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.

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 and up to 12 months follow-up, assessed by 14-day calendar of incontinence episodes.

Results: Participants will be recruited from May 2024 to December 2027.

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: EU CT 2023-510280-35-00.

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Title: “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.

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.

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 and up to 12 months follow-up, assessed by 14-day calendar of incontinence episodes.

Results
Participants will be recruited from May 2024 to December 2027.

Perspectives
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

Keywords
Urinary incontinence, withdrawal, children, solifenacin, mirabegron

Introduction

Background and rationale

The pharmacological handling of pediatric incontinence is considered temporary and withdrawal attempts are recommended after continence has been achieved[1]. 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, wherein the dosage of the drug 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[2]. Several studies have reported on the application of structured withdrawal of desmopressin, indicating that gradual withdrawal of desmopressin therapy results in prolonged intervals of continence without relapse [3 4 5]. 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 of 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.
We hypothesize that gradual withdrawal is superior to abrupt withdrawal regarding the risk of recurrence of incontinence.

Methods and analysis

Recruitment

Recruitment will take place from five outpatient clinics at pediatric departments in Denmark: Aarhus University Hospital, Aalborg University Hospital, Regional Hospital Kolding, Regional Hospital Esbjerg and Gødstrup Hospital.

Study design

This is an open-label prospective randomized trial, allocating participant to each of the three pharmaceutical groups, according to the 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.

Textbox 1. Overview of the groups

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

The study duration for each participant will be 12 months and encompasses 1 virtual meeting and 4 follow-up phone consultations. See figure 1 for an overview of the study design.

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. Diagnose with urinary incontinence as per ICCS 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 are accepted. 7. Continence remained on the same dosage of medication for a minimum of three months.
Exclusion
1. Inability of the patent(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 medication (solifenacin and/or mirabegron), they have been treated with before entering the study.
Abrupt withdrawal indicates stopping the medication on the date of withdrawal initiation.
Gradual withdrawal involves taking the 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 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, behavioral, or administrative reasons.
4. Severe compliance to 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 withdrawal and up to 12 months follow-up, assessed by a 14-day calendar of incontinence episodes.

Secondary outcome

Secondary outcome measures are development of any symptoms related to abrupt or gradual withdrawal symptoms, assessed by a questionnaire on withdrawal symptoms, as change from baseline up to 44 days after initiation of withdrawal.

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	Phonecall	Phonecall	Phonecall	Phonecall
Informed consent	X				
In- and exclusion criteria	X				
Background information incl. demographics	X				
Randomization	X				
14-day calendar with incontinence episodes		X	X	X	X

Visit 1

Participants will enter the study after providing informed consent by parents/parental custody holders.

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 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.

Visit 2, 3, 4 and 5

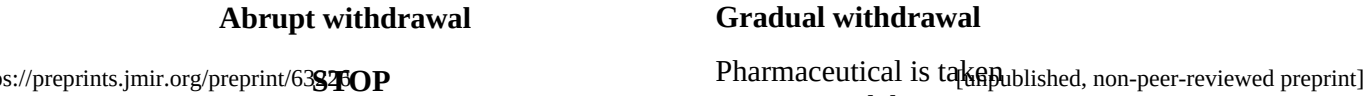
Follow-up phone consultations with the coordinating investigator or the site-investigator are planned 1-, 3-, 6- and 12-months following initiation of withdrawal.

Status of continence by 14-day calendar filled in in advantage.

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 2). 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.



2 days	
7 days	7 days
14 days	14 days
30 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. Block randomization is by a computer-generated random number list.

Statistical analysis

Distribution of data will be analyzed using histograms and QQ-plots. Non-parametric data will be reported as median with interquartile range (IQR) for non-normal distributed data and as mean ± standard deviation (SD) for normally distributed data. Categorical data will be presented as number (%). The primary outcome will be analyzed with Pearsons's test.

Sample size calculation

To our knowledge, there is no available data regarding 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 significance 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

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 anticholinergic and/or 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.

Significant additions or changes to the protocol may be conducted after the application for amendment is approved by the Regulatory Authority and the Ethics Committee. Information regarding the participants is protected according to the General Data Protection Regulation and the actual law.

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 study is registered at CTIS (EU CT 2023-510187-13-00). The results will be submitted to CTIS within one year after the end of trial. Moreover, data will be published in www.clinicaltrialsregister.eu .

Safety

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

Results

The StayDry study is authorized by the authorities. Participants will be recruited from May 2024 to December 2027.

Discussion

Anticipated findings and importance of this research

The strength of our study is the randomized design with the multicenter inclusion at five pediatric departments in Denmark. The study is embedded into and reflects daily clinical practice. The pragmatic design ensures timely inclusion of patients and ensure to exclude participants with relapse of urinary incontinence.

Limitations

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.

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 the 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 they are able to start withdrawal of medical treatment.

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.

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None of the study personnel has any economic interests in the study.

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

Conflicts of interest

Nothing to declare.

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Supplementary Files