Effectiveness of hypnotherapeutic and pharmacological treatment in primary monosymptomatic enuresis

Efectividad del tratamiento hipnoterapéutico y farmacológico en la enuresis primaria monosintomática

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Abstract:
Background: In primary monosymptomatic enuresis, it is not clear what dynamic changes occur in the efficacy of hypnotherapeutic versus pharmacological treatment plan. Objetive: Determine the changes over time in the effectiveness of hypnotherapy and a pharmacological treatment plan in primary monosymptomatic enuresis. Methods: A prospective, longitudinal and analytical study (time series) was performed on a universe of 119 patients between 7 and 16 years old, with primary monosymptomatic enuresis. 40 patients treated with imipramine and 79 patients with 1 session/1 hour/week of hypnotherapy were evaluated on the frequency of temporal changes of enuretic episodes during 14 weeks of treatments at the Hypnosis Clinic. Results: A logarithmic scale of the distributions of temporal changes in the frequencies of enuretic episodes in hypnotherapeutic and pharmacological treatments is presented, with an enuretic plateau from week 3 to week 6 in hypnotherapy. Conclusions: The hypnotherapeutic treatment was more favorable, as it had an early and efficient response compared to treatment with imipramine.

Keywords: infant enuresis; hypnotherapy; imipramine treatment.

Resumen:
Antecedentes: En la enuresis monosintomática primaria, no está claro qué cambios dinámicos ocurren en la eficacia del plan de tratamiento hipnoterapéutico versus farmacológico. Objetivo: Determinar los cambios dinámicos a lo largo del tiempo en la efectividad de la hipnoterapia y un plan de tratamiento farmacológico en la enuresis infantil no orgánica. Método: Se realizó un estudio prospectivo, longitudinal y analítico (serie temporal) en un universo de 119 pacientes entre 7 y 16 años, con enuresis nocturna no orgánica. 40 pacientes tratados con imipramina y 79 pacientes con 1 sesión / hora / semana de hipnoterapia fueron evaluados en la frecuencia de cambios temporales de episodios enuréticos durante 14 semanas de tratamientos en la Clínica de Hipnosis. Resultados: Se presenta un modelo logarítmico de las distribuciones de cambios temporales en las frecuencias de episodios enuréticos en tratamientos hipnoterapéuticos y farmacológicos, con una meseta enurética desde la semana 3 a la semana 6 en hipnoterapia. Conclusiones: El tratamiento hipnoterapéutico fue más favorable, ya que tuvo una respuesta temprana y eficaz en comparación con el tratamiento con imipramina.

Palabras clave: enuresis infantil; hipnoterapia; tratamiento con imipramina.
Introduction

Nocturnal enuresis often causes considerable distress in patients and in their parents’ lifestyle, and requires a multidisciplinary approach to its management (Sinha & Raut, 2016). A child may also be considered enuretic if the frequency or duration is less, but there is associated distress or functional impairment (Bower et al., 1996; Nevéus, 2011).

As per DSM-V, enuresis is a repeated voiding of urine into bed or clothes, whether intentional or involuntary, during the day or night. The nocturnal-only subtype of enuresis sometimes referred to as monosymptomatic enuresis, is the most common subtype and involves incontinence only during nighttime sleep, typically during the first third of the night. Two types of course of enuresis have been described: a "primary" type, in which the individual has never established urinary continence, and a "secondary" type, in which the disturbance develops after a period of established urinary continence. The behavior is clinically significant manifested by either a frequency of at least twice a week for at least 3 consecutive months or the presence of clinically significant distress or impairment in social, academic (occupational) or other important areas of functioning. To be declared enuresis, the individual must have reached an age in which continence is expected. The chronological age of at least 5 years (or equivalent level of development). It is usually first diagnosed in childhood or adolescence. In this disorder, the behavior is not attributable to the physiological effects of a substance (e.g., a diuretic, an antipsychotic medication) or another medical condition (e.g., diabetes, spina bifida, a seizure disorder) (American Psychiatric Association [APA], 2013. McClellan et al., 2007; Sinha & Raut, 2016).

