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Role of Fluoxetine in primary Monosymptomatic Nocturnal enuresis.

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Abstract

Nocturnal enuresis is involuntary voiding that occurs exclusively at night, after most children have stopped. For the diagnosis of primary monosymptomatic enuresis, at least three episodes of bed wetting in a patient who has never been dry for more than six months are required (PME). Despite a 15 % annual maturation rate, 0.5 % of all instances continue throughout adulthood, with significant effects for self-esteem. Behavioral and motivational therapy, alarm aids, and pharmacotherapy have all been recommended as therapeutic options for PME. Desmopressin or antimuscarinics like propiverine or oxybutynin are the most common medical treatments for PME. Response failure to these medications is one of the issues in the management of PME. In recent literature, the influence of medicines that modulate serotonin levels, such as selective serotonin reuptake inhibitors (SSRIs), on urination has been reported. These findings show that SSRIs might be used to treat nocturnal enuresis without the dangerous cardiac arrhythmia that tricyclic antidepressants cause or the hyponatremia that long-term desmopressin therapy causes. The goal of our research was to look at the role of fluoxetine in the treatment of enuresis in children.

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Introduction

Response failure to pharmacological treatments including desmopressin is one of the challenges in the therapy of primary monosymptomatic enuresis (PME), particularly in teenagers. Although there is a roughly 15% spontaneous remission rate each year, around one-third of all children with NE have a condition that is resistant to first-line therapy, prompting the development of novel therapeutic alternatives.

Selective serotonin reuptake inhibitors (SSRIs), which have been used primarily for treatment of depression and obsessive-compulsive disorder (OCD), have minimal cardiovascular toxic effects and low overdose risks, making them suitable for usage in children and teenagers. Fluoxetine is the first SSRI to be approved in USA for the management of Major Depressive Disordres and was available in the market in 1987.

The purpose of the current review was to summarize the current modalities of management of nocturnal enuresis with their success rates and limitations and to illustrate the clinical role of fluoxetine in treating primary nocturnal enuresis.

Methods

This review was performed by evaluating the literature on nocturnal enuresis published between 1970 and 2020, available via PubMed and using the keywords "nocturnal enuresis", "fluoxetine", "pediatric", "review" and "treatment".

Review

I. Terminology and social impact

In children, enuresis is a prevalent medical problem. It influences millions of children worldwide and is connected with a considerable detrimental impact on self-esteem and health-related quality of life **(1)** .

Nocturnal enuresis is defined as discrete episodes of urinary incontinence during sleep in children older than 5 years of age in the absence of congenital or acquired neurologic disorders. Enuresis is classified as either monosymptomatic enuresis (**MSE**) or nonmonosymptomatic enuresis (**NMSE**). MSE is characterised as enuresis in children who do not have any other LUTS or a history of bladder dysfunction. NMSE is characterised as enuresis with any daytime LUTS **(2)**. Daytime LUTS that point to NMSE include incontinence, frequency, genital or LUT discomfort, and holding techniques.

MSE is further classified as primary and secondary. **Primary MSE** affects children who have never acquired a satisfactory period of nocturnal dryness (~80% of enuretic children fulfil this criterion). **Secondary enuresis** occurs when a child develops enuresis after a dry interval of at least 6 months **(3)** .

Enuresis is a prevalent disease, with an estimated 7 million children suffering from it in the United States alone. According to a major longitudinal study conducted in the United Kingdom, at least 20% of children in the first grade wet the bed on occasion, and 4% wet the bed twice or more every week. **(4)**. There is no accurate number about the prevalence in Egypt.

At the age of five, roughly 15% of children will experience some degree of overnight

wetness, with a spontaneous resolution rate of approximately 15% every year **(5)**. As a result, only about 1% to 2% of teens will still wet the bed at the age of 15 **(6)**. It has also been demonstrated that the longer an enuresis lasts, the less likely it is to resolve spontaneously **(7)**.

Enuresis appears to be more prevalent in males than in girls, according to most reports, which show a 2:1 ratio **(8)**. It is widely acknowledged that by adolescence, both boys and females have equal frequency.

For the kid and its caregivers, nocturnal enuresis has major secondary psychological, emotional, and social implications. As a result, therapy is recommended starting at the age of six years old, taking into account mental health, familial expectations, social concerns, and cultural background.

Psychosocial difficulties, low self-esteem, dread of sleepovers, and social isolation can all be symptoms of NE. NE is a socially and mentally burdensome illness that can cause bullying and a reluctance to participate in social activities like overnight stays **(9)**. NE is the most frequent chronic condition in children, second only to asthma, and the third most unpleasant life event a kid can face **(10)**.

II. Pathophysiology

Enuresis is thought to be caused by a maturational delay in the final development of bladder control. The bladder (i.e., reduced nocturnal bladder capacity), the kidney (i.e., nocturnal polyuria), and the brain (i.e., a disorder affecting arousal from sleep) are the three organ systems implicated in the aetiology of enuresis. The disruption or maturational lag in one or more of these essential domains is assumed to be the cause of enuresis.

