AN OPEN LABEL DISCONTINUATION TRIAL OF LONG-TERM USED OFF-LABEL ANTIPSYCHOTIC MEDICATION IN PEOPLE WITH INTELLECTUAL DISABILITY; DETERMINANTS OF SUCCESS AND FAILURE

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Abstract:

Although physicians are aware of the risks of prescribing long-term off-label antipsychotics in people with intellectual disability, attempts to discontinue often fail. This study aimed to identify potential determinants of successful and failed discontinuation. Long-term used off-label antipsychotics were tapered off in 14 weeks with 12.5% of baseline dose every 2 weeks. Participants from living facilities of intellectual disability service providers, aged >6 years with an IQ<70 were eligible to discontinue as judged by their physicians. The primary outcome was achievement of complete discontinuation at 16 weeks; changes in the Aberrant Behavior Checklist (ABC) and its five subscales were secondary outcomes. Potential determinants of success or failure to discontinue antipsychotics were psychotropic drug use and participants’ living circumstances, medical health conditions, severity of behavioral symptoms and of neurological side-effects. Of 499 eligible clients 129 were recruited. Reason for non-participation were clinicians’ concerns that discontinuation might increase challenging behaviors and changes in the clients’ environment. Of the 129 participants 61% had completely discontinued antipsychotics at 16 weeks, 46% at 28, and 40% at 40 weeks. ABC total scores increased in 49% of those with unsuccessful discontinuation at 16 weeks. Autism, higher dose of antipsychotic drug, higher ABC scores and akathisia, and more frequent worsening in health during discontinuation were associated with a lower chance of complete discontinuation. Thus, in a selected sample of participants in whom the responsible clinician felt that discontinuation of antipsychotics could be attempted 40% achieved discontinuation. Physicians should try to address patients’ conditions that may hamper discontinuation.
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ABSTRACT

Although physicians are aware of the risks of prescribing long-term off-label antipsychotics in people with intellectual disability, attempts to discontinue often fail. This study aimed to identify potential determinants of successful and failed discontinuation. Long-term used off-label antipsychotics were tapered off in 14 weeks with 12.5% of baseline dose every 2 weeks. Participants from living facilities of intellectual disability service providers, aged >6 years with an IQ<70 were eligible to discontinue as judged by their physicians. The primary outcome was achievement of complete discontinuation at 16 weeks; changes in the Aberrant Behavior Checklist (ABC) and its five subscales were secondary outcomes. Potential determinants of success or failure to discontinue antipsychotics were psychotropic drug use and participants’ living circumstances, medical health conditions, severity of behavioral symptoms and of neurological side-effects. Of 499 eligible clients 129 were recruited. Reason for non-participation were clinicians’ concerns that discontinuation might increase challenging behaviors and changes in the clients’ environment. Of the 129 participants 61% had completely discontinued antipsychotics at 16 weeks, 46% at 28, and 40% at 40 weeks. ABC total scores increased in 49% of those with unsuccessful discontinuation at 16 weeks. Autism, higher dose of antipsychotic drug, higher ABC scores and akathisia, and more frequent worsening in health during discontinuation were associated with a lower chance of complete discontinuation. Thus, in a selected sample of participants in whom the responsible clinician felt that discontinuation of antipsychotics could be attempted 40% achieved discontinuation. Physicians should try to address patients’ conditions that may hamper discontinuation.

Key words: intellectual disability; antipsychotic drugs; off-label use; discontinuation; determinants; mental health; Psychopharmacology
INTRODUCTION

Individuals with intellectual disability frequently show challenging behavior. Challenging behavior is defined as culturally abnormal behavior of such intensity, frequency, or duration that the physical safety of the person or others is placed in serious jeopardy, or behavior which is likely to seriously limit or deny access to the use of ordinary community facilities. Examples are aggressive or irritable behavior, inappropriate sexual behavior, self-injurious behavior and stereotypic behavior. In Europe antipsychotics are licensed for the treatment of psychosis and symptoms of severe agitation. Besides, the antipsychotic drug risperidone is licensed for the short term treatment of aggressive behavior in adults with intellectual disability and in children aged over five years. In the US risperidone and aripiprazole are also labelled for the treatment of irritability associated with autism. Antipsychotics are often off-label prescribed for long-term treatment of challenging behavior in people with intellectual disability, although there is insufficient evidence for their effectiveness for this treatment target and an increased risk of side-effects in this population.

There is growing awareness among clinicians and policy makers that long-term off-label use of psychotropic drugs for challenging behaviors should be avoided as much as possible. Yet, the prevalence of psychotropic drug use remains high. In a recent study almost 30% of individuals with intellectual disability used psychotropic medication, of which 95% were off-label prescriptions. However, clinicians decided just in half of these cases that their clients were eligible to discontinue the long-term off-label use. Main reasons for deciding against discontinuation were fears for increasing restlessness, aggression, and other behavioral disturbances, the presence of autism, and previously unsuccessful discontinuation attempts. Furthermore, environmental factors, like unfavorable living circumstances, changes in living situations or recent life events were main issues not to discontinue. Indeed, some studies have shown that life events and changes in socio-demographic conditions were associated with challenging behavior and mental ill-health.
Although there is a substantial proportion of long-term off-label antipsychotic drug users in which discontinuation is successful, attempts to discontinue may fail because of behavioral worsening due to a variety of yet unclear causes\textsuperscript{7}. Potential causes may lay in the onset of previously suppressed symptoms of mental or physical disorders. Such symptoms of mental disorders in people with intellectual disability may be misinterpreted as maladaptive behavior. In turn, physicians may react with changes in medication, most often by again increasing dosages and/or adding new psychotropic medications\textsuperscript{8}. Also physical symptoms of chronic or acute medical conditions, including side-effects of medication often remain unrecognized and may present as behavioral disturbance. Furthermore, neurological withdrawal symptoms may occur and hinder successful discontinuation, as these may also express as behavioral symptoms and may be wrongly interpreted, e.g., dyskinesia as restlessness and akathisia as hyperactivity. Indeed, in a previous study caregivers and physicians disagreed in the identification of symptoms of dyskinesia and akathisia\textsuperscript{9}. Last, unsuccessful discontinuation in clinical practice is often attributed to changes in environmental circumstances or unfavorable living circumstances, which may cause clients to react with maladaptive behavior.

