



Discontinuing absorbent pants in children with bedwetting: a randomized controlled trial

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Abstract

The objective of this study is to examine the effect of discontinuing wearing protective garments (absorbent pyjama pants — APP) in children with severe childhood nocturnal enuresis (NE). The study employs a multicenter, parallel, randomized controlled trial. Following a 4-week run-in period, participants were randomly allocated in a 2:1 group allocation to discontinue or continue using APP. The research was conducted across seven European pediatric incontinence centers. The study included treatment-naïve children aged 4–8 years with severe (7/7 wet nights per week) mono-symptomatic NE, who had used nighttime protection for at least 6 months prior to the study. The study consisted of a 4-week run-in period (± 7 days), where all children slept wearing APP (DryNites®). At week 4 (± 7 days), if meeting randomization criteria (7/7 wet nights during the last week of run-in), participants were randomized to continue to sleep in APP or to discontinue their use for a further 4 weeks, with the option of another 4 weeks in the extension period. The primary outcome was the difference between groups of wet nights during the last week of intervention. Quality of life (QoL) and sleep were secondary endpoints. In total, 105 children (43 girls and 62 boys, mean age 5.6 years [SD 1.13]) were randomized (no-pants group $n=70$, pants group $n=35$). Fifteen children (21%) in the no-pants group discontinued early due to stress related to the intervention. Children in the no-pants group experienced fewer wet nights compared to the pants group during the last week (difference 2.3 nights, 95% CI 1.54–3.08; $p < 0.0001$). In the no-pants group, 20% responded to the intervention, of whom 13% had a full response. Clinical improvement was detected within 2 weeks. Sleep and QoL were reported as negatively affected by APP discontinuation in the extension period but not in the core period.

Conclusion: A ~10% complete resolution rate was associated with discontinuing APP. While statistically significant, the clinical relevance is debatable, and the intervention should be tried only if the family is motivated. Response was detectable within 2 weeks. Discontinuing APP for 4–8 weeks was reported to negatively affect QoL and sleep quality. No severe side effects were seen.

Trial registration: [Clinicaltrials.gov](https://clinicaltrials.gov) Identifier: NCT04620356; date registered: September 23, 2020. Registered under the name: “Effect of Use of DryNites Absorbent Pyjama Pants on the Rate of Spontaneous Resolution of Paediatric Nocturnal Enuresis (NE).”

What is Known?

- APP has been hypothesized to delay time until spontaneous resolution of bedwetting, but no prospective randomized evidence is available regarding if APP use sustains symptoms.
- No evidence whether discontinuation of APP can lead to dryness or impact sleep quality and QoL.

What is New?

- Thirteen percent became dry after removing APP for up to 8 weeks and initial response was detectable within 2 weeks.
- Even though prolonged discontinuation was reported to lead to sleep disturbances and reduced QoL, still our results suggest trying 2 weeks of the intervention if the family is motivated, prior to engaging established treatments for nocturnal enuresis.

Keywords Nocturnal enuresis · Nappy · Nappies · Diaper · Toilet training

Abbreviations

APP	Absorbent pyjama pants
CI	Confidence interval
MMRM	Mixed models for repeated measures

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NE	Nocturnal enuresis
PDSS	Pediatric Daytime Sleepiness Scale
PinQ	Pediatric Incontinence Questionnaire
SD	Standard deviation
TT	Toilet training

Introduction

Background

Nocturnal enuresis (NE) is a common disorder, affecting approximately 7–10% of all 7-year old children [1]. The condition can be distressing [2], negatively affecting self-esteem, and it can lead to bullying and social withdrawal [3]. It thus demands attention and treatment.

Common first-line treatments for NE involve behavioral modifications, standard urotherapy [4], desmopressin and/or conditioning with an enuresis alarm, along with treatment of potential comorbidities [5]. The efficacy of alarm treatment and desmopressin is well established [6, 7], whereas standard urotherapy seems ineffective at least for the monosymptomatic form of NE [8, 9].

The use of absorbent pyjama pants (APP) in coping with NE has been intensely debated in recent years, as some research has suggested that use of APP may prolong the time until spontaneous resolution of the condition [10, 11], but findings are prone to bias, especially due to concurrent toilet training (TT) practices. On the other hand, use of APP is an effective way to reduce the impact of NE and to improve sleep [12].

