Antipsychotics withdrawal in adults with intellectual disability and challenging behaviour: study protocol for a multicentre double-blind placebo-controlled randomised trial

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Abstract

Background: In people with intellectual disability (ID) and challenging behaviour, antipsychotics (AP) are often used off-label and for a long period. Despite a lack of evidence for efficacy for challenging behaviour and concerns about common and clinically relevant side effects, complete withdrawal often fails. We postulate three possible hypotheses for withdrawal failure: 1. Influence of subjective interpretation of behavioural symptoms by caregivers and family; 2. Beneficial effects from AP treatment on undiagnosed psychiatric illness, through improvement in sleep or a direct effect on behaviour; and 3. Misinterpretation of withdrawal symptoms as a recurrence of challenging behaviour.

Methods: To investigate our hypotheses, we have designed a multicentre double-blind, placebo-controlled randomised trial in which AP (pipamperone or risperidone) are withdrawn. In the withdrawal group, the AP dose is reduced by 25% every 4 weeks and in the control group the dose remains unaltered. Behaviour, sleep, psychiatric disorders, withdrawal symptoms and side effects will be measured and compared between the two groups. If drop-out from the protocol is similar in both groups (non-inferiority), the first hypothesis will be supported. If drop-out is higher in the withdrawal group and an increase is seen in psychiatric disorders, sleep problems and/or behavioural problems compared to the control group, this suggests effectiveness of AP, and indications for AP use should be reconsidered. If drop-out is higher in the withdrawal group and withdrawal symptoms and side effects are more common in the withdrawal group compared to the control group, this supports the hypothesis that withdrawal symptoms contribute to withdrawal failure.
Discussion: In order to develop AP withdrawal guidelines for people with ID, we need to understand why withdrawal of AP is not successful in the majority of people with ID and challenging behaviour. With this study, we will bridge the gap between the lack of available evidence on AP use and withdrawal on the one hand and the international policy drive to reduce prescription of AP in people with ID and challenging behaviour on the other hand.

Trial registration: This trial is registered in the Netherlands Trial Register (NTR 7232) on October 6, 2018 (www.trialregister.nl).

Keywords: Intellectual disability, Challenging behaviour, Antipsychotics, Withdrawal, Discontinuation, RCT

Background

Antipsychotic use in people with intellectual disability and challenging behaviour

Soon after the development of antipsychotics (AP) in the 1950s, they started to be prescribed to people with intellectual disability (ID) [1]. At present, AP use is still high in people with ID. Depending on the heterogeneity of the study population, 14–45% of people with ID use AP [2–8]. Only 22.5% of people with ID have a registered indication such as psychotic disorder or psychotic symptoms [2]. Therefore in the majority of people with ID, AP are prescribed off-label, mostly for challenging behaviour and over long periods [2].

The prevalence of challenging behaviour in people with ID is between 12 and 60%, depending on the definition used and type of cohort [9–11]. The most common presentations of challenging behaviour are aggression, destructive behaviour and self-injurious behaviour [9, 10, 12]. Other presentations are shouting, sexual problem behaviour and pica (an eating disorder with persistent ingestion of non-nutritive substances) [9, 11, 13]. The prevalence of challenging behaviour increases with the severity of the ID [10, 12], and is higher in people with autism or communication and/or social problems [10, 12]. Challenging behaviour can also be related to physical problems, such as pain, visual problems, sleep problems and urinary incontinence [12, 14]. Psychiatric disorders, like depression or anxiety disorder, are common in people with ID, but difficult to recognise [15–17]. Particularly in people with moderate, severe or profound ID, psychiatric disorders might present with more diffuse manifestations of symptoms. This may result in diagnostic overshadowing, as symptoms of psychiatric disorders are falsely attributed to the ID itself [18]. The consequence is that people with ID and a psychiatric disorder will not receive the right treatment, which can result in off-label AP use.

