

“Strategy for withdrawal of pharmacological treatment for urinary incontinence in children (StayDry): Protocol for an open-label prospective randomized trial”

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“Strategy for withdrawal of pharmacological treatment for urinary incontinence in children (StayDry): Protocol for an open-label prospective randomized trial”

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Abstract

Background: To the best of our knowledge, no studies have investigated the withdrawal strategy of pharmacological treatment with solifenacin and/or mirabegron in children diagnosed with urinary incontinence that have achieved continence on pharmacotherapy.

Objective: The primary objective is to investigate if abrupt withdrawal versus gradual withdrawal of pharmacotherapy (solifenacin and/or mirabegron) influences the risk of recurrence of incontinence, assessed by a self-reported online 14-day calendar of incontinence episodes.

Methods: Children aged 5-14 years diagnosed with urinary incontinence, treated with pharmacotherapy of solifenacin and/or mirabegron and ready for withdrawal will be randomized 1:1 to either abrupt or gradual withdrawal, according to the medical treatment that the child is receiving.

The primary outcome measure is recurrence of incontinence after withdrawal 1 month after initiation of withdrawal of the physician prescribed medication, assessed by a self-reported online 14-day calendar of incontinence episodes. Additionally, recurrence of incontinence after 3, 6 and 12 months after initiation of withdrawal will be measured.

Results: Recruitment began ultimo May 2024 and will continue until 216 patients are included, which is expected by December 2027. As of January 2025, 20 participants are included.

Conclusions: The results are expected to influence the withdrawal strategy of pharmacological treatment with solifenacin and/or mirabegron in children with daytime urinary incontinence. Clinical Trial: CTIS: EU CT 2023-510280-35-00
ClinicalTrials.gov ID: NCT06465576

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Original Manuscript

Title: “Strategy for withdrawal of pharmacological treatment for urinary incontinence in children (StayDry): Protocol for an open-label prospective randomized trial”

ABSTRACT

Background

To the best of our knowledge, no studies have investigated the withdrawal strategy of pharmacological treatment with solifenacin and/or mirabegron in children diagnosed with urinary incontinence that have achieved continence on pharmacotherapy.

Objectives

The primary objective is to investigate if abrupt withdrawal versus gradual withdrawal of pharmacotherapy (solifenacin and/or mirabegron) influences the risk of recurrence of incontinence, assessed by a self-reported online 14-day calendar of incontinence episodes.

Methods

Children aged 5-14 years diagnosed with urinary incontinence, treated with pharmacotherapy of solifenacin and/or mirabegron and ready for withdrawal will be randomized 1:1 to either abrupt or gradual withdrawal, according to the medical treatment that the child is receiving.

The primary outcome measure is recurrence of incontinence after withdrawal 1 month after initiation of withdrawal of the physician prescribed medication, assessed by a self-reported online 14-day calendar of incontinence episodes. Additionally, recurrence of incontinence after 3, 6 and 12 months after initiation of withdrawal will be measured.

The hypothesis that gradual withdrawal is superior to abrupt withdrawal regarding the risk of recurrence of incontinence will be analyzed by logistic regression.

Results

Recruitment began at the end of May 2024 and will continue until 216 patients are included, which is expected by December 2027. As of February 2025, 25 participants are included.

Conclusions

The results are expected to influence the withdrawal strategy of pharmacological treatment with solifenacin and/or mirabegron in children with daytime urinary incontinence.

Trial registration

EU CT 2023-510280-35-00. ClinicalTrials.gov ID NCT06465576.

Keywords

Urinary incontinence, withdrawal, children, solifenacin, mirabegron

Introduction

Background and rationale

Urinary incontinence is a common condition, affecting up to 21% of children aged 5 to 7 years^[1-4], and 4.5% of children and adolescents aged 11-16 years^[3,4]. The most common cause of urinary incontinence is an overactive bladder^[2,5]. The International Children's Continence Society defines overactive bladder as a condition with urinary urgency with or without urinary incontinence among children and adolescents above 5 years and without competitive pathology explaining the symptoms, such as neurogenic detrusor overactivity or urinary tract infection^[6].