Nocturnal enuresis is one of the most common diseases in children that can affect their mental health, (Mohammadi et al., 2019). However, there is a variability regarding its epidemiology in different regions. According to Warner et al., 2019, in a study of Danish school children, nocturnal enuresis had a prevalence of 16.8%, being higher (<0.0001) in boys (21.2%) than in girls (12.1%). The overall prevalence of nocturnal enuresis in children from Iran was 10.2% (95% CI: 7-14.8%) (Mohammadi et al., 2019).

In 2017, it was reported that the primary nocturnal enuresis prevalence in Mainland China (7.30%) had increased significantly during the past 10 years (Wang et al., 2019). In Australian pediatric practice, the overall frequency of consultation for enuresis management in children was low (De et al., 2018). In general, boys are more commonly affected than girls, and the condition tends to run in families. (Bower et al., 1996; Nevéus, 2011).

The etiology of functional enuresis has been attributed to many psychosocial factors such as sibling rivalry, disagreement between children and parents, and expressions of hostility, fear, or anxiety (Nevéus, 2011). Due to the lack of a single identifiable cause, various therapeutic modalities have been used for treating enuresis, such as toilet training, pharmacotherapy, psychotherapy, and behavioral therapy (Kaplan & Sadock, 1988). Alarm therapy subjects were more likely than hypnotherapy subjects to achieve dryness (55.3% versus 19.4%, P=0.001) (Seabrook et al., 2000), however, this behavioral therapy and drugs such as desmopressin are...
not available for patients from countries such as Cuba that, due to the US embargo, only have imipramine available.

In comparison with pharmacological methods of treatment, there is evidence that hypnotherapy was an effective alternative or adjunctive form of treatment for enuresis (Edwards & van der Spuy, 1985), and seems to be preferable over the most commonly used medication. (Milling & Costantino, 2000).

Although some studies have showed the highlight effectiveness of hypnotherapy in primary monosymptomatic enuresis (Banerjee et al., 1993), hypnotherapy is often abandoned by subjects after their second or third clinical session because the treatment was not working, and those subjects were categorized as treatment failures (Seabrook et al., 2005) and there is no consensus on the management of enuresis in the results, thus rejecting its applicability (Mellon & McGrath, 2000). Therefore, it is necessary to have studies that make it possible to know in detail the dynamic changes associated with the treatment of enuresis with hypnosis.

According to these results a prospective, longitudinal and analytical study was performed in order to determine the changes over time in the effectiveness of hypnotherapy and a pharmacological treatment plan in primary monosymptomatic enuresis.

**Method**

A prospective, longitudinal and analytical study (time series) was performed a sample of 119 patients between 7 and 16 years old with primary monosymptomatic enuresis. Using a 1:2 simple randomization with a table of random numbers, 40 patients treated with imipramine and 79 patients (1 child not complete the follow-up) with 1 session/1 hour /week of hypnotherapy were selected to evaluate the frequency of temporal changes of enuretic episodes during 14 weeks of treatment at the Hypnosis Clinic of the University of Medical Sciences in Santiago de Cuba.

**Inclusion criteria**

Enuretic patients primary monosymptomatic enuresis according to DSM-V criteria (APA, 2013) without any treatment between the ages of 7 and 16 with voluntary consent from patients and parents to get the treatment.

**Exclusion criteria**

Patients under treatment with other psychotropic drugs and/or with others associated psychiatric disorders or urological pathologies.
**Therapeutic plan with hypnosis**

After the selection of the participants, the Hypnotherapy plan was applied based on the following steps:

First step: The semi-structured interview (week 0).

- It covered various deep topics related to enuresis, as well as personal, social, family, psychological and environmental factors involving the patients and relatives.

Second step. Hypnotic sessions.

- First session (week 1): To start this session, patients must be instructed, in a simple and age-appropriate way, about the anatomy and physiology of the genitourinary system. Then, a susceptibility maneuver (moving hands apart) is done to evaluate the patients’ response and finally hypnosis is applied, leaving them a signal sign and a control map (based on the Token economy (Kazdin, 1982)), to indicate each day whether they experienced bedwetting or not, using a different, previously established symbol for each eventuality.

