Withdrawing off-label antipsychotics in people with intellectual disabilities: why does it fail?

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The study is designed to investigate why withdrawal of off-label antipsychotic drugs for behavioral problems in people with intellectual disability often fails by comparing two blinded groups (withdrawa group versus control group). This has led to...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55806

Source
ToetsingOnline

Brief title
Withdrawing off-label antipsychotics in people with ID

Condition

- Other condition
- Psychiatric and behavioural symptoms NEC

Synonym
people with intellectual disablity and challenging behavior

Health condition

gedragsproblemen bij mensen met een verstandelijke beperking

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ZonMW - GGG- projectnummer 848016008,Via de zorgorganisatie Ipse de Bruggen;Amarant en Abrona; het zogenaamde GOUD-consortium.

Intervention

Keyword: Antipsychotics, Behavior problems / challenging behavior, Intellectual Disability, Withdrawal

Outcome measures

Primary outcome

The primary outcome of the study is the failure rate in both groups, the

reduction group (antipsychotic withdrawal group, placebo) and the control group

(no change in antipsychotic dose).

Secondary outcome

Secundary outcome measures are: interpretation of behavior, challenging

behavior, psychiatric disorders, sleepproblems, movement disorders and

physical symptoms.

They will be measured as follows:

1. Challenging behavior:

- Semi-structured interview

- ABC

- VAS

- CGI

2. Psychiatric disorders:

- ADESS

- PAS-ADD

3. Circadiane rhythm problems:

- Actigraphy

- Somnography

4. Movement disorders:

- specific devices for measuring: dyskinesia, bradykinesia and akathisia

- St. Hans Ratingscale and ARMS

5. Withdrawal symptoms and side effects:

- MEDS interview

- Physical examination

- Laboratory investigation

Other secondary outcomes are:

- CYP polymorphism

- specific devices for measuring for dyskinesia, bradykinesia and akathisia

VERSUS St. Hans Ratingscale and BARS

- physical examinations

Study description

Background summary

In people with intellectual disability (ID), antipsychotics (AP) are often used offlabel,
mostly for challenging behaviour, such as aggression or agitation. Studies in both community (17-
27%) and inpatient (32-56%) settings show that the prevalence of antipsychotic drug use in people with ID

is high [1-4]. AP are often used for a long period (> 10 years in 78 %) [1]. This is remarkable, since, in case of challenging behaviour, there is no evidence for efficacy: a Cochrane review concluded that there was no evidence for the efficacy of AP for behavioural issues in ID [5] and Tyrer and colleagues demonstrated that risperidone, haloperidol and placebo all decreased aggression in patients with ID after 4 weeks, with the placebo group showing the greatest improvement [6]. Although evidence for any effect of long-term use of AP for challenging behaviour in ID is lacking, there is convincing evidence that side effects, such as diabetes, metabolic syndrome, extrapyramidal side effects, decreased threshold for seizures, emotional blunting and hyperprolactinemia, are - also in this population - common and clinically relevant [7-10]. This is particularly important because this is a vulnerable population with preexisting other risk factors for diabetes, metabolic syndrome, movement disorders, epilepsy and osteoporosis. These side effects are - at least partly - reversible after discontinuation of the AP [8, 11]. Despite concerns about side effects and dubious efficacy, successful discontinuation is not self-evident: controlled studies focusing on long-term complete discontinuation of off-label AP drugs for behavioural issues in ID achieved full withdrawal in 33-44% of patients [12, 13]. Strikingly, in these studies, no deterioration of behaviour was found during and after complete or incomplete withdrawal. In order to decrease the prevalence of AP drug use in patients with ID, it is important to understand why discontinuation is not successful in the majority of patients. We postulate 3 possible mechanisms:

1. The influence of the subjective interpretation of behavioural symptoms by caregivers and family: perceptions may be influenced by fear of worsening of behaviour after drug reduction [14]. Subsequently, attitude and apprehension may influence the behaviour of the patient with ID due to interaction, which may in turn contribute to drug reduction outcome. Successful withdrawal depends at least in part on staff and environmental characteristics [12]. In line with these findings, De Kuijper et al demonstrated that, although there was no worsening of behaviour during AP withdrawal as measured with a standardized questionnaire completed by caregivers, caregivers subjectively reported worsening of behaviour during withdrawal,