Guideline recommendations on managing NE are abundant; however, advice on using APP remains limited [13, 14]. Current guidelines suggest periods sleeping without APP, but these recommendations are not scientifically robust [15, 16]. Furthermore, although undocumented, in many countries, healthcare professionals are against using APP to manage NE. The area is controversial, and prospective studies are needed. The intervention of removing APP in children with NE is simple and could be carried out before seeking more established treatments; hence, investigation in children below the age of 6 years might be reasonable.

Until now, no prospective randomized trials have assessed whether use of APP sustains NE symptoms and severity, or whether removal of APP can lead to dryness. Furthermore, no evidence is available regarding the impact of removal of APP on sleep quality and QoL measures.

Objectives and endpoints

We aimed to investigate the effect of continuing or discontinuing use of APP (DryNites®) on NE frequency in children aged 4–8 years with severe primary monosymptomatic NE.

We further aimed to investigate quality of life (QoL) and sleep measures.

Methods

Trial design

An 8-week, investigator initiated, randomized, controlled, open-label, multicenter, two-arm, parallel-group phase IV trial was conducted to assess the effect of discontinuing (no-pants group) versus continuing (pants group) the use of APP on NE symptoms in children with severe NE, with an optional 4-week extension period (Fig. 1).

Participants needed to have 7/7 wet nights in the last week of the run-in period. Eligible participants were then randomly assigned (2:1) to either discontinuation or continuation of APP for the 4-week core intervention period. Full inclusion and exclusion criteria are defined in Table 1. Randomization was performed electronically. Children included were strictly monosymptomatic, as defined by the ICCS [5].

Protocol amendments occurred due to Covid-19 restrictions, permitting remote assessments. Study findings are reported in accordance with the CONSORT 2010 statement [17]. The study was approved by the regional ethical committees in Denmark, Belgium, and the UK (see Supplementary for details) and was carried out according to the declaration of Helsinki. Prior to enrollment, both written and oral informed consent, by both parents, were obtained.

Interventions

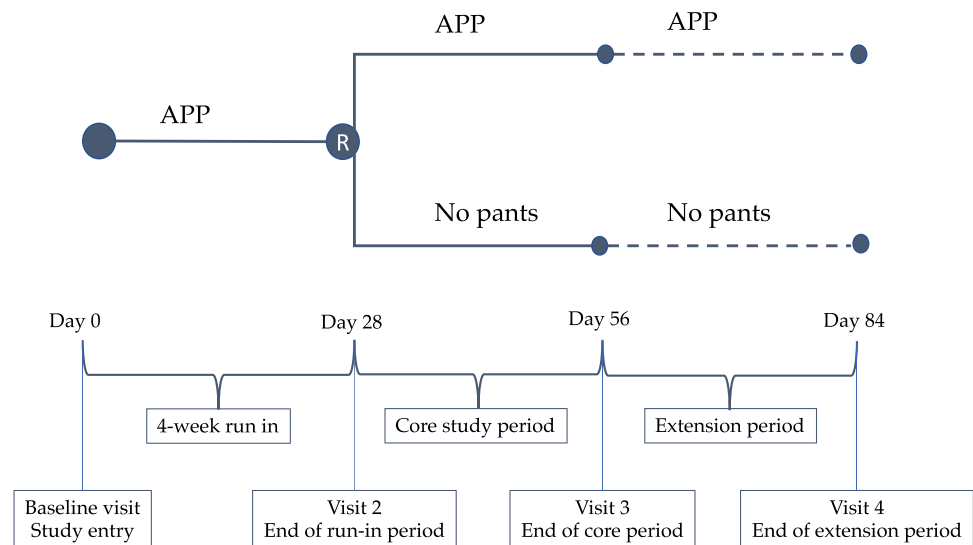
Participants fulfilling the inclusion criteria entered a 4-week run-in period during which they slept wearing the intervention APP. The children sleeping without APP were permitted to sleep with an absorbent bed mat instead. The DryNites® disposable APP was used. APP and bed mats for the study period were supplied to the families by the sponsor. No behavioral changes such as fluid restriction or lifting the child to the toilet when the parents went to bed were allowed in either group. After completing the core intervention period, participants were invited to take part in a 4-week extension period, during which they would remain on their randomly assigned treatment.

Outcomes

Demographic data was collected at enrollment (height, weight, body mass index [BMI]). The primary outcome was the average number of wet nights in the last week of the 4-week intervention period, evaluated using an electronic diary.