Regardless of urine output, there appears to be a subgroup of children with primary MSE who have nocturnal bladder overactivity **(11)**. Nearly half of treatment failures with conventional therapy (desmopressin or wetness alarm) had normal daytime bladder function but substantial detrusor overactivity during sleep, resulting in enuresis, according to Yeung et al. (1999). Almost no one in this group of kids developed nocturnal polyuria.

The bladder capacity of children with enuresis (including those without daytime symptoms) has been found to be lower than that of age-matched controls **(12)** It appears that the reduced bladder capacity is functional rather than anatomic. This was demonstrated in a study in which bladder capacity in children with enuresis was measured in the awake state as well as under general anaesthesia and compared to functional bladder capacity in controls **(13)**. The average volume of urine voided by enuretic children in the waking state was lower than that of controls. Enuretic children, on the other hand, had identical mean bladder volumes to awake controls when volumes were assessed after general anaesthesia.

In nocturnal enuresis, increased nighttime urine output appears to play a key role **(14).** The diurnal rhythm of urine production leads in a relative drop in nocturnal diuresis to around 50% of daytime levels in children and adolescents without enuresis **(15).** A nocturnal circadian peak of antidiuretic hormone (ADH) production from the posterior pituitary gland, which regulates free water excretion, is likely to be the dominating mechanism.

Whatever the reason, urine output that is supposed to decrease at night due to these circadian systems fails to do so, resulting in nocturnal polyuria, which might surpass the bladder's functional capacity and cause an enuretic episode. Rasmussen et al. (1996) shown that increasing nocturnal urine production can indeed induce enuresis in healthy youngsters **(16)**.

Despite this seemingly straightforward causal link, it is obvious that nocturnal polyuria and ADH responsiveness are extremely complicated phenomena, because nocturnal polyuria is not present in all children with enuresis, and nocturnal ADH may be normal in those who do **(17).**

III. Arousal and Sleep :

The most essential pathophysiological element is a high arousal threshold. Neither detrusor overactivity nor nocturnal polyuria can explain why a kid with enuresis is unable to wake up and void before a wetting episode. Both detrusor contractions and bladder distension are well-known arousal stimuli.

Enuresis patients are frequently described by their parents as extremely deep sleepers. Family members of patients on alarm therapy frequently face this dilemma, as parents arise from their sleep while their enuretic kid sleeps through the alert. **(18)**. Enuresis was associated with a subjectively high arousal threshold and severe confusion upon rising from sleep, according to Nevéus et al. (1999), who collected questionnaire data from 1413 students aged 6 to 10. **(18)**.

An objectively deep sleep, as assessed by EEG, is not the same as a subjectively deep sleep. It's crucial to remember that we're not implying that polysomnographic differences must represent high arousal thresholds. Even if two people have the same distribution and proportion of the various sleep phases, their arousal thresholds might be vastly different. **(19)**.

Wolfish et al. studied the arousability of boys with NE and healthy age-matched controls in 1997. In order to do this, auditory stimuli of increasing intensity were applied at all phases of sleep. This was the first study to show that children with NE have a harder time waking up in a clinical setting. In healthy controls, the success rate of waking was 98/239, compared to just 25/269 in children with enuresis. This study also proved that, as expected, it is significantly more difficult to wake up both controls and NE-children in the early hours of the night **(20)**.

Other sleep studies, on the other hand, reveal that children with and without enuresis have similar sleep patterns. **(21)**.

Yeung et al work in Hong Kong is widely cited as the first to establish that frequent, ineffective arousal reactions might disrupt bedwetting children's sleep. **(22)** . Although these children seemed to be heavy sleepers, a study of 35 children with therapy-resistant MSE in Hong Kong found that they experienced more total light sleep (stage I/II non-REM) with sleep fragmentation than deep sleep (stage III/IV non-REM).**(22)**.

The cerebral cortex received afferent input from the sleep OAB, which was accompanied by repeated cortical arousals that failed to rouse the children, resulting in a paradoxical rise in the conscious waking threshold. Because of long-term overstimulation of the sleep arousal centre by bladder signals, OAB-associated cortical arousals

may trigger a change from deep to light sleep but not total wakefulness.

Subjective signs of poor sleep are growing in number, and new research demonstrating that enuretic children have higher nocturnal blood pressure than normal controls go in the same direction **(23)**. Enuretic children's sleep may be "deep," but it is also "poor."

In conclusion, these investigations show that children who wet the bed sleep properly (i.e., the distribution and percentage of various sleep stages are within normal norms) but are unable to awaken in response to nocturnal detrusor contractions or bladder fullness. Perhaps the body prefers enuresis over fragmented sleep by raising the arousal thresholds.

Different research have looked at what time of night the enuresis episode occurs, and the results have been mixed. Early in the evening has been determined to be the most common time for NE to occur. Enuretic episodes can occur at any time during the night, according to these research, although they are most common during non-rapid eye movement (non-REM) sleep **(24)**.

The enuresis episode's timing is significant for two reasons. From a pathophysiological standpoint, because arousal is often more difficult and urine output is higher in the early hours of the night, an enuresis episode is likely to occur during this time.