possibly related to subjective beliefs [13]. However, this may also demonstrate that caregivers detect more
subtle changes in behaviour, for which the questionnaire was not sufficiently sensitive.
2. It cannot be excluded that some patients with ID and behavioural problems might benefit from AP
treatment. Measures used to assess aggressive behaviour, which is an extremely heterogeneous symptom,
may not always be sensitive enough to detect subtle treatment effects. Furthermore AP may be effective for
psychiatric illnesses that remained previously undiagnosed, possibly due to a lack of diagnostic procedures
and instruments. In addition, AP may positively influence (unrecognized) disturbances of the circadian
rhythm (sleep-wake cycle). Circadian rhythm disturbances are relatively common in people with ID [15] and,
since alterations in circadian rhythm are a side effect of AP, AP treatment as well as AP discontinuation
may affect circadian rhythm [16, 17].
3. When AP are withdrawn after long-term treatment, brain Dopamine2 receptors must downregulate. This
takes an unknown amount of time (probably depending on individual differences, and on the dose and
duration of use) [18]. When the withdrawal rate exceeds the downregulating process, withdrawal symptoms
may occur, such as agitation, mania, akathisia, and withdrawal-dyskinesia, due to an excess of input from
dopamine. Also serotonergic, histaminergic, muscarinergic or adrenergic (depending on the type of AP)
withdrawal or rebound symptoms may occur, such as decreased appetite, weight loss, anxiety, sleep
problems, agitation, confusion, flu-like symptoms and psychosis [16]. These symptoms may be
misinterpreted as recurrence of the original challenging behaviour, resulting in a request to reinstitute the
AP.
There is general consensus that reluctance regarding off-label prescribing AP for behavioural issues is
appropriate and that discontinuation of long-term off-label AP should be considered in all patients. There is
an important need for evidence on the above mechanisms in order to develop guidelines, not only for
diagnosis and treatment of behavioural problems in patients with ID, but also for clear indications for
ongoing off-label use or discontinuation of AP, as stated by Tyrer and colleagues in 2014 [19] :
*Drug treatment of challenging behaviour in people with intellectual disability

should no longer be on the
sidelines of evidence based medicine. If we are going to achieve parity of esteem for people with mental
illness, we can no longer tolerate our ignorance on this subject. Quite apart from the deficiencies in
evidence allowing dogma and opinion to rule, the cost of prescribing these drugs is enormous. If they truly
are unnecessary, clinicians, pharmacists, service managers, and those who fund services for people with
intellectual disability need to know, and soon*.

Study objective

The study is designed to investigate why withdrawal of off-label antipsychotic drugs for behavioral problems in people with intellectual disability often fails by comparing two blinded groups (withdrawa group versus control group). This has led to the following primary and secondary objectives.

Primary objective:
- Compare the number of dropouts in both groups (withdrawal versus control group). If these groups have a similar dropout this will supports hypothesis 1.

Secondary objectives:
- Sleep problems, behavioral and psychiatric problems will be compared in both groups. If the antipsychotic withdrawal group have more behavioral problems, more not previously diagnosed psychiatric disorders or sleep problems, antipsychotics may have effect and this will be support hypothesis 2.
- To investigate and compare withdrawal symptoms and side-effects in both groups during withdrawal. If withdrawal symptoms more occur in the withdrawal group (compared with the control group) hypothesis 3 will supported.

Other secondary objectives:
- To investigate patient characteristics that predict outcome of the withdrawal study.
- To evaluate whether in measuring drug induced movement disorders the use of electronic devices is superior to clinical rating scales.
- CYP polymorphism and serum levels of risperidone or pipamperone

Study design

Dubbelblind placebo controlled RCT

Intervention

Withdrawal of antipsychotics (risperidone or pipamperone)

Study burden and risks

The study question can only be studied in this group, because people with ID have specific characteristics. Participation requires effort from the patients for the measurements. In this research there the risks for the participants are similar as care-as-usual.
At the moment is withdrawing antipsychotics (AP) at people with Intellectual Disability (ID) and challenging behavior (off-label use of AP) care- as-usal. Therefore, there will be similar risks as the care-of-usual. The differences are that we will observe them more and when there are problems probably we can differ the therapy because of the addition of different examinations and diagnostics for the underlying problem (eg. sleepproblems, withdrawal symptoms, psychiatric disorders). Participants will have measurements at baseline, week 2, 4, 5, 6, 8, 10, 12, 13, 14, 16, and at follow-up (week 22 and 40). A subgroup of the participants will have repeated measurements of movement disorders at baseline.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Adults, >= 18 years
Intellectual disability, IQ < 70
Living at one of the participating care-organisations
Off-label use of risperidone or pipamperone because of challenging behavior > one year (minimal dosage of 0,2 mg risperidone or 8 mg pipamperone at a time)
ZZP >3

Exclusion criteria

On-label antipsychotic use
Active delirium >1 month
Failed antipsychotic withdrawal last 6 months
Use > 1 antipsychotic

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	01-03-2019
Enrollment:	122

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dipiperone
Generic name:	Pipamperone
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Risperdal
Generic name:	Risperidone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-09-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-08-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-04-2020

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-002859-19-NL
CCMO	NL58568.078.16