First-line treatment of urinary incontinence is urotherapy, aiming at improving the bladder reservoir function and the voluntary bladder control^[2]. If urotherapy is insufficient for achieving continence, second-line treatment in most clinical settings is addition of pharmacological treatment aiming at

suppressing bladder smooth muscle contraction^[2].

In Denmark the current stepwise pharmacological therapy consists of an antimuscarinic as solifenacin, or a beta3-adrenoreceptor agonist as mirabegron. If monotherapy of solifenacin or mirabegron is without effect, the child is treated with a combination of solifenacin and mirabegron. However, the pharmacological treatment with solifenacin and mirabegron of children with urinary incontinence is only sparsely investigated.

In children with daytime urinary incontinence, solifenacin and mirabegron have demonstrated efficacy in reducing daytime incontinence episodes^[7–13]. Solifenacin and mirabegron are widely used off-label in the pediatric population and only a few studies dealt with efficacy and tolerability of the agents^[7–10,14].

The pharmacological handling of pediatric incontinence is considered temporary, and withdrawal attempts are recommended after continence has been achieved^[15]. There is no generally accepted withdrawal strategy for solifenacin and/or mirabegron in children. Currently, two different withdrawal strategies are being employed in the clinical setting, namely abrupt withdrawal, and gradual withdrawal, where the dosage prescribed is reduced or the interval between dosages given is increased.

Studies report on the differences in withdrawal strategies of antidiuretic therapy targeted at enuresis in pediatric populations, indicating that gradual withdrawal of desmopressin therapy results in prolonged intervals of continence without relapse^[16–19]. One study has reported that gradual withdrawal of solifenacin is superior to abrupt withdrawal in adults^[20]. However, to the best of our knowledge, no studies have investigated the strategy of withdrawal of pharmacological treatment with solifenacin and/or mirabegron in children diagnosed with urinary incontinence that have achieved continence on these pharmaceuticals.

Our study is proposed to ensure an evidence-based approach to a withdrawal strategy for pharmacological treatment with solifenacin and/or mirabegron in children with urinary incontinence.

Objectives

The primary objective is to investigate if abrupt withdrawal versus gradual withdrawal of pharmacotherapy (solifenacin and/or mirabegron) influences the risk of recurrence of incontinence, assessed by a self-reported online 14-day calendar of incontinence episodes.

We hypothesize that gradual withdrawal is superior to abrupt withdrawal regarding the risk of recurrence of incontinence.

Methods

Trial design

This is an open-label prospective randomized trial, allocating participant to each of the three pharmaceutical groups, according to the physician prescribed medical treatment that the child is receiving (solifenacin, mirabegron or solifenacin in combination with mirabegron, see textbox 1). Within each pharmaceutical group, the participant will be randomized 1:1 to the intervention being compared; either abrupt withdrawal or gradual withdrawal.

The study duration for each participant will be 12 months and encompasses 1 virtual meeting and 4 follow-up phone consultations.

Textbox 1. Overview of the pharmaceutical groups, according to the physician prescribed medical

treatment

Group 1		Group 2		Group 3	
Solifenacin		Mirabegron		Solifenacin + mirabegron	
1A	1B	2A	2B	3A	3B
Abrupt withdrawal	Gradual withdrawal	Abrupt withdrawal	Gradual withdrawal	Abrupt withdrawal	Gradual withdrawal

Eligibility criteria

Inclusion and exclusion criteria for this study are provided in textbox 2.