The timing of an enuresis episode is also important from a therapeutic standpoint. It has been proposed that by delaying the period of bladder emptying, we can attain dryness by changing the enuresis episode to a nocturia event. This notion is supported by the fact that a combination of enuresis alarm and desmopressin is better to enuresis alarm alone **(25)**.

IV. Treatment

Conventional therapies for enuresis include :

- " Wait and see " approach.
- Behavioral Therapy.
- Enuresis alarm.
- Desmopressin
- Tricyclic antidepressants
- Anticholinergics
- Combination therapy
- Alternative therapies

Because enuresis is self-limiting, one therapeutic approach is to watch and wait for the natural history of the condition to play out. A cautious **"wait and see"** approach is appropriate. If the kid and his or her family are unable to adhere to a therapy, if treatment alternatives are not feasible given the family's circumstances, and if there is no societal pressure. However, it is critical to emphasise in this strategy that the kid should wear diapers at night to ensure a regular sleep quality.

The child must be extremely motivated to engage in a therapy programme that might take months to complete. Although all bedwetting children should be given basic counsel, actual treatment should not normally begin before the age of six **(14)**.

Regarding Behavioral Therapy : Data from randomized trials on the efficacy of behavioral therapy are lacking **(26)** , but clinical experience (i.e., level 4 evidence) suggests that this approach is beneficial **(14)**.

The fundamental goal of behavioral therapy centers around the practice of good bladder and bowel habits.

- Children should attempt to void regularly during the day and just before going to bed for a total of six to seven times daily.
- High-sugar and caffeine-based drinks should be avoided, particularly in the evening hours.
- Daily fluid intake should be concentrated in the morning and early afternoon, and both fluid and solute intake should be minimized during the evening. Isolated nighttime fluid restriction, without compensatory increase in daytime fluid consumption, may prevent the child from meeting his or her daily fluid requirement and is usually unsuccessful.
- Children should be reassured that enuresis is not their fault, and children should not be punished for bedwetting, because this practice is often counterproductive **(27).**

Alarm training has been shown to be the most effective long-term therapeutic modality in the treatment of MSE **(28)**. The response is more gradual and sustained than for desmopressin, with approximately two-thirds of children becoming dry during active treatment and nearly one-half remaining dry after treatment completion **(28)**.

In a large, multisite study of 2861 enuretic children (5 to 16 years of age), the overall success rate of bell-and-pad alarm therapy was 76%, irrespective of age **(29).**

Alarms have been used since the 1930s, but exactly how the alarm works remains somewhat of a mystery. Enuresis alarms are activated when a sensor, placed in the undergarment or on a bed pad, detects moisture, with both types demonstrated to be equally effective. The arousal device is usually an auditory alarm and/or a vibrating belt **(30).**

The method of action is to repeat the awakening and therefore change the high arousal to a low arousal threshold specifically when a status of full bladder is reached.

Approximately 30% of patients discontinue enuresis alarms for various reasons, including skin irritation, disturbance of other family members, and/or failure to wake the child **(31).** Adverse effects of alarms include alarm failure, false alarms, disruption of the lives of other family members, and lack of adherence because of difficulty using the alarm **(28)**.

Alarm treatment should be continued until the child has had a minimum of 14 consecutive dry nights **(14)**. Children who do not continue to improve after 6 weeks of alarm training are unlikely to become completely dry with this technique and alternative interventions may be warranted **(32).**

Therapy with the alarm can be reinitiated for relapse (more than two wet nights in 2 weeks). Children who relapse after discontinuation of the alarm usually can achieve a rapid secondary response because of preconditioning as a result of the first treatment program **(33).**

Desmopressin (1-desamino-8-D-arginine vasopressin [DDAVP]) is a synthetic analogue of ADH released by the posterior pituitary gland that reduces urine production by increasing water reabsorption by the collecting tubules. Desmopressin is fairly easy to administer, and its clinical effects appear immediately, with a serum

half-life of approximately 2 to 3 hours when taken in oral form.

The main safety issue is the risk for water intoxication with resultant hyponatremic seizures, so the drug should be taken with excessive fluids. This risk seems to be somewhat higher with the intranasal form, which has a prolonged half-life, and thus use of the spray is discouraged **(34).** Treatment should be interrupted during episodes of fluid and/or electrolyte imbalance (e.g., fevers, vomiting or diarrhea, vigorous exercise, or other conditions associated with increased water consumption).

The usual starting dose is 0.2 mg orally 1 hour before bedtime, and the drug can be titrated up incrementally by 0.2 mg to a maximum dose of 0.6 mg at bedtime. Children are instructed to void directly before going to bed. Fluid intake is reduced at the time of ingestion, with absolutely no more fluids until morning, decreasing the risk for significant hyponatremia to virtually zero **(35).**

Desmopressin is most efficient in children with nocturnal polyuria (defined by the ICCS as nocturnal urine production >130% of expected bladder capacity for age) and normal bladder reservoir function (maximum voided volume >70% of expected bladder capacity for age) **(36).**

There is a wide range of efficacy among studies, most likely because of heterogeneous patient populations (MSE vs. NMSE), differences in concomitant behavioral therapy recommendations, and differences in the dosage or formulation of DDAVP, without taking into account nocturnal urine volume. Overall, approximately 30% of patients achieve total dryness, and another 40% exhibit a significant decrease in nighttime wetting **(14).**

However, the relapse rate after discontinuation is high (60% to 70%) (37). In contrast with the enuresis alarm , treatment effects were not sustained after discontinuation of therapy, with a relapse rate of 65% versus 46% with DDAVP versus the alarm, respectively **(35).** The response to desmopressin should be assessed within 2 weeks. Treatment should be continued if there is a positive response (e.g., smaller wet patches, fewer wetting episodes) **(31).** When DDAVP is administered daily, we generally give patients regular scheduled drug holidays of approximately 1 week every 3 to 6 months to assess whether the medication is still needed.