Thus, off-label inappropriate antipsychotic drug use should be reduced, while causes of behavioral worsening during discontinuation should be identified and appropriately treated and managed. There is need for more insight in factors that may hinder successful discontinuation of long-term off-label used antipsychotics for challenging behavior. Therefore, we set up a study in which we investigated changes in challenging behavior upon gradual discontinuation of antipsychotics as well as the influence of client-related factors and environmental circumstances as potential determinants for the chance of achieving complete discontinuation.

METHODS

Design and setting

We combined data of two open label discontinuation studies; (1) discontinuation of long term used risperidone prescribed for challenging behavior (Netherlands Trial Register NTR5509) and (2) a
discontinuation study involving all other antipsychotics (NTR5519). Potential participants had received a treatment proposal from their physician involving an attempt to discontinue antipsychotics. All legal representatives of participants had provided written informed consent.

We prospectively investigated the influence of factors potentially associated with successful discontinuation, including changes in environmental circumstances. Study settings were living facilities of six care providing organizations. Two of the six organizations also provided data for the open label discontinuation of risperidone.

**Study population**

Eligible participants could be of any sex or ethnicity, were aged ≥ 6 years, were functioning below an IQ level of 70, and had used one or more antipsychotics for more than one year for challenging behavior. Excluded were subjects with schizophrenia, a bipolar disorder, or an affective psychosis according to the Diagnostic Statistic Manual (DSM)-IV TR or International Code of Diseases (ICD) -10. Another exclusion criterion was an unsuccessful attempt to discontinue the antipsychotics in the previous 6 months, as another attempt to discontinue after a short frame would be unlikely to be successful. Use of other psychotropic drugs was not an exclusion criterion.

**Outcomes**

The primary outcome measure was achievement of complete discontinuation at 16 weeks.

Secondary outcome measures were achievement of complete discontinuation at the time points of 28 weeks and 40 weeks; and changes in the Aberrant Behavior Checklist (ABC) and its five subscales i.e., irritability, lethargy, stereotypic behavior, hyperactivity, and inadequate speech. The ABC is a standardized, validated scale developed to measure severity of challenging behaviors and effects of treatment on the behavior. The ABC was completed by the main caregiver. We defined changes of > 8 points in ABC total scores (0.33 SD) as clinically relevant.
**Determinants**

Potential baseline determinants were psychotropic drug use characteristics (dosage of antipsychotic drug, use of >1 antipsychotic simultaneously, use of other psychotropic, and/or anti-epileptic drugs), participant characteristics (severity of behavioral symptoms as measured with the ABC, presence or history of medical conditions, and presence and severity of extrapyramidal and autonomic neurological side-effects), and environmental circumstances (the presence or history of life events). Potential determinants during discontinuation were the occurrence of new health problems and/or worsening in health or chronic medical conditions, changes in living situation and life events, and the severity of behavioral, extrapyramidal and autonomic symptoms as measured at the different time points of data collection during discontinuation.

For assessment of extrapyramidal symptoms we used items 1 through 9 of the Abnormal Involuntary Movement Scale (AIMS), the Barnes akathisia objective symptoms, subjective symptoms and burden scale (BARS), and motor items 20, 21, 22, and 31 of the Unified Parkinson Scale (UPDRS). Autonomic symptoms were measured by the Scale for Outcomes in Parkinson’s disease-Autonomic Symptoms (SCOPA-AUT), which we slightly adapted by adding two questions on fecal and urine continence. All these scales were completed by a trained research assistant.

To assess worsening in health during the study period we counted the number of times participants experienced new health problems as reported by their caregivers, the number of consultations of participants with their general practitioner, intellectual disability physician, and/or other specialist, the number of new medication prescriptions or dose changes, and the number of new non-pharmaceutical treatments. Also, the number of changes in living circumstances and life events were counted.

**Procedures**

Discontinuation was done by intellectual disability physicians or general practitioners according to a scheduled discontinuation time frame of 14 weeks duration. The discontinuation schedule was based
at our previous study, in which tapering of antipsychotic drugs in a relatively short time frame could safely be done\textsuperscript{12}. The study was performed as part of regular clinical care. This implied that participants remained in the study and data collection was continued to the end of the study follow-up when physicians decided the participant should no longer taper off the antipsychotic drug, should taper off in another time schedule, or should use a higher dose.

Participants were included from 1\textsuperscript{st} of January 2015 till 1\textsuperscript{st} of February 2016. Outcome measures were collected at baseline, at 4, 8, 12, and 16 weeks (during the discontinuation period per protocol) and at 22, 28 and 40 weeks (follow-up) after the first dose reduction.

**Sample size**

The sample size was based on potential associations of determinants with achievement of complete discontinuation by means of logistic regression analyses. With a total of 12 variables and a small effect size of 0.15, a power of 0.80 and a probability level of 0.05 a sample size of 127 was required.

**Statistical analyses**

We used Statistical Package for the Social Sciences (SPSS) version 23 for statistical analyses. The main study parameter was achievement of complete discontinuation at 16 weeks (i.e., 2 weeks after the scheduled complete discontinuation); we also considered achievement of discontinuation at two follow-up time points, i.e., 28 and 40 weeks after the first dose reduction. We distinguished groups with complete and incomplete discontinuation status at the three different time points.