Textbox 2. In- and exclusion criteria

Inclusion
1. The participants' custody holder(s) must voluntarily sign and date an informed consent prior to initiation of any study specific procedures.
2. Age 5 to 14 years (inclusive) at the time of signing the consent and inclusion.
3. Diagnosed with urinary incontinence as per The International Children's Continence Society criteria.
4. Pharmacological treatment with solifenacin and/or mirabegron.
5. Continence has been achieved on pharmacological therapy with solifenacin and/or mirabegron.
6. Previously withdrawal attempts were accepted.
7. Continence remained on the same dosage of medication for a minimum of three months.
8. Continence remained for a minimum of three months (defined as urinary incontinence maximum 1-time á month or less during the last three months), self-reported by the participant and the participants' custody holder(s).
Exclusion
1. Inability of the parent(s) or parental custody holder(s) to understand the Danish written and oral information.
2. Neurogenic detrusor overactivity (neurogenic bladder)

Intervention

Eligible children will be randomized 1:1 to either abrupt or gradual withdrawal of the physician prescribed medication (solifenacin and/or mirabegron), the children have been treated with before entering the study.

Abrupt withdrawal indicates stopping the prescribed medication on the date of withdrawal initiation.

Gradual withdrawal involves taking the prescribed applied dosage of the medication every other day over a period of 14 days, with the complete cessation of the medication occurring 14 days after the gradual withdrawal process begins.

Withdrawal of participants and criteria of discontinuation of study

A study participant should be withdrawn from the study, if at any time one of the following criteria applies:

1. Recurrence of incontinence during course of the study (defined as >2 episodes of

incontinence assessed by a 14-day calendar of incontinence episodes).

2. It is the wish of the participant (or their parents/ parental custody holder(s)) for any reason (withdrawal of informed consent).
3. The discretion of the investigator for safety reasons.
4. Severe compliance to study procedure as described in protocol as judged by the investigator.
5. The investigator judges it necessary due to medical reasons.
6. Participant with a condition and/or a situation that, in the investigator's opinion, may put the participant at significant risk, or may interfere significantly with the participants participation in the study.
7. Participant with any other condition and/or situation, that in the investigator's opinion may be valid for discontinuation from the study.

Primary outcome

The primary outcome measure is recurrence of incontinence after 1 month after initiation of withdrawal of the physician prescribed medication, assessed by a self-reported online 14-day calendar of incontinence episodes. Additionally, recurrence of incontinence after 3, 6 and 12 months after initiation of withdrawal will be measured.

Secondary outcome

Secondary outcome measures are as follows. Development of symptoms occurring after abrupt withdrawal of the prescribed medication (solifenacin and/or mirabegron), assessed by self-reported questionnaires on listed symptoms, as change from baseline up to 30 days after initiation of withdrawal. Development of symptoms occurring after gradual withdrawal of the prescribed medication (solifenacin and/or mirabegron), assessed by self-reported questionnaires on listed symptoms, as change from baseline up to 44 days after initiation of withdrawal. See the appendix for the listed symptoms. The online questionnaires are constructed by the authors and not validated or applying CHERRIES items.

Procedures during the trial

The participant timeline is illustrated in textbox 3.

Textbox 3. Schedule of assessment

	Visit 1 Baseline	Visit 2	Visit 3	Visit 4	Visit 5 End of study
Day	0	30	91	182	365
Visit schedule window	-	± 5 days	± 5 days	± 5 days	± 5 days
Type of consultation	Virtual	Phone call	Phone call	Phone call	Phone call
Informed consent	X				
In- and exclusion criteria	X				
Background information incl. demographics	X				
Randomization	X				
Online 14-day calendar with		X	X	X	X

incontinence episodes					
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Recruitment

The participants will be included from outpatient incontinence clinics at the Department of Pediatrics at Aarhus University Hospital, Aalborg University Hospital, Regional Hospital Kolding, Regional Hospital Esbjerg and Gødstrup Hospital.

Doctors and nurses specialized in urinary incontinence at the involved departments will be asked to screen patients. Possible eligible participants will be carefully informed orally and in writing about the objectives of the study, possible risks, the study procedures, and answer questions regarding the study. Doctors and nurses employed at the involved outpatient clinics will call or send a direct note through the electronic patient journal to the coordinating investigator, site investigator or his/her representative (a nurse with speciality in childhood incontinence, affiliated at the involved paediatric departments and trained in the protocol).