Monotherapy with **anticholinergic drugs**, such as oxybutynin or tolterodine, has been demonstrated not to be effective as a first-line treatment for MSE **(38)**. Anticholinergics clearly do have a role is combination therapy in the treatment of children who are refractory to DDAVP monotherapy.

There is some evidence that nocturnal detrusor overactivity (especially without nocturnal polyuria) plays a role in the pathogenesis of enuresis and therefore makes anticholinergics an attractive pharmacotherapeutic option **(39).**

Given the efficacy and safety of enuresis alarms and DDAVP, TCAs (e.g., imipramine, amitriptyline, and desipramine) are considered a third-line treatment for therapy-resistant MSE.

TCAs have been demonstrated to decrease the amount of time spent in REM sleep, stimulate ADH secretion, and relax the detrusor muscle via weak anticholinergic properties. Its anti-enuretic effect has been theorized to be less likely because of its action at the kidney or bladder level and more likely a result of noradrenergic stimulation at

the brainstem, specifically the locus coeruleus **(40)**.

Level 1 evidence demonstrates that, compared with placebo, TCAs are more effective at reducing the number of wet nights and at achieving 14 consecutive dry nights (i.e., cure) but essentially become ineffective once treatment is discontinued.

The response to imipramine should be assessed after 1 month. If there is no improvement after 3 months, it should be discontinued as a gradual taper (as is done with other TCAs).

As is the case with other pharmacotherapy for enuresis, we give patients a drug holiday every 3 to 6 months, gradually tapering the dose over a 2-week period **(40).**

Adverse effects of TCA therapy are relatively uncommon. Approximately 5% of children treated with TCAs develop neurologic symptoms, including nervousness, personality change, and disordered sleep. TCAs (as with other antidepressants) are required by the FDA to carry a black box warning regarding the possibility of increased suicidality, particularly in individuals with preexisting depressive symptoms.

The most serious adverse effects of TCAs involve the cardiovascular system: cardiac conduction disturbances and myocardial depression, particularly in cases of overdose **(41).** Before initiation of therapy with a TCA, a thorough cardiac history (e.g., palpitations, syncope) and family cardiac history (e.g., arrhythmias, sudden cardiac death) should be obtained with a baseline electrocardiogram to rule out a prolonged QT interval if history or physical examination raises suspicion. Common side effects of dizziness, headache, mood changes, gastrointestinal discomfort, and neutropenia were observed **(42)**.

V. Fluoxetine Pharmacological properties

Fluoxetine, the first SSRI approved in the United States for the treatment of MDD, was made commercially available in 1987.

U.S. Food and Drug Administration (FDA) and the U.K. Medicine and Health Care Products Regulatory Agency (MHRA) maintain that an acceptable risk/benefit relationship exists for fluoxetine for use in the pediatric population for depression **(43)**.

Fluoxetine has no or negligible influence on the ability to drive and use machines. Fluoxetine has been shown not to affect psychomotor performance in healthy volunteers.

Fluoxetine is a selective inhibitor of serotonin reuptake. SSRIs inhibit the serotonin transporter (SERT) at the presynaptic axon terminal. By inhibiting SERT, an increased amount of serotonin (5-hydroxytryptamine or 5HT) remains in the synaptic cleft and can stimulate postsynaptic receptors for a more extended period **(44)** .

Unlike other classes of antidepressants, SSRIs have little effect on other neurotransmitters, such as dopamine or norepinephrine, so they have relatively fewer side effects than TCAs and MAOIs due to fewer effects on adrenergic, cholinergic, and histaminergic receptors.

The mean fluoxetine concentration in children is approximately 2-fold higher than that observed in adolescents. Steady-state plasma concentrations are dependent on body weight and are higher in lower-weight children. As in adults, fluoxetine accumulated extensively following

multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing.

Dose

The starting dose is **10** mg/day. Dose adjustments should be made carefully, on an individual basis, to maintain the patient at the lowest effective dose. After one to two weeks, the dose may be increased to **20** mg/day. If no clinical benefit is achieved within 9 weeks, treatment should be reconsidered.

Withdrawal symptoms (seen on discontinuation of fluoxetine)

Abrupt discontinuation should be avoided. When stopping treatment with fluoxetine, the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions.

If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate. Dizziness, sensory disturbances, sleep disturbances (including insomnia and intense dreams), asthenia, agitation or anxiety, nausea and/or vomiting, tremor, and headache are the most commonly reported reactions. Generally, these symptoms are mild to moderate, self-limiting and usually resolve within 2 weeks.