With paired sampled t-tests, we compared baseline severity of behavioral measures and symptoms of neurological side-effects with these at 16, 28, and 40 weeks.
With independent sample T-test for continuous variables and Pearson Chi-square test for categorical variables we compared participants’ characteristics of those with complete and those with incomplete discontinuation at baseline, 16, 28, and 40 weeks, and of those who used typical versus atypical antipsychotics at baseline and 16 weeks.

In case of non-normal distribution of continuous variables we used the Wilcoxon signed rank test for paired sampled test and Mann-Whitney U test for independent sampled test.

To select variables for the multivariate regression analyses we used univariate logistic regression analyses to investigate potential associations of participants characteristics (sex, age, severity of intellectual disability, living situation) and determinants with the odds for complete discontinuation at 16, 28, and 40 weeks, respectively. Subsequently, we used variables with a p-value< 0.1 in multivariate logistic analyses. Here, we used scores of the continuous variables ABC, AIMS, BARS, and UPDRS at the previous time point as baseline determinants for the time point in step wise regression analyses, e.g., ABC score at 16 weeks as baseline value for ABC at 28 weeks.

Finally, we investigated potential associations of neurological side-effects and/or withdrawal symptoms with behavioral symptoms as measured with the ABC subscales in univariate regression analyses at the different time points.

A p-value of <0.05 was used to indicate significant differences.

RESULTS

We included 129 participants. Figure 1 shows the flow chart of the study.

Table 1a shows the baseline participant characteristics, including the presence and severity of extrapyramidal and autonomic symptoms associated with antipsychotic drug use. Table 1b shows the psychotropic drug use of participants. Atypical antipsychotic medication was prescribed in 35% of participants. There was no significant difference in mean baseline dosage between participants who used atypical versus typical antipsychotic drugs. Furthermore, there were no significant differences in achievement of complete discontinuation, in severity of behavioral symptoms as measured with the
ABC, and in severity of extrapyramidal and autonomic symptoms during discontinuation at the time point of 16 weeks after the first dose reduction (time point of scheduled discontinuation) between these groups.

**Achievement of complete discontinuation**

Figure 2 shows the numbers of participants who achieved complete discontinuation of their long-term off-label antipsychotic drug use at 16 weeks (discontinuation per protocol), and at 28 and 40 weeks after the first dose reduction.

Of the 79 participants who completely discontinued antipsychotics at 16 weeks, 25 participants (32%) restarted the use of antipsychotics between 16 and 28 weeks. Of those 60 participants who were completely off antipsychotics at 28 weeks, 8 (13%) restarted the use between 28 and 40 weeks.

Of the 49 participants who incompletely discontinued at 16 weeks, 6 (12%) yet discontinued between 16 and 28 weeks. Of the 67 participants who had incompletely discontinued or had restarted the use at 28 weeks 3 (4%) were completely off antipsychotics at 40 weeks.

**Behavioral outcomes, neurological side-effects, and worsening in health during discontinuation**

At 16 weeks 46 participants (36%) showed a decrease and 35 participants (27%) a clinically relevant increase of ABC total scores (>8 points) compared to baseline. In 32 participants there were no clinically relevant differences in ABC scores at 16 weeks compared to baseline. ABC data of 16 participants was missing in the medical records. In those with incomplete discontinuation there was more often a clinically relevant increase in ABC total scores than in those with complete discontinuation (49% versus 21%; Pearson Chi-square=10.1; p=0.006).

Table 2 shows the mean, median, and confidence interval of ABC total and subscale scores for both groups at 16 weeks after the first dose reduction (discontinuation per protocol).

The group of participants who had completely discontinued showed a significant decrease in severity of behavioral symptoms as measured with the ABC total score and ABC subscale 2 at the time points of 16, 28, and 40 weeks, and of ABC subscale 1 and ABC subscale 4 at 40 weeks. Also, there was a
decrease in parkinsonism in those with complete discontinuation. In those with incomplete
discontinuation there was a significant decrease of akathisia at 40 weeks and a significant increase in
severity of autonomic symptoms at 16 weeks.

See Supplemental table 1 for all within groups comparisons of severity of behavioral and of
neurological symptoms before (baseline) and after discontinuation of antipsychotics at the time
points 16, 28, and 40 weeks of participants who had completely and incompletely discontinued at
these time points.

Worsening in health occurred in 76 of the 129 participants. The worsening in health included
temporary ill-health conditions and exacerbations of chronic mental and somatic conditions, and
related treatments, as reported by the main caregiver or as reported by physicians. Examples are
pain caused by muscle spasms in cerebral palsy followed by physiotherapy, abdominal pain due to
constipation followed by prescription of laxatives, heart burn, infectious diseases, increased severity
of sleep problems or symptoms of anxiety, and staff's perceptions of clients feeling uncomfortable.
The mean number of a worsening in health between baseline and 40 weeks was 2.7. These were
reports of caregivers in 28%, consultations of the general practitioner in 21% (mostly related to ill-
health and the chronic medical conditions), prescription of new medication or dose changes in 22%
(mostly related to consultation of general practitioner or intellectual disability (ID) physician),
consultation of the ID physician in 15% (of these were 45% for somatic conditions and 55% for
mental health conditions), consultation of a medical specialist in 7% (often for chronic medical
conditions), and non-pharmaceutical treatments in 6%.

Changes in environmental circumstances occurred in 68 participants. The mean number of changes
between baseline and 40 weeks was 1.3. The changes were mostly in daily activities, in composition
of the residential group, in the main caregiver, and moving to a new residence.

**Differences between groups achieving complete and incomplete discontinuation**
Participants who had achieved complete discontinuation had a less severe intellectual disability, less often presence of autism and chronic neurological conditions, less severe parkinsonism, had less often worsening in health during the study period, and had more often a history of dermatoses and surgical conditions; with regard to psychotropic drug use they used a lower baseline dosage and used less often > 1 antipsychotic simultaneously. They also experienced fewer severe behavioral symptoms as measured with the ABC. See Supplemental table 2 for all differences between participants with complete versus those with incomplete discontinuation at the time points 16, 28, and 40 weeks after the first dose reduction.