The secondary outcomes of quality-of-life (QoL) and sleep parameters were assessed using the following

Fig. 1 Flow of the study. Initially, all participants underwent 4 weeks (± 7 days) in the run-in period. If eligible (wet 7/7 days), the children were randomized to continue or discontinue the use of APP during sleep in the core period. If motivated, the families could choose to enter the extension period for 4 weeks more after the core period. APP, absorbent pyjama pants



validated questionnaires: Pediatric Incontinence Questionnaire (PinQ) [18], World Health Organization Quality of Life Brief Version [19], Pediatric Daytime Sleepiness Scale (PDSS) [20], and Checklist Individual Strength [21].

Study outcomes were recorded using an electronic diary and embedded into an online electronic data capture system, which was accessible from the parents' own devices. Originally, we aimed to analyze the data in two age groups: 4–5 and 6–8 years. However, it proved hard to include children older than 5 years, as the families had already begun or wanted to try more established treatments first. Hence, we changed this aim, and we present data here on all children, 4–8 years of age, combined. Questionnaires were completed jointly by children and parents.

Statistical methods

Analyses were performed with guidance from the IQvia biostatistician team and the core facility Biostatistical Advisory Service at Aarhus University, Aarhus, Denmark.

The primary outcome was assessed by comparing the last 7 days of intervention between groups, and a risk difference was calculated. To handle missing data, imputations, sensitivity and intention-to-treat analyses were performed (see Supplementary for details).

Secondary outcomes were assessed by comparing mean scores and individual items between groups at the different timepoints.

Post hoc analyses were performed for both primary and secondary outcomes, including responder group analyses performed according to the International Children's Continence Society recommendations [22]. Time-to-effect and time-to-dropout were evaluated using time-to-event plots. For full statistical methods, see the Supplementary.

Results

Participant flow and recruitment

Between February 21, 2020, and October 2022, 116 patients were assessed for eligibility, 105 of whom were randomized (Fig. 2). End of follow-up was 2022. After run-in, 70 children were allocated to the no-pants group and 35 were allocated to the pants group. Demographics can be seen in Supplementary Table 1. In total, 85 and 52 children completed the core and extension periods, respectively. No participants experienced severe adverse events.

Primary outcome and estimations of response

The difference in the average number of wet nights between groups after the core and extension periods can be seen in Table 2. In summary, the analyses indicated a significant difference between groups at both the end of the core and the end of the extension period, favoring a lower frequency of enuresis in the no-pants group. In the sensitivity analysis imputed from participant data, the risk difference marginal mean was 0.33 (95% CI 0.22–0.44), which is equivalent to a difference of 2.31 (95% CI 1.54–3.08) wet nights less in the no-pants group at the end of the core period ($p < 0.0001$).

Post hoc responder group results can be seen in Table 3. Results indicated a significant improvement in the no-pants group compared with the pants group in children who completed the study ($p = 0.016$), but this was not significant when using an intention-to-treat analysis ($p = 0.056$). Half of the nine full responders ($n = 5$) achieved a full response during the extension period (Fig. 3).

The time to effect and time to dropout in the intention-to-treat population ($n = 105$) is shown in Fig. 3. Approximately

Table 1 Inclusion and exclusion criteria**Inclusion criteria**

The following criteria must be met for the participant to be enrolled in the study

1. Patient aged between 4 and 8 years at the time of enrolment
2. Have a clinical diagnosis of monosymptomatic primary NE
3. Have been dry in the day for ≥ 6 months prior to enrolment
4. Have on average no more than one dry night per month during the past 6 months at enrolment
5. Using absorbent pants/nappies to manage NE for at least 6 months prior to enrolment
6. Have an informed consent form (ICF) signed by their parent(s)/carer(s)
7. For randomization: have NE 7 nights per week over week 4/last week of the run-in period

Exclusion criteria

Patients meeting ANY of the following criteria are not eligible for participation

1. Children in foster/court care
2. Have implemented any previous intervention to address NE (use of prescribed alarm schedule, desmopressin, imipramine, anticholinergics), or withdrawal of pants/nappies for > 7 days in the previous 6 months
3. Have secondary NE
4. Have wetting in the day
5. Have fecal soiling
6. Have known urinary tract disease
7. Have diabetes
8. Receive any regular intake of medication
9. Have a known developmental/neurological disorder
10. Have links to Kimberly-Clark of any kind (including family relations employed by Kimberly-Clark, holding stocks or shares in Kimberly-Clark)

NE nocturnal enuresis, ICF informed consent form

20% of children experienced a reduction in enuresis frequency of more than 50% compared with baseline in the no-pants group ($n = 70$); most of these children had a visible effect after week 1 of intervention. Approximately 20% of children in the no-pants group could not cope with the intervention and discontinued within the first 3 weeks.