Contraindications

Hypersensitivity to the active substance or to any of the excipients. Fluoxetine is contraindicated in combination with irreversible, non-selective monoamine oxidase inhibitors (e.g. iproniazid) or in combination with metoprolol used in cardiac failure.

Side effects

The safety and effectiveness in pediatric patients <8 years of age in Major Depressive Disorder and <7 years of age in OCD have not been established.

The most commonly reported adverse reactions in patients treated with fluoxetine were headache, nausea, insomnia, fatigue and diarrhea. Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

- QT interval prolongation and ventricular arrhythmia : rare
- **Serotonin syndrome** (rare): particularly when given in combination with other serotonergic (among others L-tryptophan) and/or neuroleptic drugs. It is characterized by clusters of symptoms such as flushing, tachycardia, hyperthermia, rigidity, myoclonus, autonomic instability, gastrointestinal symptoms (e.g., nausea, vomiting and diarrhea) with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability and agitation progressing to delirium.
- Hemorrhage (rare): fluoxetine, may increase the risk of bleeding reactions. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs,

warfarin, and other anti-coagulants may add to this risk.

- Psychomotor restlessness, anxiety.
- Rash and allergic reactions: Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these reactions were reported to recover completely.
- Weight loss: Weight loss may occur in patients taking fluoxetine, but it is usually proportional to baseline body weight.
- Sexual dysfunction: Includes ejaculation failure, ejaculation dysfunction, premature ejaculation, retrograde ejaculation.

VI. History of using Fluoxetine for MSE

The effect of drugs which manipulate serotonin levels such as selective serotonin reuptake inhibitors (SSRIs) on urination has been noted in recent literature (45)**.**

MacLean, in 1960, while treating emotional problems in a patient, unexpectedly noticed that imipramine (a tricyclic antidepressant drug) improved the patient's enuresis **(46)**.

Mesaros , in 1993, while treating a patient for dysrythmia, also unexpectedly discovered the therapeutic effect of fluoxetine on nocturnal enuresis **(47) .** The Previous studies – before that study - had shown fluoxetine to be somewhat efficacious for obesity and depressive disorders but not for enuresis in adolescents.

In that study, a 15-year-old boy with a history of primary nocturnal enuresis (occurred 6 nights per week) and a positive family history, first presented for therapy for depressive disorder and obesity. He was prescribed 25 mg of imipramine per day to begin with. His weight increased after two weeks, and he was diagnosed with essential hypertension. He was prescribed 40 mg of fluoxetine per day to address dysthymia and obesity. Two weeks later, the patient noticed that his enuresis had completely resolved. He experienced one episode of enuresis every third to fourth week after 24 weeks of fluoxetine 40 mg. He was weaned off and then kept off fluoxetine for eight weeks, which resulted in an increase in enuresis to once a week. His mental state continued to improve gradually, but his weight returned to basal. He was put on fluoxetine 40 mg daily for the following 8 weeks, with the number of enuretic episodes reduced to once every 4 weeks.

After that, it has been reported that children with psychiatric diseases, mainly depression, and nocturnal enuresis received relief of enuretic symptoms with some SSRIs.

Feeney, in 1997, used fluoxetine (Prozac) to treat enuretic symptoms in 2 cases **(48)**.

The first patient was a 13-year-old boy who had anxiety, depression, and ADHD. He also suffered from primary nocturnal enuresis. He was given fluoxetine 20 mg orally once daily, and his enuresis was completely resolved within the first month of treatment. He was observed for a year while on fluoxetine, and he remained symptom-free.

In the second case, an 11-year-old girl was diagnosed with depression, an eating disorder, and

ADHD. She had primary nocturnal enuresis and a prior negative urological workup. She had a total cure of enureric symptoms two weeks after beginning a regimen of fluoxetine 20 mg orally daily. She continued to exhibit an improvement in enuretic symptoms after 9 months of therapy with fluoxetine 40 mg.

Sprenger , in 1997, used sertraline to treat a 13year-old male who presented with history of irritable, angry, and depressed mood, initial and middle insomnia, decreased energy, and impaired concentration **(49).**

The patient reported a minor improvement in mood after one week, but also noticed that enuresis had improved to once every two weeks. His depression symptoms took around 4 weeks to totally resolve. After 5 months of sertraline 50 mg daily, the patient's enuresis has resolved and his depressed symptoms have significantly improved.

That patient's behavior was considerable because of many reasons. First, the patient's response was fairly strong, ranging from nearly every night bedwetting to only once every two weeks when he forgot to take his prescription. Second, the enuresis was unknown to the physician prior to initiating the sertraline, and the sertraline was initiated for the patient's mood disturbance rather than his enuresis. Third, the patient's antienuretic reaction was significantly faster than his antidepressant response. This study might support the presence of a serotonergic mechanism in, which could be at least relatively independent of the serotonergic mechanism in mood disorders.

Murray, in 1997, used paroxetine to treat enuretic symptoms in another case with attention-deficit disorder and poor gross motor coordination **(50)**. Then, many trials reported that fluvoxamine or paroxetine were effective and safe for children with MNE and no psychiatric disease.