**Determinants of successful discontinuation at the time points 16, 28, and 40 weeks**

A number of participant characteristics and determinants were associated with the chance of complete discontinuation at the different time points. No history of dermatoses, no history of surgical conditions, no stressful family conditions, higher dose of antipsychotic drug, higher scores of ABC, and higher scores of akathisia were all associated with a lower chance of complete discontinuation. Absence of autism, no recent hospitalization, and no use of more than one antipsychotic drug simultaneously were associated with higher chance of complete discontinuation. Furthermore, more frequent worsening in health during discontinuation was associated with lower chance of complete discontinuation.

Table 3 presents the results of multivariate logistic regression analyses at the different time points, with achievement of complete discontinuation as the dependent variable. As independent variables we included those variables with p-values <0.1 in univariate analyses (see Supplemental table 3)

Because we were interested in the influence of neurological (withdrawal) symptoms on the severity of challenging behavior we also investigated potential associations of extrapyramidal and autonomic symptoms with ABC subscales. Higher ratings of ABC subscale lethargy were associated with more severe akathisia and autonomic dysregulation, and higher ratings of ABC subscale stereotypy and of
ABC subscale hyperactivity with more severe dyskinesia, akathisia, and autonomic dysregulation (see table 4).

**DISCUSSION**

In this open label discontinuation study 61% of participants were able to discontinue off-label antipsychotics completely in 16 weeks. At follow-up, three months later (28 weeks after the first dose reduction) 46% of participants were still completely off their antipsychotic medication, and at 40 weeks follow-up 40%. These results are in line with other discontinuation studies but somewhat better than those in our previous study in which 43% achieved complete discontinuation and 36% were still off antipsychotic medication three months later.

The severity of behavioral symptoms as assessed with the ABC total and subscales had decreased in those participants who were completely off medication at all three time points, and had not changed significantly in those who had not achieved full discontinuation. These of improved behavioral symptoms in those achieving complete discontinuation and on average no change in those with incomplete discontinuation confirm our previous findings. Furthermore, in general, in both groups there were individual participants with an increase or decrease in severity of behavioral symptoms during discontinuation.

Results with regard to the course of neurological side-effects were mixed. On the one hand there was a decrease in parkinsonism in those with complete discontinuation, on the other hand a decrease in akathisia in those with incomplete discontinuation at 40 weeks. The decrease in akathisia in those participants who still used antipsychotic drugs may be explained by the potential of these agents to mask this extrapyramidal symptom or by the disappearance of withdrawal akathisia. Autonomic symptoms increased in those having incompletely discontinued at 16 weeks. This may have been caused by again increasing the dosage r additional prescriptions of psychotropic drugs following the behavioral disturbances which had led to termination of the discontinuation trajectory.
The present study indicated some determinants which might help to predict whether discontinuation will be successful. The presence of autism, akathisia, higher ABC scores, and more frequent worsening in health during discontinuation were clearly associated with lower odds of successful discontinuation. In people with intellectual disability co-morbid mental disorders, neurological side-effects of antipsychotics and ill-health conditions may express as behavioral symptoms, which may be difficult to manage. Indeed, more severe dyskinesia, akathisia, and autonomic symptoms were associated with higher scores on the ABC subscales lethargy, stereotypy, and hyperactivity. When underlying causes of maladaptive behaviors are not recognized, appropriate treatments will be lacking, and the severity of behavioral symptoms may increase, which in turn may hinder successful discontinuation. The commonly accepted idea that changes in environmental circumstances should be a reason not to start or even to stop antipsychotic discontinuation trajectories could not be confirmed, given no association between changes in living circumstances and life events with lower chance of successful discontinuation.

**Strengths and limitations**

A strength of the present study was that it reflects discontinuation in clinical practice. We took the influence of negative changes in health conditions and environmental circumstances into consideration. However, recruitment of participants was difficult. In only half of cases physicians judged their clients with off-label antipsychotic drug use were eligible to discontinue, and of those just 26% consented to participate in the study. Fear of clinicians, caregivers, and legal representatives for behavioral worsening were main reasons not to discontinue. McNamara et al (2017)\(^4\) also encountered major recruitment problems in their double blind randomized controlled discontinuation trial of risperidone used for challenging behaviors. They suggested that lack of alternative behavioral interventions to manage the potential re-emergence of challenging behaviors of clients may be reasons for the poor recruitment.
Another limitation of this study was missing data which reduced the available cases for multivariate analyses. Therefore, the results of this study should be confirmed in larger scale studies. However, the sample size was large enough to assess associations in univariate analyses reliably and we think the results have clinical importance and add to the knowledge in ongoing off-label antipsychotic drug use in people with intellectual disability. The open label study design is another limitation, although it does reflect discontinuation in clinical practice which is also typically open label. Also, no correction for multiple testing was done, to reduce the risk of type 2 errors. However, we cannot exclude that some results may have been spurious. Last, because the study took place in living facilities of congregate care centers, in a selected sample, the results may not be generalizable to people with intellectual disability who live in the community and to clients not eligible to discontinue according to their clinicians' judgements.

CONCLUSIONS/CLINICAL AND RESEARCH IMPLICATIONS

Forty percent of participants with intellectual disability who were judged by their responsible clinicians to be eligible for a withdrawal trial of their long-term off-label antipsychotic drugs were able to discontinue in a time frame of approximately four to seven months with on average no behavioral worsening.