Possible eligible participants and their parents/legal guardians will be contacted directly by the coordinating investigator, the site-investigator or his/her representative. The procedure of obtaining informed contents is elaborated in the section *Informed consent*.

The site-investigator or his/her representative must ensure eligibility.

If a possible participant and their parents/legal guardians are willing to participate after relevant time for consideration, they are invited to visit 1 in the outpatient clinic or by phone or virtual contact. Here, informed oral and written consent from the parents/legal guardians will be obtained and signed and dated by the parents/legal guardians and an investigator.

Informed consent

As a part of the process of obtaining informed consent, it is considered essential that face-to-face communication takes place. If the first visit is a virtual meeting it will take place using Central Denmark Region's virtual meeting application. The virtual meeting application is encrypted to protect the confidential information that will be discussed.

The investigator will carefully explain orally the objectives of the study, possible risks, the study procedures, and answer questions regarding the study. It must be ensured by the investigator that the possible participant or the parents have understood the information, and that consent is informed. The possible participant should be informed within the limits of his/her understanding and with age-appropriate words.

If a possible participant and parents/parental custody holder(s) are willing to participate, informed oral and written consent from the parent/parental custody holder(s) will be obtained, signed and dated by the parents/parental custody holder(s) and the investigator. In case of a virtual visit the informed consent is signed electronically.

Visit 1

Participants will enter the study after providing informed consent by parents/parental custody holder(s).

Background information (incl. age, gender, height, weight, urinary incontinence history, any other medical diagnosis incl. psychiatric diagnosis, any comedication, any withdrawal of comedication)

will be obtained.

The participant will be allocated to each of the 3 pharmaceutical groups, according to the physician prescribed medical treatment that the child is receiving. Within each pharmaceutical group the participant will be randomized 1:1 to the intervention being compared; abrupt withdrawal or gradual withdrawal.

Date of initiation of withdrawal of pharmacotherapy will be decided.

Visits 2, 3, 4 and 5

Follow-up phone consultations with the coordinating investigator or the site-investigator are planned 1-, 3-, 6- and 12-months following initiation of withdrawal.

Data collected at the follow-up visits is status of continence. The participant will fill an online 14-day calendar of incontinent episodes prior to each visit.

Recurrence of incontinence (defined as >2 episodes of incontinence assessed by a self-reported online 14-day calendar of incontinence episodes) or no recurrence of incontinence will be registered.

Questionnaire on withdrawal symptoms

During the study period, participants will be instructed to complete electronic questionnaires regarding withdrawal symptoms associated with withdrawal of medication. The number of times and when the participant must complete the questionnaire is dependent on the allocated withdrawal method (Figure 1). The questionnaires can be completed with assistance from the parents.

Figure 1. A detailed description and timeframe of how questionnaires on withdrawal symptoms should be answered regarding applied withdrawal method.

Abrupt withdrawal

STOP

2 days

7 days

14 days

30 days

Gradual

Pharmaceutical is taken every second day

2 days

7 days

14 days

STOP

16 days

21 days

28 days

44 days

Randomization procedure

Randomization will be performed in the Redcap portal and will occur centrally. An electronic CRF is built for the study data to be entered and for the randomization to be performed. Following written informed consent randomization is stratified by a 1:1 allocation within each stratum using predefined block sizes for sites. Randomization is by a computer-generated random number list.

Statistical analysis

Continuous variables will be presented as median with interquartile range for non-normal distributed data, and as mean $\pm$ standard deviation, for normally distributed data. Categorical data will be presented as number and percentage. Distribution of data will be analyzed using histograms and QQ-plots.

The hypothesis that gradual withdrawal is superior to abrupt withdrawal regarding the risk of recurrence of incontinence will be analyzed by logistic regression.