Kano, in 2001, investigated The effect of fluvoxamine in 18 children (7 girls, 11 boys) aged between 7 and 13 years with a diagnosis of monosymptomatic nocturnal enuresis and no psychiatric diseases **(51)**.

All patients were treated with motivation therapy, conditional therapy, and bladder retention + training before pharmacological therapy, but these were not effective. They also administered desmopressin in 11 of 18 patients at a dose of 10 to 20 μg intranasally at bedtime for 3 months. In 8 (73%) of these 11 patients, the frequency of nocturnal enuresis decreased.

Fluvoxamine was effective in 14 (78%) of 18 patients. The effectiveness rate of fluvoxamine was similar to that of desmopressin. Fluvoxamine had no serious adverse effects in that small case study .

Toren and collegues were the first to evaluate the efficacy of Fluvoxamine in the treatment of enuresis in children and adolescents by an open label pilot study **(52)**. In their case series, no improvement in the mean voiding frequency of patients was observed. Conversely, 4 of 9 patients showed a trend toward an increase in the frequency of enuresis during treatment. The author concluded that fluvoxamine had no antidiuretic properties.

However, the small number of subjects and mixed target population of the patients should be considered (enuresis as the only focus of clinical attention and enuresis as comorbid to another psychiatric disorder) **(52).**

In 2014, the efficacy of sertraline in treating adolescents with PME refractory to desmopressin at the maximal dosage of 0.6 mg per night was evaluated **(53)**. The trial involved 25 patients ranging in age from 13 to 18 years (mean ± SD = 15.48 ±1.5 yrs.). For 12 weeks, the patients were instructed to take one sertraline (50 mg) oral pill after meal every morning. The medication was tapered by 25 mg every two weeks at the ending of the third month. The final follow-up appointment occurred six months following the end of therapy.

After 6 weeks of therapy, there was a significant decrease in the mean number of wet nights (P=0.01). Nine months after starting sertraline, the overall number of responders was 18 out of 25 (72 %). Twelve individuals had a complete response, while six had a partial response. However, after a 6-month off-sertraline follow-up, they discovered considerable decrease in the response rate compared to the initial results, and 4 (16%) patients relapsed. This decline throughout follow-up shows that sertraline may have a limited effectiveness and its impact may progressively decreased over time.

Only three patients had mild adverse drug effects. Patients who were affected, experienced headaches and nausea. The small sample size, short follow-up duration, and absence of placebo control are the primary drawbacks of this study.

In 2016, A randomized placebo-controlled trial with a double-blind cross-over design was done to compare desmopressin with reboxetine (a selective norepinephrine reuptake inhibitor) **(54)**. The study included 18 individuals ranging in age from 7 to 21 years. Seventeen patients completed the study. They were all suffering from severe enuresis, with at least 7 wet nights out of 14, and had all attempted but failed therapy with desmopressin, enuresis alarms, and anticholinergics. Patients with Non-monosymptomatic nocturnal enuresis were also involved. The patients were treated over three four-week periods: one with reboxetine 4 mg and desmopressin 0.4 mg, one with reboxetine 4 mg and placebo, and one with double placebo.

One patient obtained complete response with reboxetine in monotherapy. Three patients were intermediate responders, while the remaining 13 were non-responders. The number of intermediate responders was five throughout therapy with reboxetine and desmopressin, leaving 12 children non-responders. There were no complete responses to the combined treatment. There was no response to double placebo treatment in any of the participants.

A small number of patients experienced side effects, although they were not serious. Six individuals suffered adverse effects when receiving reboxetine monotherapy, whereas three experienced side effects while receiving reboxetine in combination with desmopressin. The most common negative effects were mood fluctuations and, to a lesser extent, sleeping issues. All negative effects were completely and quickly reversible, and the majority were moderate and temporary.

The study concluded that reboxetine appeared to be less effective than imipramine, raising the question of whether imipramine's serotoninergic activity adds to the substance's efficacy, given that both medications have noradrenergic properties. The small sample size was the study's major limitation.

VII. Effect of fluoxetine on sleep

Serotonin is synthesized from the amino acid L-tryptophan by the enzyme tryptophan hydroxylase. This enzyme is only present in serotonergic neurons. The immediate serotonin precursor 5-HTP is the first step. 5-HTP decarboxylase catalyses the conversion of 5-HTP to 5-HT or serotonin. This conversion can also occur outside the serotonergic neurons. Serotonin is mostly converted to 5-HIAA by the liver. The first step in metabolism is the oxidation by monoamine oxidase to the corresponding aldehyde **(55)**

Serotonin is mainly found in the enteric nervous system which is located in the GIT. However, it is also synthesized in the central nervous system (CNS), particularly in the Raphe nuclei located in the brainstem, Also, serotonin is stored in blood platelets and is released during agitation and vasoconstriction, where it works as an agonist to other platelets.

In 1976, researchers published the first trial of unit recordings from the dorsal raphe nucleus region in spontaneously sleeping cats **(56)**. The serotonergic neurons were most active when awake, and their activity decreased throughout SWS to practically complete stoppage of firing during REM sleep. It was also discovered that stimulating the dorsal raphe nucleus caused wakefulness **(57)**.