- Second and other sessions (week 2 until 13): This session included:
  - Psychotherapy support - offered in all the sessions to raise patients’ self-esteem.
  - Use of suggestions through exercises - focused on how to avoid bedwetting. (For example: Every day before going to bed you must do a push-up so that the abdomen becomes strong, and in this way the urine could be retained.) This is symbolic, as well as a visualization process.
  - Regression- looking for some interesting information as a psychotraumatizing factor or as an entity causing enuresis.
  - Metaphors - their use depends on each patients’ social and personal values. They were compared to their preferred or chosen heroes, convincing them that they were equal to them, but that their battle in this case was against enuresis. It was emphasized that they were brave, determined and strong children, that their parents loved them and that willpower leads to miracles.
  - Posthypnotic suggestions - including suggestions given for cognitive behavioral therapeutic recommendations, which are also used by therapists in other fields to improve enuretic conditions. Patients were instructed to do the following before bedtime:
    - To drink less water or liquids two hours before going to bed.
    - To visit the toilet before bed.
    - To do a push-up before bed.

**Pharmacological treatment plan**

After the selection of the participants, the Pharmacological treatment plan was applied based
on the following steps:

First step: The semi-structured interview (week 0).

- It covered various deep topics related to enuresis, as well as personal, social, family, psychological and environmental factors involving the patients and relatives.

Second step. Pharmacological treatment sessions.

- First session (week 1 until 13): Psychotherapy support - offered in all the sessions to raise patients’ self-esteem. Treatment was prescribed at the second session. The control map, based on the Token economy (Kazdin, 1982), and cognitive-behavioral therapeutic recommendations were provided as if they were patients under hypnotherapy. In patients taking imipramine, the minimum dose started at 25 mg and increased to a maximum of 75 mg, in a single dose at 8:00 p.m. for 13 weeks maximum. This dosage was prescribed to avoid adverse reactions.

**Statistical Analysis**

We conducted an a priori power analysis to check which sample size would be adequate for the statistical tests. For the power analysis we used G*Power 3.1 software (Faul et al., 2007). For pharmacological treatment group and hypnotherapy group sample size calculation, a comparative study with hypnosis and imipramine therapy in management of nocturnal enuresis (Banerjee et al., 1993) that report a medium effect (w= .49) (p = .05). Based a power analysis of .80, a sample size of 33 participants would be sufficient to replicate these results, however in our study, the sample for pharmacological treatment was 40 participants and in hypnotherapy group was 79 participants.

With the use of the JASP (Version 0.16) [Computer software https://jasp-stats.org] the statistical analysis was performed. Bivariate (independence) chi-square tests was used to differentiate therapeutics output in hypnotic and pharmacological treatments. Binomial test was used to determine the probability of obtaining 95% therapeutic success in hypnotic and pharmacological treatments. Repeated Measures ANOVA was used with the verification of the assumption of sphericity through the Mauchly test and the multivariate normality to determine weekly dynamic changes within each treatment and the differences between them.

The Octave software 2019 version 5.1.0 (https://www.gnu.org/software/octave/download.html) was used to find the best goodness of fit with the coefficient of determination (R²) of the average distribution of the enuretic episodes during the application of the therapeutic plans, generating in a regressive analysis the estimation equations. Kaplan Meier Survival Analysis with the log-rank test was applied to estimate time of therapeutic effectiveness with univariate chi-square (goodness of fit).
Results

Table 1 showed a chi-square statistic of 3.0934, with a p-value of 0.079 and there were no significant result independency between both treatments. However, the hypnotherapy had a higher probability of obtaining 95% therapeutic success (p<0.05) versus the lower probability present in the imipramine treatment.

Table 1. Therapeutic output in hypnotherapeutic and pharmacological treatment models in primary monosymptomatic enuresis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Therapeutic output</th>
<th>Hypnotherapy (n=79)</th>
<th>Imipramine (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>77</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Significance of the binomial probability of obtaining 95% therapeutic success</td>
<td>*p&lt;.001</td>
<td>p=.138</td>
<td></td>
</tr>
<tr>
<td>Difference in Therapeutic output</td>
<td>Chi-square $X^2=3.094$</td>
<td>p=.079</td>
<td></td>
</tr>
</tbody>
</table>