We identified a number determinants explaining failure to achieve complete discontinuation with clear clinical implications. Especially worsening in chronic medical conditions or temporary ill-health conditions in clients, which were negatively associated with successful discontinuation should be addressed appropriately and should be no reason to stop the discontinuation trajectory. Also, the presence of neurological side-effects should be carefully examined and appropriately managed, since these symptoms were associated with higher severity of maladaptive behavior, which in turn was associated with a higher chance of failed discontinuation. Finally, the presence of autism spectrum disorder, which was also associated with failed discontinuation, perhaps indicating that antipsychotics are more effective in those with autism spectrum disorder.
Because just over 25% of eligible participants took part in the study, we ought to be cautious in drawing final conclusions as results may not be generalizable to the whole population using long term antipsychotics; however, this low percentage of those willing to attempt discontinuation reflects clinical reality. Larger scale studies in various settings of intellectual disability care are needed to confirm our results and to investigate which treatments should be offered in case of unsuccessful attempts to discontinue off-label antipsychotics.

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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflict of interest

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INTRODUCTION

Nowadays, individuals with intellectual disability frequently show challenging behavior. Challenging behavior is defined as culturally abnormal behavior of such intensity, frequency, or duration that the physical safety of the person or others is placed in serious jeopardy, or behavior which is likely to seriously limit or deny access to the use of ordinary community facilities. Examples are aggressive or irritable behavior, inappropriate sexual behavior, self-injurious behavior and stereotypic behavior. In Europe antipsychotics are licensed for the treatment of psychosis and symptoms of severe agitation. Besides, the antipsychotic drug risperidone is licensed for the short term treatment of aggressive behavior in adults with intellectual disability and in children aged over five years. In the US risperidone and aripiprazole are also labelled for the treatment of irritability associated with autism. Antipsychotics are often off-label prescribed for long-term treatment of challenging behavior in people with intellectual disability, although there is insufficient evidence for their effectiveness for this treatment target and an increased risk of side-effects in this population.

There is growing awareness among clinicians and policy makers that long-term off-label use of psychotropic drugs for challenging behaviors in people with intellectual disability should be avoided as much as possible. Has become more and more accepted by clinicians and policy makers. Yet, the prevalence of psychotropic drug use remains high. In a recent study we showed a prevalence of antipsychotic drug use of almost 30% of individuals with intellectual disability used psychotropic medication, of which 95% were off-label prescriptions. However, clinicians decided just in half of these cases that their clients were eligible to discontinue the long-term off-label use. Main reasons for deciding against discontinuation clinicians indicated that were fears for increasing in restlessness, aggression, and other behavioral disturbances, the presence of autism, and previously unsuccessful discontinuation attempts were main reasons not to discontinue. Furthermore, environmental factors, like unfavorable living circumstances, changes in living situations or recent life events were main issues not to discontinue. Indeed, some studies have shown that life events and
changes in socio-demographic conditions were associated with challenging behavior and mental ill-
health\textsuperscript{4,5,6}.

Although there is a substantial proportion of long-term off-label antipsychotic drug users in which
discontinuation is successful, attempts to discontinue may fail because of behavioral worsening due
to a variety of yet unclear causes\textsuperscript{7-9}. Potential causes may lay in the onset of previously suppressed
symptoms of mental or physical disorders. Such symptoms of mental disorders in people with
intellectual disability may be misinterpreted as maladaptive behavior. In turn, physicians may react
with changes in medication, most often by again increasing dosages and/or adding new psychotropic
medications\textsuperscript{8}. Also physical symptoms of chronic or acute medical conditions, including side-effects
of medication often remain unrecognized and may present as behavioral disturbance. Furthermore,
neurological withdrawal symptoms may occur and hinder successful discontinuation, as these may
also express as behavioral symptoms and may be wrongly interpreted, e.g., dyskinesia as restlessness
and akathisia as hyperactivity. Indeed, in a previous study we found a disagreement between
caregivers and physicians disagreed in the identification of symptoms of dyskinesia and akathisia\textsuperscript{9}.

Last, in clinical practice causes of unsuccessful discontinuation in clinical practice are\textsuperscript{10} often
attributed to changes in environmental circumstances or unfavorable living circumstances, which
may cause clients to react with maladaptive behavior.

Thus, on the one hand off-label inappropriate antipsychotic drug use should be reduced, while on the
other hand causes of behavioral worsening during discontinuation should be identified and
appropriately treated and managed. There is need for more insight in factors that may hinder
successful discontinuation of long-term off-label used antipsychotics for challenging behavior.

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medication, changes in challenging behavior upon gradual discontinuation of antipsychotics and as
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METHODS

Design and setting

We combined data of two open label discontinuation studies; (1) discontinuation of long term used risperidone prescribed for challenging behavior (Netherlands Trial Register NTR5509) and (2) a discontinuation study involving all other antipsychotics. The study had been approved by the Medical Ethical Committee University Groningen, METc 2014/402 and is registered in the Netherlands National Trial Register, [NTR5519]. Potential participants had received a treatment proposal from their physician involving an attempt to discontinue antipsychotics. All legal representatives of participants had provided written informed consent.

Design and setting

This study investigated determinants of successful achievement of discontinuation of antipsychotics and used data of an open label discontinuation trial of long term used antipsychotics for challenging behaviors plus data on open label discontinuation of risperidone (NTR5519 excludes use of risperidone). We prospectively investigated the influence of participants related factors that were potentially associated with successful discontinuation, including changes in environmental circumstances. Study settings were living facilities of six care providing organizations. Two of the six organizations also provided data on for the open label discontinuation of risperidone.

Study population

Eligible participants could be of any sex or ethnicity, were aged ≥ 6 years, were functioning below an IQ level of 70, and had used one or more antipsychotics for more than one year for challenging behavior. Excluded were subjects with schizophrenia, a bipolar disorder, or an affective psychosis according to the Diagnostic Statistic Manual (DSM)-IV TR or International Code of Diseases (ICD) -10 were excluded. Another exclusion criterion was an unsuccessful attempt to discontinue the antipsychotics in the previous 6 months, as another attempt to discontinue after a short frame would be unlikely to be successful. Use of other psychotropic drugs was not an exclusion criterion.
Outcomes

The primary outcome measure was achievement of complete discontinuation at 16 weeks.