5-HT2 receptors are thought to influence thalamic activity toward the single spike activity, i.e. waking. As a result, serotonin acting on 5-HT2 receptors in the thalamus may promote single spike activity and awakening **(58)**. The 5-HT1A receptors are located postsynaptically on many neurones, as well as somatodendritically on dorsal raphe neurons. Stimulation of 5-HT1A receptors via systemic administration of agonists has repeatedly been shown to increase waking.

Pharmaco-EEG analysis had shown mild encephalotropic and activating effects in normals (decreased slow activity) **(59)** . There was a dose-dependent rise in plasma levels up to the 4th to 6th hour, followed by a slow decline, consistent with the reported long half-life. Maximal CNS efficacy occurred between the 8th and 10th hours postdrug.

In a pilot PSG study, 9 depressed patients were tested before and after treatment with an initial dose of 20 mg fluoxetine. If remission did not occur, the dosage was increased to up to 40 mg **(60)**. After treatment, sleep stage 1 and REM latency (the time span between the start of sleeping and the start of REM sleep) were increased, and the REM percentage was decreased. It seems that sleep shifted from **deeper** (non-REM stages 2, 3) to **lighter** stages with more wakefulness. Non-REM-sleep eye movements were observed in sleep stage 1.

In a PSG study, 9 depressed patients receiving 10–80 mg fluoxetine were compared to 6 unmedicated depressed patients. Fluoxetine patients showed prolonged REM latency, and significantly more eye movements and **arousals** during **nonREM** sleep. Eye movement and arousals were significantly correlated **(61)**.

Thirty-four patients with major depression were treated with either fluoxetine 60 mg or amitriptyline150 mg in a double-blind trial. Both drugs showed similar antidepressant effects, but fluoxetine caused significantly **fewer adverse effects**. Concerning sleep, patients treated with fluoxetine showed an increase in the number of

stage shifts and awakenings. REM sleep was significantly decreased **(62)**.

In summary , Regarding PSG measures, fluoxetine increased the number of awakenings , lengthened sleep stage 1 and REM latency, and reduced slow-wave sleep and REM sleep. Some difficulties for instance concerning sleep onset and sleep continuity were most pronounced in the initial days of treatment and decreased thereafter (adaptation phenomena).

Objective awakening quality (attention, concentration, fine motor activity, reaction time performance) in normals showed no decrements after SSRIs as has been described with the classical sedative amitriptyline-type antidepressants **(63)** .

Subjective sleep and awakening quality as rated by observer- and self-rating scales in normal volunteers hardly exhibited any changes after SSRIs, while in patients an improvement was observed.

The main 5-HT center in the brain, the dorsal raphe nuclei (DRN), sends inhibitory afferents to pontine generators of **REM sleep**. During wakefulness and non-REM sleep the 5-HT neurons in the DRN inhibit pontine neuronal generators of REM sleep. Regarding **deep-sleep** stages, the potent 5-HT reuptake inhibition by SSRIs may lead to an activation of the 5-HT2c receptor and therefore decrease deep sleep **(64)** .

VIII. Effect of fluoxetine on Bladder

Spinal reflex circuits involved in voiding function have a dense serotonergic (5-hydroxytryptamine [5-HT]) innervation **(65).** Lumbosacral autonomic, as well as somatic, motor nuclei (Onuf's nuclei) receive a dense serotonergic input from the raphe nuclei **(66)**.

Multiple 5-HT receptors have been found at sites where afferent and efferent impulses from and to the LUT are processed. The main receptors shown to be implicated in the control of micturition are the 5-HT1A, 5-HT2, and 5-HT7 receptors.

Activation of the central serotonergic system can suppress voiding by inhibiting the parasympathetic excitatory input to the urinary bladder, and 5-HT elicits a prolonged activation of thoracic sympathetic preganglionic neurons. Stimulation of the raphe nuclei in the cat inhibits reflex bladder activity **(67)**.

However, in different species, serotonin (5-HT) may have varying functions in the central nervous control of bladder activity. For example, activation of 5-HT1A receptors facilitates reflex bladder activity in rats **(65).**

It has been speculated that selective serotonin reuptake inhibitors (SSRIs) may be useful for treatment of DO/OAB. On the other hand, there are reports suggesting that the SSRIs in patients without incontinence actually can cause incontinence, particularly in the elderly, and one of the drugs (sertraline) seemed to be more prone to produce urinary incontinence than the others.

Patients exposed to serotonin uptake inhibitors had an increased risk (15 out of 1000 patients) for developing urinary incontinence. So far, there are no RCTs demonstrating the value of SSRIs in the treatment of DO/OAB.

In a bladder-irritated model, Duloxetine, which is a combined norepinephrine and serotonin reuptake inhibitor, was demonstrated to enhance the neuronal activity of the urethral

sphincter and the bladder **(68).** Duloxetine seems to have bladder and sphincter effects and has been recommended for the management of stress and urgency incontinence.