Before analyzing the results of table 2, compliance with the assumptions was checked with the presence of multivariate normality and the Mauchly test of sphericity indicates that the assumption of sphericity is not fulfilled, therefore, the variances of pairs of differences differ from each other ($X^2 (90) = 1475.556$, p <.05), being thus, the degrees of freedom have been corrected with the Greenhouse–Geisser sphericity estimate, in this case it is less than 0.75 and it is capable of detecting the existence of significant differences. Table 2, with Repeated Measures ANOVA of weekly changes and differences on hypnotherapeutic versus pharmacological treatment models in primary monosymptomatic infant enuresis shows that there is an interaction effect between the weeks of treatment and the type of treatment on the average enuretic episodes ($F (5,022, 587,549) = 5.077$, p <.05, n2 = 0.012), which means
that 1.2% of the variance of the differences in enuretic episodes, depending on the weeks of treatment and the type of treatment, is explained by this relationship. (low effect size). There is a main effect associated with the weeks of treatment, which positively affect the response to treatment with hypnotherapy ($F(5022,587,549) = 191,628$, $p < .05$, $n^2 = 0.471$), that is, 47.1% of the variance of the differences in enuretic episodes as a function of weeks of treatment is explained by this relationship. In the comparison between groups with the different treatments, it is obtained that there are significant differences depending on the type of therapy with imipramine and hypnosis respectively ($F(1,117) = 17.198$, $p < .05$, $n^2 = 0.029$). This effect indicates that 29% of the variance of the differences in enuretic episodes between the groups depending on the type of therapy, is explained by this relationship. The t test for independent groups reports that there are statistically significant differences between treatment with hypnosis and imipramine ($t = -4.147$, $p < .05$). Post hoc tests for peer comparisons indicate that there are statistically significant differences between treatment with hypnosis at week 0 in relation to treatment with imipramine in weeks 0 and in relation to treatment with hypnosis in the rest of weeks. Imipramine treatment at week 0 showed statistically significant differences with this treatment in all weeks.

Figure 1. Repeated Measures ANOVA of weekly changes and differences on hypnotherapeutic and pharmacological treatment models in primary monosymptomatic enuresis.

Figure 2 showed how the temporary changes in the frequency of the enuretic episodes have a logarithmic distribution, both in the pharmacological treatment model ($R^2 = 0.9629$) and in the hypnotherapeutic ($R^2 = 0.8693$), presenting a lower goodness of fit in hypnotherapy, due to the presence of an enuretic peak that shows a therapeutic plateau.
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Figure 2. Logarithmic distribution of hypnotherapeutic and pharmacological treatment models in primary monosymptomatic enuresis.

Table 3 (Kaplan–Meier estimator) shows the effectiveness in the therapeutic response. There is a mild difference in favor of hypnotherapy in week 10 and with imipramine in week 11.

Although significant differences were not found, there is a quick decrease of enuretic episodes with hypnotherapy at earlier times.

Table 3. Estimate time of therapeutic efficacy in hypnotherapeutic and pharmacological treatment models in primary monosymptomatic enuresis.
Discussion

The study of the treatment of nocturnal enuresis with hypnotherapy is essential, as this condition affects around 20% of 5-year-old children (Glazener et al., 2003). It also manifests itself in other age groups, such as adolescence, having a high emotional and psychological cost. However, there is a shortage of research addressing this topic, the size of the samples, as well as the longitudinal monitoring of the response to mind-body therapy (Mellon & McGrath, 2000). Other comparative studies with these therapeutic modalities show a greater percentage of effectiveness for the therapeutic response with hypnotherapy, compared to imipramine (Banerjee et al., 1993). However, these results present limitations due to the lack of systematicity and control over the study’s time, as well as the lack of representativeness in the sample. Similarly, this happens with other study that highlight the use of hypnotherapy in nocturnal enuresis, where visualization and imagery techniques were used and a 6-month follow-up was performed, revealing a remission of enuretic symptoms. However, the sample was small (M.D, 1980).

In our study, treatment with imipramine had favorable results with the same therapeutic response rate in relation to hypnosis. In a study by Banerjee (1993), of the patients treated with imipramine, 76% had a positive response (all dry beds); meanwhile, 72% of patients treated with hypnotic strategies responded positively. However, at the 9-month follow-up, 68% of patients in the hypnosis group maintained a positive response, whereas only 24% of the imipramine group did.