Effectiveness of antipsychotics for challenging behaviour in people with ID

Despite the long history, almost no research has been done on the (long-term) effectiveness of AP for challenging behaviour in people with ID. Brylewski et al. (2004) concluded in their Cochrane review that there is no evidence from randomised controlled trials that suggests that AP is either helpful or harmful for adults with ID and challenging behaviour [19]. Their review highlighted a lack of good-quality trials [19]. Tyrer et al. (2008) demonstrated that, after 4 weeks of risperidone, haloperidol or placebo use, aggression decreased in people with ID, with the placebo group showing the greatest improvement [20]. Possible causes for this reduction in aggression were a placebo effect, a psychological effect of an external intervention and/or a spontaneous improvement in their behaviour [20].

Jesner et al. (2007) concluded in their Cochrane review that risperidone can be beneficial for some features of autism in people with and without ID, but the available evidence is limited due to the small sample sizes of the three included studies, the lack of a standardised outcome measure allowing comparison of the studies and a lack of long-term follow-up.

One of the possible positive effects that AP might have is a reduction in sleep disturbances, which are common in people with ID [21]. The sedating effect of AP may improve sleep in people with ID and challenging behaviour [22]. Sleep disturbances are associated with problem behaviour in people with ID [23]. Therefore off-label AP for challenging behaviour may in fact be treating (unrecognised) sleep problems.

Despite the lack of evidence for the effectiveness of AP in reducing challenging behaviour, AP are often prescribed for a long period in people with ID. To illustrate, 78% of the participants in the study of De Kuijper et al. (2010) had used AP for more than 10 years [2].

Relevant side effects of antipsychotics

Although evidence for any effect of the long-term use of AP on challenging behaviour in people with ID is missing, there is convincing evidence that side effects, such as diabetes, metabolic syndrome, extrapyramidal side effects, decreased threshold for seizures, emotional blunting and hyperprolactinemia, are common and clinically relevant [24–27]. The occurrence of side effects is particularly important because this is a vulnerable population with many comorbidities. These side effects are at least partly reversible after withdrawal of AP [25, 28].
Extrapyramidal side effects may frequently be missed in people with ID. Comorbidities such as spasticity, hypertonia, tics or repetitive behaviour make it difficult to distinguish between these comorbidities and extrapyramidal side effects due to AP use. Certain movement disorders, such as akathisia and dyskinesia, can also incorrectly be regarded as challenging behaviour. This can lead to an inadequate treatment with a further increase of the AP dose, while withdrawal is indicated.

Antipsychotic withdrawal
Despite concerns about side effects and questionable efficacy, the successful withdrawal of AP is not self-evident. In a systematic review, it was found that complete withdrawal from off-label AP was achieved in 4–74% of the people with ID and challenging behaviour, and the proportion of unsuccessful attempts to reduce or discontinue AP was between 0 and 96% [29]. The effects of withdrawal on challenging behaviour are not clear. De Kuijper et al. found that mean ABC (Aberrant Behaviour Checklist) ratings improved significantly for those who achieved complete withdrawal, but baseline ABC scores were significantly lower in people who achieved complete withdrawal versus those who had not achieved complete withdrawal [30]. The wide range in the degree of success of withdrawal could be explained by differences in study designs, heterogeneity of study populations, and methodological shortcomings such as lack of a good description of the intervention, small sample size, selection bias, a lack of blinding of the intervention, no control group or no matched control group and incomplete reporting [29].

We hypothesised three possible reasons for AP withdrawal failure [31]. These hypotheses are as follows:

1. Subjective expectations and interpretations of behavioural symptoms by caregivers, the person with ID and their family have an influence. Their perceptions might be influenced by fear of worsening behaviour after AP withdrawal [32]. Subsequently, this influences the interpretation of behaviour, and the attitudes and apprehensions of caregivers and family with respect to the person with ID. This might contribute to the withdrawal outcome. It has been suggested that successful withdrawal depends, at least in part, on staff and environmental characteristics [33].

2. It cannot be excluded that some people with ID and without a registered indication for AP might benefit from AP treatment. AP may be effective for previously undiagnosed psychiatric illnesses for which AP is indicated [17], possibly due to a lack of (adequate) diagnostic procedures and instruments. In addition, AP may have a beneficial effect on (unrecognised) sleep problems [23]. Furthermore, it cannot be excluded that some people with ID and challenging behaviour (without underlying psychiatric disorders or sleep problems) might benefit from AP treatment.