Secondary endpoints and estimations of response

Per-protocol and post hoc analyses were conducted, with mean (SD) and least-squares mean (standard error) values, along with the mixed models for repeated measures (MMRM) models of the included questionnaires — PinQ, PDSS, World Health Organization Quality of Life Brief Version, and CIS (data not shown).

Overall, no findings were significant in the core analysis set, including all randomized participants, in all four questionnaires. Looking to the extension analysis set, only including participants who completed the core and the extension period, the comparison between groups of the total score in the PinQ, between visit 2 and at visit 3, was significantly higher in the no-pants group ($p = 0.029$). This tendency was also seen at visit 2 between the groups; however, this finding was not statistically significant. The MMRM model comparing total scores between groups at

visit 3 showed a significantly higher LS mean in the no-pants group (17.7 (SE 2.2) vs 10.4 (SE 2.4), $p = 0.029$). The same became evident in the extrinsic and intrinsic items at visit 3 of the PinQ ($p = 0.011$ and $p = 0.044$, respectively). The overall MMRM model including data from all visits was significant in the extrinsic score only, comparing no-pants to the pants group (LS mean 4.9 (SE 0.6) vs 2.9 (SE 0.6), $p = 0.019$). These findings suggest a higher impact of the NE in the no-pants group.

In post hoc analysis of PinQ data, no significant difference was found in the total score. In item 11: “*I wake up during my sleep because of my bladder problem,*” the non-responders in the no-pants group had a mean score of 1.9 (SD 1.32) versus 1.11 (SD 1.10) in the pants group ($p < 0.05$), suggesting children were awake for more of their NE episodes in the no-pants group. In a post hoc analysis of the PDSS questionnaire, in item 4: “*How often are you ever tired and grumpy during the day?*,” the mean value for the non-responders in the no-pants group was 1.63 (SD 0.81) compared with 1.17 (SD 0.60) in the pants group ($p = 0.019$), suggesting a significantly higher level of tiredness/grumpiness during the day. In a post hoc analysis, the Checklist Individual Strength questionnaire suggested that items 1: “*I feel tired,*” 7: “*I do quite a lot within a day,*” and 12: “*I feel rested,*” seems more negatively affected in the no-pants group, but not significantly.