Duloxetine enhances neural activity to the External Urethral Sphincter and inhibits bladder activity in cats via Central nervous effects. In a rat experiment, duloxetine improves the urethral continence reflex during sneezing, as demonstrated by an increase in sneeze-induced pressure responses at the middle urethra, however the effect appears to be mediated mostly by α1-adrenoceptors.

In a placebo-controlled trial involving women with OAB, duloxetine demonstrated a significant improvement in voiding and incontinence events, prolongation in daytime voiding intervals, and improvement in quality-of-life scores when compared to placebo. Urodynamic investigations revealed no statistically significant improvements in maximal cystometric capacity or DO volume threshold **(69)**.

IX. Effect of fluoxetine on ADH

In animal studies , Fluoxetine caused a significant increase in AVP concentrations in peripheral plasma as well as a significant increase of AVP concentrations in hypophysial portal plasma **(70)**. These data suggest that increased secretion of ACTH induced by fluoxetine is mediated, at least in part, by an increase in the hypothatanuc secretion of both CRF and AVP.

Peripheral plasma AVP concentrations in rats treated with fluoxetine increased 4-fold within 20 min ($P < 0.05$) and continued to increase throughout the collection period. Also, There were case reports of fluoxetine-induced SIADH in the literature **(71)**.

SIADH is an apparently rare complication of the use of fluoxetine. One study reported three cases of the fluoxetine-induced syndrome of inappropriate secretion of antidiuretic hormone (SIADH). All three cases occurred in elderly psychiatric inpatients treated for depression with standard doses of fluoxetine within one month of starting the medication. All three patients were clinically symptomatic of SIADH. In all three patients the medication was ceased and fluid restriction commenced. One patient required intravenous saline **(71)** .

All three patients recovered fully within three weeks. So that study concluded that The symptoms of hyponatraemia due to fluoxetine-induced SIADH may be difficult to distinguish from the symptoms of depression, unless appropriate laboratory investigations are made.

X. Effect on emotional stress

One of the important etiologies of MNE may be emotional stress, especially in secondary MNE. Children with MNE had an abnormality of the stress barometer (i.e. high values of urinary 17-OHCS and low values of 17-KS-S/17-OHCS). Urinary 17-OHCS acts as a stress barometer and was related to the ‘wear and tear’ of stress, and 17-KS-S acts as a stress barometer and was related to ‘repair and recovery’. Therefore, this stress barometer becomes a marker of a personal reaction to emotional stress. Many reports illustrated that children with MNE in whom antidepressive drugs were effective had an abnormality of the stress barometer (i.e. high values of 17-OHCS and low values of 17-KS-S/17-OHCS).

In one study, the relationship between the stress barometer and the effect of fluvoxamine in children with NE was examined excluding patients with psychiatric diseases **(45)**.

Fluvoxamine showed a complete effect (no wet nights) in 14 of 40 children (35%) with primary MNE and an incomplete effect (a greater than 50% reduction in the number of wet nights in 18 of 40 children (45%). Fluvoxamine showed a complete effect in three of seven children (43%) with secondary MNE, and an incomplete effect in three of seven patients (43%).

Fluvoxamine produced a greater than 50% reduction in the number of wet nights in 26 of 28 children (93%) with primary MNE and abnormality of the stress barometer, and in six of six children (100%) with secondary MNE.

One patient had headache, one had nausea and one had both headache and nausea, but these adverse effects disappeared with continued treatment with fluvoxamine. No serious clinical adverse effects or abnormal laboratory data in blood or urine were noted.

In conclusion, fluvoxamine might be useful clinically for the treatment of children with MNE and an abnormality of the stress barometer because fluvoxamine is more effective than imipramine or desmopressin. Our results also suggest that the stress barometer is useful clinically for evaluating the therapeutic effect of fluvoxamine in children with MNE.

Results

In this review, we have efficiently illustrated the feasibility and safety of using fluoxetine in management of nocturnal enuresis. Enuresis is thought to be caused by a maturational lag in the final development of bladder control. The bladder, kidney, and brain are the three organ systems involved in the pathophysiology of enuresis. The most significant pathophysiological component is the high arousal threshold.

There are many theories of mechanism of action of fluoxetine for the treatment of MSE. The first one is that changes in serotonin levels have specific effects on micturition. Serotonin suppresses ureteral peristalsis and micturition by interacting with spinal reflexes, principally via 5-HT3 receptor agonism. The second theory is the effect of SSRI, Fluoxetine on arousal state during sleep. Many studies confirm that fluoxetine leads to increasing of the number of awakenings, lengthening of sleep stage 1 and REM latency, and reduction of the slow-wave sleep and REM sleep. The third theory is the association between fluoxetine and ADH. Several lines of study have suggested that fluoxetine increases plasma ADH in both humans and animals. The fourth theory is the effect on emotional stress. One of the important etiologies of MSE may be emotional stress, especially in secondary MSE. Fluoxetine was associated with a significant decrease in the stress barometers.

Conclusion

Fluoxetine, a selective serotonin reuptake inhibitor, may be a successful line of treatment for nocturnal enuresis in children. Randomized controlled trials are encouraged to evaluate the safety and efficacy of fluoxetine in management of primary monosymptomatic nocturnal enuresis in children especially in refractory cases.

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