Two logistic regressions models with different variations of adjustment. One logistic regression model with adjustment of each prescribed medication, as the randomization stratifies within the prescribed medication group. Another logistic regression model in which variables are adjusted due to suspicion of possible effect modification. The degree of adjustment will follow the event per Variable rule. The logistic regression models will be analyzed at data of recurrence or not after 1 month, and hereafter 3, 6 and 12 months for a decreasing population who remain.

Participants with recurrence of urinary incontinence will be described with descriptive statistics.

The secondary outcome of side effects related to withdrawal will be presented with descriptive statistics.

Sample size calculation

To our knowledge, there is no available data regarding the efficacy of withdrawal strategies for pharmacological treatment with solifenacin and/or mirabegron in children diagnosed with urinary incontinence. Few studies have evaluated desmopressin withdrawal in children with enuresis. In lack of alternatives, we have based our sample size calculation on these available desmopressin data, assuming a relapse rate of 40% with abrupt withdrawal of pharmacological treatment and 10% with gradual withdrawal of pharmacological treatment. With a significant level of 0.05 and a power of 80%, the minimal required sample size for adequate power is 64 participants in each group. We expect a maximum dropout rate of 10%. Therefore 72 participants are included in the groups, in total 216 participants.

Ethics Approval

The study is authorized by the authorities The Danish Medicines Agency and The Danish Health Research Ethics Committee and registered at CTIS (EU CT 2023-510280-35-00).

Ethical considerations

To our knowledge, no studies have been performed investigating the potential outcomes of abrupt versus gradual withdrawal of solifenacin and/or mirabegron used by children diagnosed with urinary incontinence. To our knowledge, no literature has assessed the connection between the abrupt withdrawal of antimuscarinic drugs and the development of withdrawal syndrome in children with urinary incontinence.

All pharmacological side effects will be handled in accordance with the Danish legislation. No risk or unknown side effects are expected to medical treatment or withdrawal. The therapeutic potential for future patients justifies the project to be carried out. Participation in this study will not lead to any disadvantages for the patient in their treatment.

The study will be conducted in accordance with the protocol, applicable regulatory requirements according to Good Clinical Practice and the ethical principles of the Declaration of Helsinki. Information regarding the participants is protected and anonymized according to the General Data

Protection Regulation and the actual law.

Safety

Safety evaluation includes registration of adverse events and adverse reactions, additionally serious adverse events and reactions.

Registration

The trial is in accordance with the CONSORT checklist.

CTIS: EU CT 2023-510280-35-00.

ClinicalTrials.gov ID: NCT06465576.

The study is registered at the research inventory of the Regions of Denmark (1-16-02-211-24) and at Aarhus University (ARG-2024-731-23833).

The results will be submitted to CTIS within one year after the end of the trial. Moreover, data will be published in www.clinicaltrialsregister.eu.

Results

The StayDry study is authorized by the authorities. Recruitment began at the end of May 2024 and will continue until 216 patients are included, which is expected by December 2027. As of February 2025, 25 participants are included.

Discussion

Anticipated findings and prior work

This study is designed to provide valuable insights into the optimal withdrawal strategy for solifenacin and mirabegron in children with urinary incontinence, as this trial will fill a significant gap in the current literature.

The existing literature on pharmacological withdrawal in pediatric populations does not exist, particularly regarding antimuscarinics like solifenacin and mirabegron. A more established literature exists on the withdrawal of desmopressin, a treatment used for enuresis. Studies examining the withdrawal of desmopressin therapy in children have found that gradual withdrawal is associated with lower risk of relapse compared to abrupt cessation. Several studies have reported that gradual tapering of desmopressin results in longer periods of continence after discontinuation without relapse^[17–19]. These findings have led to widespread adoption of gradual withdrawal as the preferred approach for discontinuing desmopressin therapy.

Prior research in adult populations has focused on the effects of discontinuing antimuscarinics for overactive bladder^[20], but findings may not be directly applicable to children.