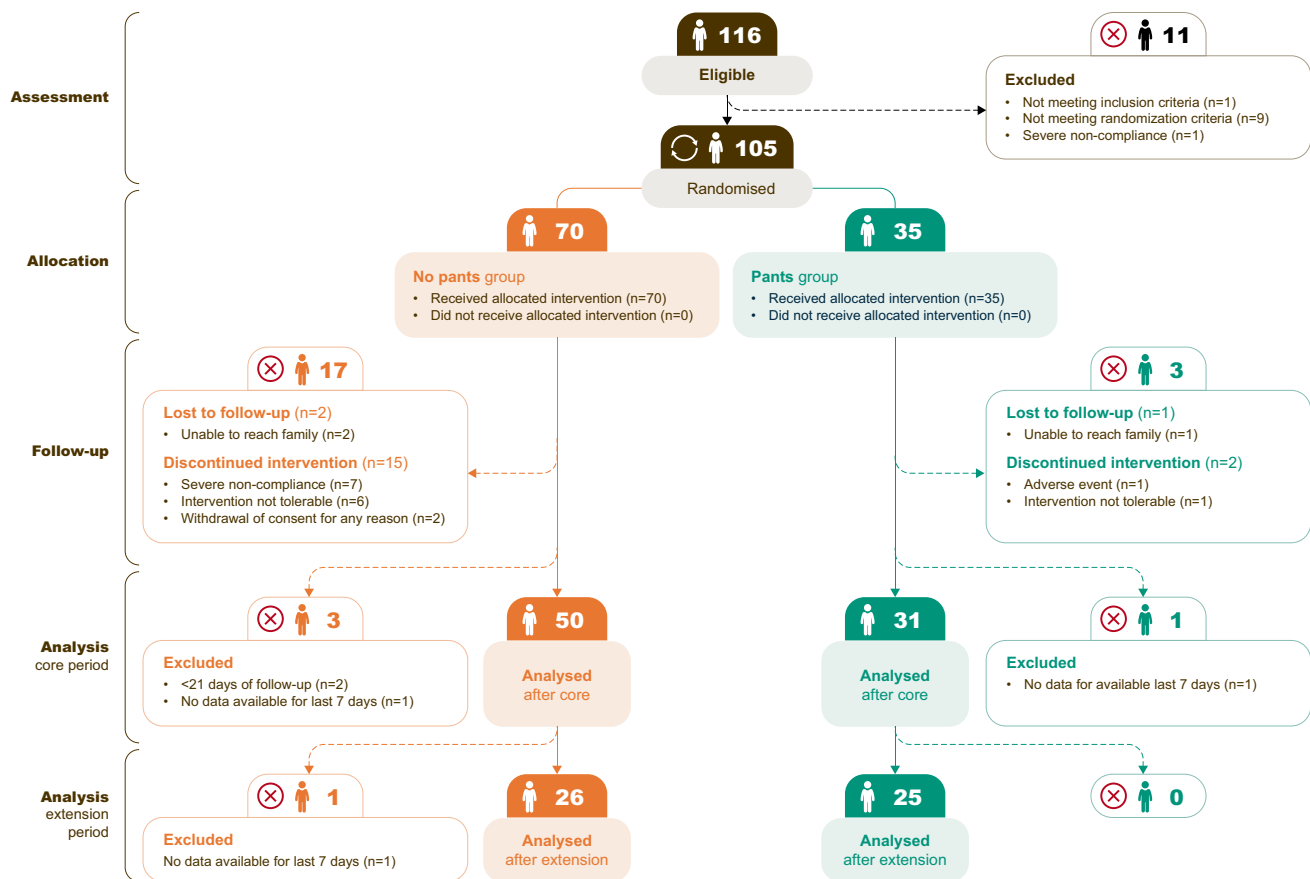


Fig. 2 Overview of children enrolled, randomized, allocation, and reasons for discontinuation following the CONSORT flowchart recommendations

Discussion

In this study, children sleeping without APP had a statistically significantly greater reduction in NE frequency compared with those who continued to use APP. In the no-pants group, 20% of children had $\geq 50\%$ reduction of enuresis frequency. Complete resolution of NE was achieved by 13% of the no-pants group, compared with 3% in the pants group. Response, if any, was seen early in the intervention. QoL and sleep was reported by the families to be negatively affected by the intervention. To our knowledge, this is the first randomized controlled trial investigating the effect of removing absorbent pants on the severity of childhood NE.

The prevalence of NE has been reported to be increasing, especially in countries where the use of APP has recently been adopted, like China [10], and a discussion of whether or not APP have affected this increase, together with a change of practice in TT, is ongoing [23]. Current evidence on the effect of use of APP on incontinence is based upon cross-sectional and retrospective questionnaire studies, and the body of evidence from prospective studies is limited to smaller case studies [24, 25], both of which

suggested a positive effect on incontinence frequency of not using APP. In these studies, the intervention of not using APP was combined with TT, and conclusions on the impact of isolated APP removal are unclear. One large prospective trial performed by van Dommelen et al. [26] investigated the effect of different behavioral interventions in children with NE and identified APP use as a significant risk factor for not responding to the interventions after 6 months of training. Again, conclusions were hard to draw as no randomization was performed regarding APP use. In summary, no prospective evidence has supported the hypothesis that use of APP prolongs NE, as many factors, especially TT practices, are hard to adjust for. The results of the present randomized controlled study suggesting a significantly lower number of wet nights after the intervention are in support of the hypothesis generated from these case and epidemiological studies.

We found a statistically significant reduction in frequency of wet nights of approximately 2 nights per week after 4 weeks of intervention, and approximately 13% of children had a full response after the study period. The efficacy of other, more established first-line treatments for NE (i.e.,

Table 2 Primary outcome results**Last 7 days analysis — crude^a**

Group	End of core period (<i>n</i> = 81)				End of extension period (<i>n</i> = 51)			
	Estimated marginal mean	SE	95% CI	<i>p</i> -value	Estimated marginal mean	SE	95% CI	<i>p</i> -value
Pants	0.96	0.015	0.93–0.99		0.92	0.036	0.85–0.99	
No-pants	0.64	0.052	0.54–0.74		0.47	0.079	0.31–0.62	
Risk difference	Estimate	SE	95% CI		Estimate	SE	95% CI	
Pants — no-pants	0.32	0.054	0.22–0.43	<0.0001	0.45	0.087	0.28–0.62	<0.0001

Last 7 days analysis — sensitivity analysis 1 (all missing values as dry nights)