3. When AP are withdrawn after long-term treatment, withdrawal symptoms such as agitation, mania, akathisia, withdrawal-dyskinesia, anxiety and sleep problems may occur [22, 34]. These symptoms may be misinterpreted as recurrence of the original challenging behaviour, resulting in a request to reinstitute AP treatment.

Objectives
The aim of the current study is to unravel the mechanism for AP withdrawal failure by testing these three possible hypotheses. We are therefore currently conducting a double-blind, placebo-controlled randomised AP withdrawal trial in people with ID and off-label AP use for challenging behaviour. In this paper, we describe our study protocol.

To investigate the first hypothesis we will compare the percentage of participants completing the protocol in the withdrawal group (AP dose is reduced gradually) compared to the control group (AP dose is kept the same). This resembles the clinical practice decision process, where the decision to discontinue AP withdrawal is mostly based on the subjective judgement of professional caregivers, physicians and behavioural scientists. If the failure rate is similar (non-inferiority) in both groups, AP withdrawal failure cannot be caused by AP withdrawal effects and our first hypothesis is supported.

To investigate the second hypothesis, the effects of AP on psychiatric, sleep and behaviour symptoms will be compared in both groups. If AP withdrawal unmasks previously undiagnosed psychiatric disorders or sleep problems or results in increased behavioural problems in the withdrawal group compared to the control group, accompanied by increased drop-out in the withdrawal group, our second hypothesis will be supported.

To investigate the third hypothesis, symptoms commonly associated with withdrawal and side effects will be diagnosed and compared in both groups. If these withdrawal symptoms are more common in the withdrawal group, accompanied by increased drop-out in this group, this supports the third hypothesis that withdrawal symptoms contribute to the failure of AP withdrawal.

Methods/design
Setting and design
The study is being conducted within the Academic Collaborative Center ‘Healthy Ageing and Intellectual Disabilities’ (HA-ID). This is a collaboration between three care organisations for people with ID in the Netherlands (Abrona, Amarant and Ipse de Bruggen)
and the Intellectual Disability Medicine research group of Erasmus MC, University Medical Center Rotterdam. In order to include enough participants, we are also recruiting participants within other care organisations (Prinsenstichting and Zideris). The care organisations are located in the west, east and south of the Netherlands. They give support to people with borderline to profound ID.

To investigate our hypotheses, we designed a multi-centre double-blind, placebo-controlled randomised AP withdrawal trial with a non-inferiority design. See Fig. 1 for the flow chart of the study procedures.

**Intervention**

In this study we focus on the withdrawal of risperidone or pipamperone. These AP are the most commonly used AP (over long periods) in people with ID and challenging behaviour in the Netherlands [30]. They are also available in liquid form, enabling gradual dosage adaptation in a placebo-controlled design. For all participants, risperidone or pipamperone tablets will be replaced with medication in a liquid form at the same dose with the same daily administration. If a participant takes the AP more than twice a day, their own physician will be asked to convert it into administration twice a day, in accordance with the prescription policy, before the start of the study. The withdrawal group will have their AP dose reduced by 25% every 4 weeks. In the control group the AP dose will remain unchanged. This is a cautious withdrawal scheme, which has been used in previous studies [30, 33]. We have also opted for this relatively long...
period between dose reductions to extinguish acute withdrawal symptoms [34]. Dose reduction will start 2 weeks after the participant has switched to the liquid form. The blinding of risperidone/pipamperone or placebo will be broken after 22 weeks. Thereafter, participants will be followed for an open-label period of 18 weeks and they will receive their care as usual. In this follow-up period, the participant’s own team of physicians and behavioural scientists decide on the further treatment: e.g. maintaining the withdrawal, restarting AP, maintaining AP or starting AP withdrawal if no withdrawal was done. The total study duration is 40 weeks (or shorter in case of premature breaking of the randomisation; in other words the duration is equal to ‘week of breaking the randomisation’ + 18 weeks). See Fig. 2 for visualisation of the intervention design.