The trial has potential to optimize the medical withdrawal and minimize the risk of recurrence of urinary incontinence after withdrawal of pharmacotherapy. The results are expected to influence the withdrawal strategy of children with urinary incontinence.

Strengths and limitations

The strength of our study is the randomized multicenter design, encompassing five pediatric departments across Denmark. This ensures broad applicability and relevance in daily clinical practice. The study is embedded into and reflects daily clinical practice. The pragmatic design ensures timely inclusion of patients and ensures to exclude participants with relapses of urinary incontinence.

The main limitation is the lack of blinding, which could introduce bias by influencing outcome assessment, or potentially introducing placebo effects. Without blinding, investigators and participants are aware of withdrawal allocation, which can lead to biased behaviour while answering the questionnaires and data interpretation.

Another limitation is no background knowledge about socioeconomic factors.

By conducting the study in real-life settings with medication that is familiar to patients and parents, the findings are more likely to be applicable to clinical practice, as they reflect the challenges and circumstances encountered in routine medical care. Moreover, patients are more likely to adhere to treatment protocols involving medications they are familiar with or have easy access to through standard prescriptions, increasing the feasibility of recruitment and retention in the study.

Conclusion

If gradual withdrawal is superior to abrupt withdrawal, the children with urinary incontinence treated with solifenacin and/or mirabegron, will benefit significantly from this knowledge once children with urinary incontinence are able to start withdrawal of medical treatment.

Acknowledgements

The study participants and their families will not be economically compensated for participating in the study.

Conflicts of interest

Nothing to declare.

Disclosure

Generative AI tools were not used for this study.

Funding Statement

The present study is partly financed by grants from the Health Science Research Fund of Central Denmark Region and by economic support from the involved pediatric departments.

Data Availability

The data sets generated during this study are planned to be available on reasonable request.

Author contributions

All authors contributed to conceptualization, methodology, writing reviewing and editing of the published work. The investigation process and project administration are planned to be performed by SH, KK, LB and AS.

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Appendix Questionnaire on withdrawal symptoms

Dear participant and parents,

Thank you for participating in the StayDry research project. As part of your participation in the project, we would like to ask you to answer this questionnaire. Please tick the statement that best suits you as a participant/your child based on the question.

Have you since last had ...?	Never	Sometime s	Often	Always
Symptoms that may result from treatment with med solifenacin and/or mirabegron				
Dry mouth				

Blurred vision/difficulty seeing clearly				
Discomfort with bright light				
Constipation				
Difficulty urinating				
Heartbeating				
Dizziness				
Falling trend				
Symptoms that may be due to withdrawal of solifenacin and/or mirabegron				
Increased saliva flow				
Nausea				
Vomiting				
Diarrhea				
Urgency				
Increased sweating				
Headache				
Sleep disorders				
Vivid dreams				
Nightmare				
Restlessness				
Anxiety				
Been confused				

Supplementary Files

Untitled.

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URL: <http://asset.jmir.pub/assets/d22d6d6d7193d4ad98ad8337a658856f.docx>

Multimedia Appendixes

Textbox 1. Overview of the pharmaceutical groups, according to the physician prescribed medical treatment.

URL: <http://asset.jmir.pub/assets/2345c2a5c7eea8e1cbef640a5b7b19e8.png>

Textbox 2. In- and exclusioncriteria.

URL: <http://asset.jmir.pub/assets/83565ea61465afb8c140e5a0819f2275.png>

Textbox 3. Schedule of assessment.

URL: <http://asset.jmir.pub/assets/7bed58c6c290e66e84c745219bcef5e1.png>

Questionnaire on withdrawal symptoms.

URL: <http://asset.jmir.pub/assets/a8575ad7ed6cd44161471bc037ad389f.png>

Related publication(s) - for reviewers eyes onlies

Figure 1. A detailed description and timeframe of how questionnaires on withdrawal symptoms should be answered regarding applied withdrawal method.