Secondary outcome measures were achievement of complete discontinuation at the time points of 28 weeks and 40 weeks; and changes in the Aberrant Behavior Checklist (ABC) and its five subscales i.e., irritability, lethargy, stereotypic behavior, hyperactivity, and inadequate speech. The ABC is a standardized, validated scale developed to measure severity of challenging behaviors and effects of treatment on the behavior. The ABC was completed by the main caregiver. We defined changes of > 8 points in ABC total scores (0.33 SD) as clinically relevant.

Determinants

Potential baseline determinants were psychotropic drug use characteristics (dosage of antipsychotic drug, use of >1 antipsychotic simultaneously, use of other psychotropic, and/or anti-epileptic drugs), participant characteristics (severity of behavioral symptoms as measured with the ABC, presence or history of medical conditions, and presence and severity of extrapyramidal and autonomic neurological side-effects), and environmental circumstances (the presence or history of life events).

Potential determinants during discontinuation were the occurrence of new health problems and/or worsening in health or chronic medical conditions, changes in living situation and life events, and the severity of behavioral, extrapyramidal and autonomic symptoms as measured at the different time points of data collection during discontinuation.

For assessment of extrapyramidal symptoms we used items 1 through 9 of the Abnormal Involuntary Movement Scale (AIMS), the Barnes akathisia objective symptoms, subjective symptoms and burden scale (BARS), and motor items 20, 21, 22, and 31 of the Unified Parkinson Scale (UPDRS). Autonomic symptoms were measured by the Scale for Outcomes in Parkinson’s disease-Autonomic Symptoms...
(SCOPA-AUT), which we slightly adapted by adding two questions on fecal and urine continence. All these scales were completed by a trained research assistant.

To assess worsening in health during the study period we counted the number of times participants experienced new health problems as reported by their caregivers, the number of consultations of participants with their general practitioner, intellectual disability physician, and/or other specialist, the number of new medication prescriptions or dose changes, and the number of new non-pharmaceutical treatments. Also, the number of changes in living circumstances and life events were counted.

Procedures

Discontinuation was done by intellectual disability physicians or general practitioners according to a scheduled discontinuation time frame of 14 weeks duration. The discontinuation schedule was based at our previous study, in which we found tapering of antipsychotic drugs in a relatively short time frame can safely be done\(^1\). The study was performed as part of regular clinical care. This means implied that participants remained in the study and data collection was continued to the end of the study follow-up when physicians decided the participant should no longer taper off the antipsychotic drug, should taper off in another time schedule, or should use a higher dose, participants remained in the study and data collection was continued to the end of the study follow-up.

Participants were included from 1\(^{st}\) of January 2015 till 1\(^{st}\) of February 2016. Outcome measures were collected at baseline, at 4, 8, 12, and 16 weeks (during the discontinuation period per protocol) and at 22, 28 and 40 weeks (follow-up) after the first dose reduction.

Sample size

The sample size calculation was based on potential associations of determinants with achievement of complete discontinuation by means of logistic regression analyses. With a total of 12 variables and a
small effect size of 0.15, a power of 0.80 and a probability level of 0.05 a sample size of 127 was
required.

**Statistical analyses**

We used Statistical Package for the Social Sciences (SPSS) version 23 for statistical analyses. The main
study parameter was achievement of complete discontinuation at 16 weeks (i.e., 2 weeks after the
scheduled complete discontinuation); we also considered achievement of discontinuation at two
follow-up time points, i.e., 28 and 40 weeks after the first dose reduction. We distinguished groups
with complete and incomplete discontinuation status at the three different time points.

With paired sampled t-tests, we compared baseline severity of behavioral measures and symptoms
of neurological side-effects with these at 16, 28, and 40 weeks.

With independent sample T-test for continuous variables and Pearson Chi-square test for categorical
variables we compared participants’ characteristics of those with complete and those with
incomplete discontinuation at baseline, 16, 28, and 40 weeks, and of those who used typical versus
atypical antipsychotics at baseline and 16 weeks.

In case of non-normal distribution of continuous variables we used the Wilcoxon signed rank test for
paired sampled test and Mann-Whitney U test for independent sampled test.

To select variables for the multivariate regression analyses we used with univariate logistic
regression analyses we investigated potential associations of participants characteristics
(gender, age, severity of intellectual disability, living situation) and determinants with the odds for
complete discontinuation at 16, 28, and 40 weeks, respectively. Subsequently, we used variables
with a p-value< 0.1 in multivariate logistic analyses. Here, we used scores of the continuous variables
ABC, AIMS, BARS, and UPDRS at the previous time point as baseline determinants for the time point
in step wise regression analyses, e.g., ABC score at 16 weeks as baseline value for ABC at 28 weeks.
Finally, we investigated potential associations of neurological side-effects and/or withdrawal symptoms with behavioral symptoms as measured with the ABC subscales in univariate regression analyses at the different time points.

A p-value of <0.05 was used to indicate significant differences.

RESULTS

We included 129 participants. Figure 1 shows the flow chart of the study.

Table 1a shows the baseline participant characteristics, including the presence and severity of extrapyramidal and autonomic symptoms associated with antipsychotic drug use. Table 1b shows the psychotropic drug use of participants. Atypical antipsychotic medication was prescribed in 35% of participants. There was no significant difference in mean baseline dosage between participants who used atypical versus typical antipsychotic drugs. Furthermore, there were no significant differences in achievement of complete discontinuation, in severity of behavioral symptoms as measured with the ABC, and in severity of extrapyramidal and autonomic symptoms during discontinuation at the time point of 16 weeks after the first dose reduction (time point of scheduled discontinuation) between these groups.