Group	Estimated marginal mean	SE	95% CI	<i>p</i> -value	Estimated marginal mean	SE	95% CI	
Pants	0.81	0.033	0.74–0.87		0.70	0.063	0.57–0.82	
No pants	0.54	0.047	0.45–0.63		0.36	0.072	0.22–0.50	
Risk difference	Estimate	SE	95% CI		Estimate	SE	95% CI	
Pants — no-pants	0.27	0.058	0.16–0.38	<0.0001	0.34	0.096	0.15–0.52	0.0005

Last 7 days analysis — sensitivity analysis 2 (all missing values as wet nights)

Group	Estimated marginal mean	SE	95% CI	<i>p</i> -value	Estimated marginal mean	SE	95% CI	
Pants	0.97	0.013	0.94–0.99		0.94	0.026	0.87–0.99	
No pants	0.68	0.044	0.61–0.78		0.58	0.058	0.47–0.70	
Risk difference	Estimate	SE	95% CI		Estimate	SE	95% CI	
Pants — no-pants	0.27	0.046	0.18–0.36	<0.0001	0.36	0.064	0.23–0.48	<0.0001

Last 7 days analysis — sensitivity analysis 3 (imputed from participant data)

Group	Estimated marginal mean	SE	95% CI	<i>p</i> -value	Estimated marginal mean	SE	95% CI	
Pants	0.96	0.016	0.93–0.99		0.86	0.056	0.75–0.97	
No-pants	0.63	0.051	0.53–0.73		0.42	0.079	0.27–0.58	
Risk difference	Estimate	SE	95% CI		Estimate	SE	95% CI	
Pants — no-pants	0.33	0.053	0.22–0.44	<0.0001	0.44	0.097	0.25–0.63	<0.0001

Last 7 days analysis — sensitivity analysis 4 (intention-to-treat, all randomized patients included, *n* = 105)

Group	Estimated marginal mean	SE	95% CI	<i>p</i> -value
Pants	0.95	0.018	0.91–0.98	
No-pants	0.72	0.040	0.64–0.79	
Risk difference	Estimate	SE	95% CI	
Pants — no-pants	0.24	0.044	0.14–0.32	<0.0001

SE standard error, CI confidence interval

^aApproximately 25% missing data for the last 7 days

desmopressin and the enuresis alarm) is markedly higher; the proportions achieving full response may reach 50–70% [27, 28]. It is important to stress that the response rates in the present study are obtained in children with severe NE. The

response rates in children with less severe symptoms might be different. Most children experiencing full and partial response after extension obtained some visible effect during the first or second week of intervention. Half of the nine

Table 3 Response groups analysis results

Per protocol		
Children who completed the study		
Response group	No-pants group (n = 50)	Pants group (n = 32)
Full response ^a (%)	9 (18)	1 (3)
Partial response ^b (%)	5 (10)	0 (0)
No response ^c (%)	36 (72)	31 (97)
Chi-square value	8.21, 2 degrees of freedom, $p=0.0164$	
Intention to treat		
All randomized children, missing children (dropouts, non-compliers, non-responders stopping at visit 3) imputed with a probability of 0.961 of being wet		
Response group	No-pants group (n = 70)	Pants group (n = 35)
Full response ^a (%)	9 (13)	1 (3)
Partial response ^b (%)	5 (7)	0 (0)
No response ^c (%)	56 (80)	34 (97)
Chi-square value	5.75, 2 degrees of freedom, $p=0.056$	

^a100% improvement of symptoms

^b50–99% improvement of symptoms

^c< 50% improvement of symptoms

full responders ($n = 5$) achieved a full response during the extension period. This suggest that children experiencing a partial response during the initial weeks of intervention may expect further improvement if continuing the intervention.

Whether children experiencing dry nights start waking up to go to the toilet or simply postpone bladder emptying until the next morning and why this effect is seen so early during the intervention is worth considering. Sleep studies have suggested both an increased arousal index [29] and others that some enuretic children are awake (on electroencephalogram) when emptying their bladder at night [30]. The mechanism could be similar to enuresis alarm treatment, in which the suggested mode of action is the conditioning of bladder-brain communication either by enabling/training the brain to awaken just before bladder emptying occurs or by suppressing the voiding reflex during sleep. In the present study, no systematic registration of nighttime awakenings was performed. However, six participants in the no pants group with treatment response uniformly described several nights with awakenings and nocturia followed by dry nights with uninterrupted sleep. This mode of developing dryness has also been reported in enuresis alarm treatment (Hagstrøm et al. unpublished data).