Participants

Inclusion and exclusion criteria
To be included in this study, participants must be 18 years or older, have an ID (IQ ≤ 70), have used off-label AP (risperidone or pipamperone) for challenging behaviour for more than 1 year, and live in homes run by the participating ID care organisations. Their own physician(s) and behavioural scientist(s) will be asked to distinguish between challenging behaviour and a psychiatric diagnosis as indication for AP. For this distinction a review of the medical file is necessary if psychotic symptoms or schizophrenia associated with ID were diagnosed in the past. This is an important consideration given the inclusion and exclusion criteria. People are excluded in the case of a current diagnosis of psychosis, psychotic disorder not otherwise specified, dementia, schizophrenia, an active delirium or a delirium in the past month, a failed attempt to withdraw AP in the last 6 months, and/or usage of more than one AP. Participants are allowed to use co-medication or to start co-medication (except for AP) during the study. Medication changes during the study and indications for prescription will be registered.

Recruitment and informed consent procedure
The physicians of the care organisations will request a list from the pharmacy of people who are 18 years or older and who use monotherapy risperidone or pipamperone. The physician and behavioural scientist will screen this list against the inclusion and exclusion criteria. The physician and behavioural scientist will decide if the potential participant and/or their legal representative may be approached. Reasons why the physician and behavioural scientist decide not to approach potential participants will
be noted anonymously. Individuals who meet the inclusion criteria and may be approached by the physician and behavioural scientist will be asked if they would like to receive the study information. Because not all people with ID are able to give informed consent themselves, their behavioural scientist and/or physician will be asked if the potential participant is able to understand the adapted study information and decide whether to give informed consent for participation. If the potential participant is able to understand the adapted study information and informed consent form, both are sent to the potential participant. If the potential participant is unable to understand the information and unable to give consent for participation, the information and informed consent form will be sent to their legal representative. Also, an information letter will be sent to the professional caregivers of the potential participant by e-mail. If the potential participant and/or their legal representative decline to participate, the reasons why are noted. After permission to participate has been given, participants can withdraw from the study at any time without any consequences.

Randomisation and blinding

The trial pharmacist will randomise the participants with the use of a schedule in Excel. This schedule will be created by an independent biomedical statistician. Participants will be randomly assigned to one of two groups: the withdrawal group or the control group. Block stratification with a size of four will be used to ensure that the participants are properly distributed over both groups. Stratification will take place for the following factors: care organisation (to eliminate possible differences between organisations), pervasive developmental disorders (due to the possible effectiveness of AP [35]), and being able to undergo home polysomnography. Participants, care staff, physicians and researchers are blinded for the allocation to the withdrawal or control group. If premature breaking of the randomisation code is necessary, the physician and behavioural scientist can ask the researchers for this information. Also, the participant and/or legal representative can, after consultation with their own physician and behavioural scientist, ask the researchers for premature breaking of the randomisation code. The trial pharmacist is the only person who can break the randomisation code. The pharmacist will break the randomisation code on the request of a researcher; both functionaries are available 24/7.

Sample size

The primary outcome measure in this study is the percentage of participants completing the protocol in the withdrawal group compared to the percentage in the control group. This will be studied based on a non-inferiority design (the withdrawal group is non-inferior compared to the control group). The sample size is determined using the following formula: 

\[
 n \geq \left( \frac{(p_e(1-p_e) + p_w(1-p_w))}{\delta^2} \right) 
 \times 
 \left( Z_\alpha + Z_\beta \right)^2
\]

where \( p_\text{e} = 0.82 \) is the percentage completing the protocol in the control group; \( p_w \) is the percentage completing the protocol in the withdrawal group. A previous study showed that 82% completed the protocol [38]. Because we assume non-inferiority, \( p_\text{e} = p_w = 0.82 \). We have assumed a drop-out rate in the control group of 20% (based on previous experiences with research in people with ID). We consider a difference of 20% in the drop-out rate between the two groups to be clinically relevant (\( \delta = 0.2 \)). For a power of 0.8 (\( Z_\alpha = Z_{0.2} = .84 \)), one-tailed with \( \alpha = 0.025 \) (\( Z_\alpha = Z_{0.025} = 1.96 \)), we need a sample size of 56 participants in each group (\( n = 112 \) in total). In order to correct for drop-out from the study that is not related to the intervention, we aim to include 10% more (\( n = 122 \)).