Achievement of complete discontinuation

Figure 2 shows the numbers of participants who had achieved completely and incompletely discontinuation of their long-term off-label antipsychotic drug use at 16 weeks (discontinuation per protocol), and at 28 and 40 weeks after the first dose reduction, including those participants who had restarted their use and who had yet discontinued between the time points during follow-up.

Of the 79 participants who had completely discontinued antipsychotics at 16 weeks, 25 participants (32%) restarted their use of antipsychotics between 16 and 28 weeks. ABC total scores decreased in 8 participants, increased in 8 participants, and remained the same in 4 participants; data of 5 participants were missing. In the 54 participants who were still off antipsychotics at 28 weeks, ABC total scores decreased in 22 participants, increased in 11.
participants, and did not change in 16 participants; data of 5 participants were missing. In all but two
cases (see Figure 1) the missing data was caused by incomplete medical and pharmaceutical record
keeping. In 2560 participants who were completely off antipsychotics at 28 weeks, 8 (13%) restarted the use between 28 and 40 weeks. Of the 49 participants who incompletely discontinued at 16 weeks, 6 (12%) yet discontinued between 16 and 28 weeks. Of the 67 participants who had incompletely discontinued or had restarted the use at 28 weeks 3 (4%) were completely off antipsychotics at 40 weeks.

Behavioral outcomes, neurological side-effects, and worsening in health during discontinuation

At 16 weeks 46 participants (36%) showed a decrease and 35 participants (27%) a clinically relevant
increase of ABC total scores (>8 points) compared to baseline. In 32 participants there were no
clinically relevant differences in ABC scores at 16 weeks compared to baseline, scores were similar
and ABC data of 16 participants was missing in the medical records. In those with incomplete
discontinuation there was more often a clinically relevant increase in ABC total scores than in those
with complete discontinuation (49% versus 21%; Pearson Chi-square=10.14; p=0.006).

Table 2 shows the mean, median, and confidence interval of ABC total and - subscale scores for both
groups at 16 weeks after the first dose reduction (discontinuation per protocol).

The group of participants who had completely discontinued showed a significant decrease in severity
of behavioral symptoms as measured with the ABC total score and ABC subscale 2 at the time points
of 16, 28, and 40 weeks, and of ABC subscale 1 and ABC subscale 4 at 40 weeks. Also, there was a
decrease in parkinsonism in those with complete discontinuation. In those with incomplete
discontinuation we found there was a significant decrease of akathisia at 40 weeks and a significant a
increase in severity of autonomic symptoms at 16 weeks.

See Supplemental table 1 for all within groups comparisons of severity of behavioral and of
neurological symptoms before (baseline) and after discontinuation of antipsychotics at the time
points 16, 28, and 40 weeks of participants who had completely and incompletely discontinued at these time points.

Worsening in health occurred in 76 of the 129 participants; the mean number of a worsening in health between baseline and 40 weeks was 2.7. The Health worsenings in health included temporary ill-health conditions and exacerbations of worsening in chronic mental and somatic conditions, and related treatments, as recorded reported by the main caregivers or as reported by physicians. Examples are pain caused by muscle spasms in cerebral palsy followed by physiotherapy, abdominal pain due to constipation followed by prescription of laxatives, heart burn, infectious diseases, increased severity of sleep problems or symptoms of anxiety, and staff’s perceptions of clients feeling uncomfortable. The mean number of a worsening in health between baseline and 40 weeks was 2.7. These were reports of caregivers in 28%, consultations of the general practitioner in 21% (mostly related to ill-health and the chronic medical conditions), prescription of new medication or dose changes in 22% (mostly related to consultation of general practitioner or intellectual disability physician), consultation of the ID physician in 15% (of these were 45% for somatic conditions and 55% for mental health conditions), consultation of a medical specialist in 7% (often for chronic medical conditions), and non-pharmaceutical treatments in 6%.

Changes in environmental circumstances occurred in 68 participants. The mean number of changes between baseline and 40 weeks was 1.3. Mostly the changes were mostly in daily activities, in composition of the residential group, in the main caregiver, and moving to a new residence.

Differences between groups achieving complete and incomplete discontinuation

Participants who had achieved complete discontinuation had a less severe intellectual disability, less often presence of autism and chronic neurological conditions, less severe parkinsonism, had less often worsening in health during the study period, and had more often a history of dermatoses and surgical conditions; with regard to psychotropic drug use they used a lower baseline dosage, and used less often > 1 antipsychotic simultaneously and had less severe parkinsonism. They also
experienced fewer severe behavioral symptoms as measured with the ABC. See Supplemental table 2 for all differences between participants with complete versus those with incomplete discontinuation at the time points 16, 28, and 40 weeks after the first dose reduction.

**Determinants of successful discontinuation at the time points 16, 28, and 40 weeks**

We found a number of participant characteristics and determinants which were associated with the chance of complete discontinuation at the different time points. No history of dermatoses, no history of surgical conditions, no stressful family conditions, higher dose of antipsychotic drug, higher scores of ABC, and higher scores of akathisia were all associated with a lower chance of complete discontinuation. The absence of autism, no recent hospitalization, and no use of more than one antipsychotic drug simultaneously were associated with higher chance of complete discontinuation. Furthermore, more frequent worsening in health during discontinuation was associated with lower chance of complete discontinuation.

Table 3 presents the results of multivariate logistic regression analyses at the different time points, with the achievement of complete discontinuation as the dependent variable. As independent variables we included those variables with p-values <0.1 in univariate analyses (see Supplemental table 3).