In this sense, results of both treatment responses for nocturnal enuresis were found to have a logarithmic distribution, however, the adjustment is much better with the use of imipramine. Treatment with hypnosis presents less goodness of fit due to an enuretic peak between the 2nd and 4th weeks, then showing a therapeutic plateau in weeks 5 to 8, with a deceleration or a pause in the progress of the response to treatment in that period. This is due to a readjustment process (Cobian M, A.E; 2004) that usually occurs in response to treatment of enuresis with hypnosis therapy.

It is advisable in this period to manage parents concerns about the readjustment process and to emphasize that this is a natural process during the treatment that after this period, a total recovery is guaranteed.

On the other hand, pharmacological treatment is one of the therapeutic models commonly used in the management of childhood enuresis (Glazener et al., 2003). While combined desmopressin plus oxybutynin therapy produces the best and fastest results in childhood bedwetting in comparison with single-drug therapy using desmopressin or Imipramine (Lee Tack et al., 2005), the latter is a useful treatment for bedwetting when all else has failed, especially among older children (Gepertz & Nevéus, 2004).

Until week 13, the frequency of enuretic episodes was lower in hypnotherapy in relation to imipramine. Similar responses were observed between both treatments in the 5th and 6th weeks,
and after the 13th week. According to Gepertz, S., & Neveus, T. (2004), the favorable response to imipramine in individuals who have shown therapeutic resistance will depend on advanced age and the bladder’s low spontaneous capacity, including constipation and a history of daytime incontinence, which are indicators of poor prognosis. Although the imipramine tends to decrease attention deficit and hyperactivity, it has the disadvantage of not being exempt from adverse reactions such as nausea or other minor problems as well as cognitive problems in children after its prolonged use (Glazener et al., 2003).

Other results in this study showed an effective response in reducing the minimum frequency of enuretic episodes, obtained at 10 weeks with hypnotherapy and at 11 weeks with imipramine. Comparative studies on the treatment of nocturnal enuresis with behavioral, tricyclic and hypnosis techniques, show a lower frequency of urination per week with imipramine compared to therapy with hypnosis, in a shorter period of time (Glazener et al., 2003). However, the low relapse that exists in hypnosis therapy stands out, which is attributed to the patients’ practice of self-hypnosis, especially in children under 7 years of age, which favors permanence in time in terms of remission of symptoms. (Banerjee et al., 1993) These results do not differ with our study, as a lower frequency of urination was obtained with hypnotherapy in a shorter period compared to treatment with imipramine. Here it turns out that treatment with imipramine achieves desired effects in terms of stopping urination more quickly when compared to hypnosis.

The usefulness of this study is that it can be given as a recommendation to hypnotherapists for good therapeutic adherence and to reduce the rate of therapy abandonment reported by the literature (Seabrook et al., 2005) that informs patients and parents that there is a stagnation in therapeutic improvement and which is a normal transitory process that lasts from 2 to 3 weeks.

After this period, hypnotherapy guarantees an improvement in symptoms. Future research should be carried out based on the recommendations suggested in this research. The limitations of this study are related to the fact that the sample was not random and that the patients were not followed after having finished the therapies to know if the results lasted over time.

**Conclusion**

After having analyzed the results, we reach the conclusion that there are logarithmic distributions of temporal changes in the frequency of enuretic episodes in hypnotherapeutic and pharmacological treatments, with an enuretic plateau from week 5 to week 8 in hypnotherapy. This lower goodness of fit in hypnotherapy was due to a rearrangement process that naturally occurs as a response to the therapeutic process. Hypnotherapeutic treatment had a more favorable, early and efficient response compared to the treatment with imipramine.
Acknowledgment

Our thanks to the “Dirección de Investigaciones de la Universidad Católica de la Santísima Concepción” for financial support in the language correction process and to Mary Kathleen Hayes for the language correction. Also, our thanks to the “Facultad de Ciencias de la Salud, Universidad Adventista de Chile” for financial support. The author want acknowledgment to Dr. Arthur Hesam Rowshan for the recommendations made to this study.

Referencias


Effectiveness of hypnotherapeutic and pharmacological treatment in primary monosymptomatic enuresis.


Para citar en APA