Outcome measures and diagnostic measurements

Outcome measures

The percentage of participants completing the protocol in the withdrawal group compared to the control group is the primary outcome measure. Other outcome measures are differences between the two groups in behavioural changes, newly diagnosed psychiatric disorders, sleep problems and side effects/withdrawal symptoms. Data will be collected according to Table 1.

Diagnostic measurements

Most assessments in this study will be performed at baseline, and 2 and 4 weeks after each dose reduction. This is to identify signs and differentiate between acute withdrawal symptoms and other symptoms due to a reduced dose of AP that may only be noticed later. The measurements and questionnaires will be repeated during follow-up at 22 weeks (blinded) and 40 weeks (not blinded). The home polysomnography (done in a subgroup), and measurements for diagnosing movement disorders and psychiatric disorders will be performed less frequently to minimise the burden on the participants. If breaking the randomisation code is required e.g. in case of an emergency or severely challenging behaviour, we will ask if it is possible to assess the participant before breaking the randomisation and try to perform all measurements and complete the questionnaires as would normally be done at week 22 (blinded). The week 40 (not blinded) measurements and questionnaires are then rescheduled 18 weeks later.

Participant characteristics

Data on participants’ characteristics will be collected using questionnaires which are completed by the physician and behavioural scientist. The following characteristics are collected: sex (male/female), age, level of ID (mild (IQ 50–70), moderate (IQ
35–50), severe (IQ 20–35), profound (IQ < 20)), aetiology of ID (syndrome/acquired brain injury/unknown), autism (present/not present/suspicion) and other psychiatric comorbidities (anxiety disorder/depression/other mood disorder/attention deficit hyperactivity disorder/attachment disorder), sleep problems (settling problems/night-waking problems/short sleep/sleep-related breathing problems/nocturnal epilepsy/day napping), neurological comorbidity (epilepsy/spasticity/hypotonia), movement disorders (parkinsonism/dyskinesia/dystonia/akathisia/not otherwise specified), and other medical conditions. Details about the living environment, day programme activities, substance abuse, sleeping habits and support for the AP withdrawal will be collected with questionnaires completed by the participant’s professional caregiver. Data will also be collected on the psychotropic drug history for challenging behaviour, other (AP) withdrawal trials, recorded side effects of AP and the Daily Defined Dose (DDD) of the risperidone or pipamperone. Measurements of blood level of risperidone or pipamperone and a CYP2D6 test will be performed at baseline.

**Behaviour** Behaviour will be measured using the sub-scales of the Aberrant Behaviour Checklist (ABC; Dutch version), completed by the participant’s main caregiver [39, 40]. The ABC is designed to measure severity of behaviour disorders or treatment effects of psychotropic drugs on challenging behaviour [39, 40]. It consists of 58 items spread over five subscales: irritability, hyperactivity, lethargy, stereotypicbehaviour and inappropriate speech. Several studies on the reliability and validity of this instrument have been carried out by the authors as well as by independent researchers [40–46]. The internal
consistency of the subscales is excellent for the ‘hyperactivity’ and ‘lethargy’ subscales, good for the ‘irritability’ and ‘stereotypic behaviour’ subscales, and moderate for the ‘inappropriate speech’ subscale. Differences over time in both groups for the five subscales will be compared.