The spontaneous resolution rate of NE has been calculated to be approximately 15% per year and seems to be stable throughout childhood [31]. However, children with severe NE seems to have a lower resolution rate [32].

Whether or not the rate of resolution is affected by using APP is debatable and beyond the scope of this study as it would require a much longer observation period. Such a study would be very difficult to perform as it would be unethical to continue an intervention if no effect was observed. Another important point is that one participant in the pants group had spontaneous resolution, emphasizing that children can get dry even when sleeping with APP.

The removal of APP was not tolerable in a substantial number of the families, as approximately 20% discontinued early due to inconvenience and/or anxiety related to the intervention.

Discontinuation rates as high as 60% have been reported with use of the enuresis alarm [33]. Between countries, health-care professionals' advice differs regarding APP, spanning from the notion that they may prolong bedwetting [34] to the belief that they are an easy way of coping with NE symptoms until active treatment initiation. Our results suggest that only a small subset of children will benefit from APP removal. We believe that the choice of using APP or not should be the family's decision after appropriate information on the expected outcomes, advantages, and disadvantages along with their evaluation on other existing treatment options.

The secondary outcome questionnaires used were originally not designed specifically to investigate an intervention such as this, and hence, total scores were not expected to be affected. Instead, when analyzing specific questions of interest, we found several significant associations. Overall,

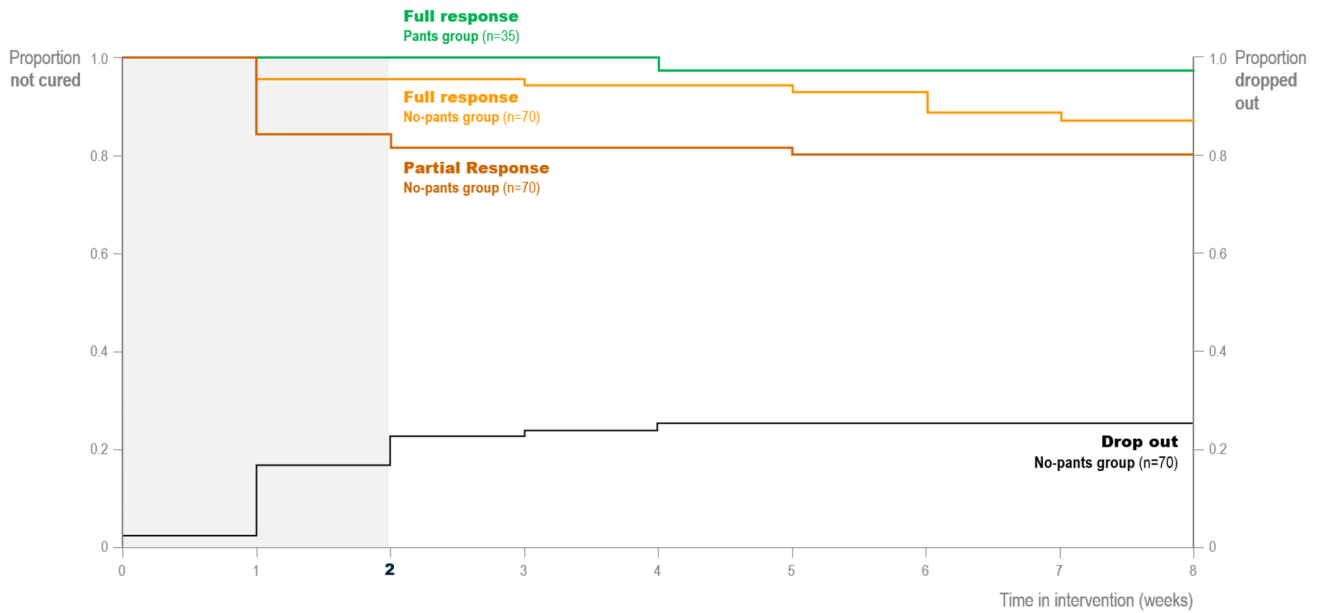


Fig. 3 The different trajectories depict the number of full (orange) and partial (brown) responders in the no pants and the full responders (green) in the pants group. The *x*-axis represents the time in weeks. The *y*-axis to the left shows the proportion of children not cured. The black trajectory depicts the dropout rate, and the *y*-axis to the right

shows the proportion of children who dropped out. Assessments of status were done at the end of each week. If all seven nights in a week were dry, then the child was a full responder for that week; if they had \geq four dry nights, the child was a partial responder; and if they left the study, they were a dropout

in the extension set, QoL was reported to be negatively affected in the no-pants group, and post hoc analyses suggested that children were less rested and had more awakenings in the no-pants group. If the intervention is seen as a potential treatment for NE, discomfort must be expected, as with the enuresis alarm. However, sleeping without APP for longer periods of time without experiencing improvement might be unwise as the intervention may affect daytime energy levels.

