparatively greater

relapse rates; and finally, avoiding injection of negative factors coupled with appropriate toilet training may prevent the development of childhood enuresis.

In light of these conclusions, researchers have opportunities to systematically study the many risk factors associated with childhood enuresis and its outcome. Some particular areas of research interest might include: 1) A multicenter epidemiological study in Saudi Arabia that would be able to assemble a large population and assess the incidence and other vital sociodemographic parameters of childhood enuresis. 2) The identification of children at high risk for childhood enuresis. This would allow elucidation and studying of the specific risk factors including hereditary,³² which will finally help in developing the preventive strategies for these children. 3) Closer attention should be paid to the definitions of childhood enuresis that are used in research. Future research must have standard definitions and operational criteria for diagnosing childhood enuresis. 4) Further research studying the knowledge, attitudes and practice that parents and physicians have when dealing with enuretic children. This could focus on an attempt to enhance the knowledge and modify the negative attitudes and practice of various health providers including parents through relevant health promotional and educational campaigns. 5) Further work to study the psychopharmacology of childhood enuresis through controlled trials with particular emphasis on its outcome. 6) This team of researchers is currently conducting 2 researches; a) clinical profiles of enuretic children in Al-Qassim region, Saudi Arabia and 2) the parental knowledge, attitude, and practice towards enuretic children. Given scanty literature on childhood enuresis from Gulf countries, it is extremely important to give priority to these researches.

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