A Visual Analogue Scale (VAS) for behavioural symptoms and the Checklist Life Events (CLE) will be completed by the participant’s main caregiver as well. The VAS (range 0–10) has been adapted for this current study to measure the severity of one or two individualised target behavioural symptoms. The CLE is a checklist for counting life events and is specially designed for the population of adults with ID (good internal consistency (α = 0.81)) [47]. Subjective participant and caregiver opinions and expectations of withdrawal will be assessed with semi-structured interviews. Questionnaires will be given to caregivers, ID physicians and behavioural scientists to investigate their impression of whether the participant is receiving placebo or verum, and to check for any additional interventions during the study. These semi-structured interviews and questionnaires were compiled by our research group, which consists of ID physicians and behavioural scientists. The Clinical Global Impression - Improvement scale (CG-I), which addresses changes in behavioural functioning, will be completed by the behavioural scientist and the physician to measure the severity of the challenging behaviour (range 1–7; or normal, not at all ill - among the most extremely ill) and is specially designed for the population of adults with ID. Earlier research in people with ID recommended using objective instruments for the measurement of akathisia in addition to the rating lists [57]. Where possible, new objective electronic devices have been added to see if it is feasible to measure preclinical movement disorders in this population in this way.

To detect underlying existing psychiatric disorders that were not previously identified, the Psychiatric Assessment Schedule for Adults with Developmental Disability (PAS-ADD) clinical interview (Dutch version) will be conducted by the researchers with the participant’s main caregiver and, if possible, with the participant himself/herself [49]. The PAS-ADD clinical interview focuses on axis I diagnoses of the DSM-IV (present/not present) and has been validated for people with ID [49]. In addition, the Anxiety, Depression and Mood Scale (ADAMS; Dutch version) will be completed by professional caregivers to detect depressive and anxiety symptoms [50]. This questionnaire is reliable and valid for adults with ID [50, 51]. The feasibility, test-retest reliability, inter-rater reliability and internal consistency are fair to excellent for this population [50, 51].

Sleep Sleep parameters will be measured using actigraphy (Actiwatch, Philips Respironics: Actiwatch 2 and Actiwatch Spectrum Plus) [52, 53]. Actigraphy is a valid method for determining the sleep-wake rhythm in people with ID [52–56]. Participants wear an Actiwatch (a watch-like devise) for seven consecutive days per measurement to detect changes in sleep parameters and sleep problems, in accordance with the procedure followed by Van de Wouw et al. [21].

To explore AP effects on sleep more extensively, home polysomnography will be performed during two consecutive days in a subgroup of participants who can tolerate this (n = 20 in both groups, total n = 40). Polysomnography is the gold standard for sleep assessments. This will be performed at baseline and in week 21. The home polysomnography will take place in the home situation to minimise the burden for the participants. In a home polysomnography limited EEG derivations are combined with the registration of respiratory movements (elastic strap around the abdomen and chest), leg movements (patch electrode on the leg), ECG (patch electrodes on the chest) and transcutaneous oxygen saturation measurement on the finger. The air flow is measured by a sensor under the nose. Home polysomnography has proven to be reliable for comfortable outpatient sleep recording [53].

Movement disorders Movement disorders will be assessed using rating scales and new electronic devices. The rating scales have been chosen for their applicability in the population of adults with ID. Earlier research in people with ID recommended using objective instruments for the measurement of akathisia in addition to the rating lists [57]. Where possible, new objective electronic devices have been added to see if it is feasible to measure preclinical movement disorders in this population in this way.

The following rating scales will be used: the St. Hans rating scale (SHRS) and the Barnes Akathisia Rating Scale (BARS) [58–60]. The SHRS has been validated in psychiatric patients and has a high inter-rater reliability [58, 59]. The SHRS has four subscales: dyskinesia (8 body areas), parkinsonism (8 items), akathisia and dystonia (4 body areas), measured on a 7-point rating scale (range 0–6) [58, 59]. The precise interpretation of the SHRS subscores and total scores is not clear [61]. The scores (range 0–6) for the dyskinesia, parkinsonism and dystonia subscales will be used in our study. The BARS is a rating scale for akathisia; it has a good inter-rater reliability in the psychiatric population and has been used in previous research in people with ID [60, 62]. Akathisia will be defined based on objective symptoms (range 0–3), subjective symptoms (range 0–3) and global clinical assessment (range 0–5) [60].