Limitations

This study suffered from a skewed dropout rate between groups, most likely due to the inconvenience of the intervention, as well as missing data in diaries. We have statistically attempted to adjust and interpret the findings following appropriate methods and believe that the findings are relatively robust.

Questionnaire data at visit 3 were not obtained in the majority of the families who discontinued early, and this is a clear limitation, as we would expect these families to have reported a higher amount of stress compared with families who actually completed the study. This might explain the smaller difference in questionnaire data in the per-protocol analysis. Furthermore, the questionnaires regarding child QoL [18] and sleep [20] used were not validated for children

down to the age of 4 years, and hence, interpretation should be made cautiously.

The intervention period could have been longer to enable investigation of long-term effects. However, the intervention period was chosen considering well-being of the participants. Also, there might be a possible selection bias in the enrollment, as all families participating were actively seeking help for NE.

This study investigates only children with a prior use of APP, and hence results, especially secondary outcomes, cannot be extrapolated to children who do not use APP or similar to cope with NE.

The mean ages of the children in this study were 5.6 and 5.4 years of age, in the no-pants and pants groups, respectively. We might speculate that the response rates may be different in older age groups, as maturity and developmental stage could potentially influence the response.

Generalizability

As several study centers were spread across Europe, we argue that our findings have a high external validity, and generalization to other children in countries with similar healthcare systems and toileting culture seems appropriate, in children with severe NE.

Conclusion

While statistically significant, the clinical relevance of the modest symptom amelioration achieved by discontinuation is limited, and the decision to attempt the intervention must be based on family motivation. During prolonged (4–8 weeks) discontinuation, unmanaged NE was reported by the families to lower the sleep quality and QoL of caregivers and their children. We propose attempting a 2-week period without APP, continuing if response is obtained. If no response is seen in the families who have used APP prior to the intervention, it is advisable to reinstate APP use to restore sleep quality and QoL in children and caregivers.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00431-024-05502-w>.

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Authors' contributions Dr A.B. collected the majority of the data, assisted in data analysis, drafted the initial manuscript, and critically reviewed and revised the manuscript. Prof S.T., Prof J.V.W., and Dr K.K. conceptualized and designed the study and critically reviewed and revised the manuscript. Dr K.T., Dr C.S.J., Dr L.B., J.R., Dr L.D., and Prof S.H. collected data and critically reviewed and revised the manuscript. J.Z. and D.G.R. reviewed and revised the manuscript critically. Prof S.R. conceptualized and designed the study, helped in data analysis, and critically reviewed and revised the manuscript. All authors had full access to study data, reviewed, edited, and provided final approval of the manuscript content, and had final responsibility for the decision to submit for publication.

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Data availability Availability of the data underlying this publication will be determined later according to Kimberly-Clark's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing". This pertains to scope, time point and process of data access. As such, Kimberly-Clark commits to sharing upon request from qualified scientific and medical researcher's patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for products approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. Interested researchers can use andbre@clin.au.dk to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Data access will be granted to anonymized patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Kimberly-Clark is not involved in the decisions made by the independent review panel. Kimberly-Clark will take all necessary measures to ensure that patient privacy is safeguarded.

Declarations

Ethics approval The study was approved by the local ethical committees in all participating centers and was carried out according to the declaration of Helsinki.

Consent to participate Prior to enrollment, both written and oral informed consents, by all parents, were obtained.

Consent for publication Not applicable.

Competing interests Anders Breinbjerg has received financial support from Kimberly-Clark Corporation to participate in the 2023 ACA conference (Birmingham, UK). Furthermore, Anders Breinbjerg has consulted for Kimberly-Clark Corporation in regards with this study, receiving a research grant. Konstantinos Kamperis has consulted for Kimberly-Clark Corporation and has lectured for Ferring Pharmaceuticals and Novo Nordisk. Debora Garcia Rodrigues and Jin Zhang are employees of Kimberly-Clark Corporation. Søren Rittig has consulted for Kimberly-Clark Corporation. The rest of the authors have nothing to disclose. Study results has been presented as a poster during the ACA conference 2023, Birmingham, UK, and the study is scheduled for oral presentation at the 2023 ICCS conference, Salvador, Brazil.

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