New electronic devices will also be used to measure bradykinesia, dyskinesia and akathisia. Bradykinesia will be assessed using wireless inertial sensors (Mtw, XSENS). In the psychiatric population, these sensors are valid and reliable when compared with the Unified
Parkinson’s Disease Rating Scale (UPDRS) bradykinesia subscale (a validated rating scale) [63, 64]. Dyskinesia will be measured using a device that assesses dyskinesia by measuring variability in force while applying pressure to a button. This device can measure dyskinesia objectively and reliably [65, 66]. An actigraph (GT3X+), worn on a belt, will be used to measure akathisia. This instrument has been used in the psychiatric population to measure akathisia [67, 68], but has never been used in a population with ID.

Withdrawal symptoms and side effects Withdrawal symptoms and other side effects will be measured with the Matson Evaluation of Drug Side Effects (MEDS). The MEDS is a 90-item validated assessment that can detect side effects of psychotropic drugs in people with ID [69–71]. It includes nine domains: cardiovascular and hematologic effects, gastrointestinal effects, endocrine/genitourinary effects, eye/ear/nose/throat effects, skin/allergy/temperature effects, CNS (central nervous system)-general, CNS-dystonia, CNS-parkinsonism/dyskinesia and CNS-behavioural-akathisia [69]. Each item is rated as to the occurrence, severity and duration [69]. This assessment has been translated into Dutch (using ‘forward and backward’ translation). Furthermore, a physical examination will be performed repeatedly to measure height, weight, waist circumference, blood pressure and heart rate; see Table 1. Blood tests will be performed to give the glucose and lipid profile and determine any metabolic syndrome. Changes in epileptic seizures will be noted during the study.

Data collection and management
All the assessments will be carried out by trained behavioural scientists, ID physicians or trainee ID physicians. Each participant will be measured by the same researcher throughout the entire study period wherever possible. The clinical assessment (height, weight, blood pressure etc.) will be performed by a doctor’s assistant or nurse. Data from these assessments will be collected and stored using a web-based electronic data collection system (OpenClinica). Data from the questionnaires and surveys will be collected using Lime Survey and GemsTracker. These programs are password protected.

Data will be processed and stored for a period of 15 years. At the end of the study, signed informed consent forms and other participant documents will be stored at the participant’s care organisation. Recruitment of the participants started in March 2019 and is still ongoing as at July 2021. We expect to complete data collection by summer 2022.

Statistical analysis
Baseline characteristics, short-term and long-term analyses
Descriptive statistics will be used to present the participant characteristics of the two groups at baseline. Baseline imbalances will be investigated using the independent t-test for normally distributed continuous data, the Mann-Whitney test for non-normally distributed continuous data and the chi-square test for categorical data. We will investigate the short-term (intervention period: baseline – week 22) and long-term (including the follow-up period until week 40) effects of AP withdrawal.

First hypothesis
There will be a 95% Wilson score interval calculated for \( p_c - p_o \). If the upper limit of this interval is below the non-inferiority margin \( \delta \) of 0.2, we will reject the null hypothesis and we will have shown that the success rate in the AP withdrawal group is not lower than in the control group. As an additional analysis, the time to drop-out will be analysed using a Cox proportional hazard model. Non-inferiority is determined as: the upper limit of the two-tailed 95% confidence interval for the withdrawal group’s hazard ratio with respect to the control group is less than 1.25. We will explore if baseline imbalances impact the results, and adjustments will be made if necessary.

Second and third hypotheses
Linear mixed models will be used to evaluate differences between the groups for the sleep, psychiatric and behavioural problems and withdrawal symptoms at the various measurement points. We will use a model in which we assume that the evolution of both groups is the same at baseline and then develops according to a third-degree or smaller polynomial. We will first choose the most suitable correlation structure based on the AIC (Akaike information criterion) and then use the likelihood ratio test to test whether we can simplify the structure of the average profiles. We will explore whether baseline imbalances impact the results and adjustments will be made if necessary. Finally, the mean profiles of both groups will be compared with each other using a likelihood ratio test where the null hypothesis is that they are the same over the entire study period.

Discussion
To our knowledge, this is the first multicentre double-blind, placebo-controlled randomised AP withdrawal trial in people with ID and challenging behaviour aimed at unravelling the mechanisms explaining why off-label AP withdrawal so often fails.

A unique and systematic recruitment method will be used. The aim of this method is to reduce selection bias as much as possible. In previous studies, physicians and/
or behavioural scientists identified potential participants and did not always use a clear, properly described method to do so. In our study, we ask the physicians and behavioural scientists to identify potential participants using the medication lists. After a systematic check of the inclusion and exclusion criteria by their physician and behavioural scientist, potential participants will be approached and asked if they would like to receive the study information. If physicians and behavioural scientists decide not to approach potential participants, the reasons why will be noted anonymously. This ensures that physicians and behavioural scientists think systematically about approaching a participant and/or legal representative for participation and it will prevent them from approaching only those participants who they believe are likely to have a successful withdrawal. Also, the reasons why potential participants and/or their legal representatives decide not to participate will be noted.

It is important to understand why AP withdrawal often fails in people with ID and challenging behaviour. The international policy is to reduce the prescription or continuation of AP in people with ID and challenging behaviour [29, 31]. Because withdrawal of AP often fails, care professionals caring for people with ID are calling for guidelines and interventions supporting AP withdrawal. By assessing the mechanisms explaining why AP withdrawal is often not successful, this study will provide important knowledge about AP use and AP withdrawal that is needed for these guidelines. By conducting this study, we will learn more about the influence of attitudes and apprehension on the AP withdrawal outcome. More knowledge will be obtained about the influence of AP on previously undiagnosed psychiatric disorders, on sleep problems and on behavioural problems. The study will also provide more knowledge about the influence of withdrawal symptoms on AP withdrawal failure.

Evidence regarding AP withdrawal, the effects of AP and AP withdrawal will serve as input for the guidelines and may result in a decrease of off-label AP use in people with ID. Because of the highly prevalent and clinically relevant side effects of AP, AP withdrawal and more consideration prior to starting AP use will result in important health benefits for people with ID.

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Authors’ contributions
SB contributed to the development of the trial design, study protocol, the data collection, overall management and data management. She also wrote the first draft of this article. PH is contributing to the overall management of the study and critically reviewed the versions of the manuscript. AO contributed to the development of the trial design and the statistical analysis plan and critically reviewed the versions of the manuscripts. DM contributed to the development of the trial design, study protocol and funding and critically reviewed the versions of the manuscript. All authors approved the final version for publication.

Authors’ information
Not applicable.

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Availability of data and materials
Generated data or analysed data from the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
Our research is conducted in accordance with the principles of the Declaration of Helsinki (64th WMA General Assembly, October 2013) and in accordance with the Dutch law (Social Support Act and Medical Treatment Agreement Act). Ethical approval of the current study was obtained for all care provider services by the Ethics Committee of the Erasmus University Medical Center Rotterdam in the Netherlands (MEC 2016-336). The Central Committee on research involving human subjects (CCMO) has also issued an extension “No grounds for non-acceptance” to execute this study. The EudraCT number of this study is 2016–002859-19. Written informed consent will be obtained from all participants and/or their legal representatives; see 3.3.2 ‘recruitment and informed consent procedure’. The guideline of the Dutch Association of Intellectual Disability Physicians will be applied if there is resistance during the measurements. This means that if a participant shows verbal or non-verbal resistance before or during a test or measurement, it will not be performed or completed. Behaviour will be interpreted as resistance if behaviour is different from regular behaviour that the participant shows in everyday situations. This will be determined by a caregiver who the participant trusts and knows well.

Abbreviations
ABC: Aberrant Behaviour Checklist (Dutch version AGS); ADAMS: Anxiety, Depression and Mood Scale (Dutch version, ADESS); AP: Antipsychotic(s); BARS: Barnes Akathisia Rating Scale; CGI-I: Clinical Global Impression Depression and Mood Scale (Dutch version, ADESS); AP: Antipsychotic(s); VAS: Visual Analogue Scale

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