Because we were interested in the influence of neurological (withdrawal) symptoms on the severity of challenging behavior we also investigated potential associations of extrapyramidal and autonomic symptoms with ABC subscales. We found that higher ratings of ABC subscale lethargy were associated with more severe akathisia and autonomic dysregulation, and higher ratings of ABC subscale stereotypy and ABC subscale hyperactivity with more severe dyskinesia, akathisia, and autonomic dysregulation. [See table 4].

**DISCUSSION**
In this open label discontinuation study, we found that 61% of participants were able to discontinue off-label antipsychotics completely in 16 weeks. At follow-up, three months later, (28 weeks after the first dose reduction), 46% of participants were still completely off their antipsychotic medication, and at 40 weeks follow-up, 40%. These results are within the range of line with other discontinuation studies and somewhat better than those in our previous study in which 43% succeeded in achieving complete discontinuation, and 36% were still off antipsychotic medication at three months later follow-up.

The severity of behavioral symptoms as assessed with the ABC total and subscales had decreased in those participants who were completely off medication at all three different time points, but not significantly in those who had not achieved full discontinuation. These results also confirm our previous findings of improved decrease in severity of behavioral symptoms as measured with the ABC in those achieving complete discontinuation and on average no change in those with incomplete discontinuation. Furthermore, in general, in both groups there were individual participants with an increase and/or decrease in severity of behavioral symptoms during discontinuation. We found it was not the difference in severity, but the severity of symptoms itself which was related to the chance of complete discontinuation.

Results With regard to the course severity of neurological symptoms of side-effects were found mixed results. On the one hand, there was a decrease in parkinsonism in those with complete discontinuation, on the other hand a decrease in akathisia in those with incomplete discontinuation at 40 weeks. Furthermore, autonomic symptoms had increased in those having incompletely discontinued at 16 weeks. The decrease in akathisia in those participants who still used antipsychotic drugs may be explained by the potential of these agents to mask this extrapyramidal symptom or by the disappearance of withdrawal akathisia. Furthermore, autonomic symptoms had increased in those having incompletely discontinued at 16 weeks. These increases in autonomic symptoms may have been caused by again increasing the dosage or additional prescriptions of psychotropics following the behavioral disturbances which had led to termination of the

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discontinuation trajectory. Overall, with the exception of parkinsonism the severity of extrapyramidal and autonomic symptoms did not differ between participants who achieved complete versus incomplete discontinuation. This may be caused by the nature of dyskinesia and akathisia, symptoms of which may persist for long periods or may even be irreversible, and by already present or emerging autonomic symptoms caused by comorbid medical conditions. Although a substantial proportion of participants succeeded in completely tapering off their antipsychotic drug use, at follow-up the majority of participants had failed to do so. In the present study we found indicated some determinants which might help to predict whether discontinuation will be successful. The presence of autism, akathisia, higher ABC scores, and more frequent worsening in health during discontinuation were clearly associated with lower odds of successful discontinuation. In people with intellectual disability co-morbid mental disorders, neurological side-effects of antipsychotics and ill-health conditions may express in as behavioral symptoms, which may be difficult to manage. Indeed, more severe dyskinesia, akathisia, and autonomic symptoms were associated with higher scores on the ABC subscales lethargy, stereotypy, and hyperactivity. Moreover, when underlying causes of maladaptive behaviors are not recognized, appropriate treatments will be lacking, and the severity of behavioral symptoms may increase. Furthermore, since we found that more severe dyskinesia, akathisia and autonomic symptoms were associated with higher scores of ABC subscales lethargy, stereotypy and hyperactivity, these symptoms which in turn may also hinder successful discontinuation.

Remarkably was the finding of the association between a history of dermatoses and of surgical disorders, and stressful family conditions with a higher chance of successful discontinuation. This may be explained by the nature of these disorders/circumstances. Although these conditions may lead to behavioral worsening, these will be easily recognized and will be no reason for continued use of antipsychotics.
We could not confirm the commonly accepted idea that changes in environmental circumstances should be a reason not to start or even to stop antipsychotic discontinuation trajectories could not be confirmed, since we did not find any association between changes in living circumstances and life events with lower chance of successful discontinuation.

Strengths and limitations

A strength of the present study was that it reflects discontinuation in clinical practice. We accounted for the influence of negative changes in health conditions and environmental circumstances into consideration. However, recruitment of participants was difficult. In only half of cases physicians judged their clients with off-label antipsychotic drug use were eligible to discontinue, and of those just 26% consented to participate in the study. Fear of clinicians, caregivers, and legal representatives for behavioral worsening were main reasons not to discontinue. McNamara et al (2017) also encountered major recruitment problems in their double blind randomized controlled discontinuation trial of risperidone used for challenging behaviors. They suggested that lack of alternative behavioral interventions to manage the potential re-emergence of challenging behaviors of clients may be reasons for the poor recruitment.

Another limitation of this study was that there were missing data which reduced the available cases for multivariate analyses. Therefore, the results of this study with regard to factors associated with successful discontinuation of long-term used antipsychotic drugs should be confirmed in larger scale studies. However, the sample size was large enough to assess associations in univariate analyses reliably and we think these results have clinical importance and will add to the knowledge in ongoing off-label antipsychotic drug use in people with intellectual disability. The open label study design is another limitation, although it does reflect discontinuation in clinical practice which is also typically open label. Also, no correction for multiple testing was done to reduce the risk of type 2 errors. Therefore, we cannot exclude that some results may have been spurious. Last,
because the study took place in living facilities of congregated care centers, in a selected sample, the results may not be generalizable to people with intellectual disability who live in the community and to clients not eligible to discontinue according to their clinicians’ judgements. However, our results have clear implications with regard to health care for those who use long-term off-label antipsychotics and these implications apply for community mental health care workers and general practitioners as well.

CONCLUSIONS/CLINICAL AND RESEARCH IMPLICATIONS

Forty percent of participants with intellectual disability who had been declared were judged suitable by their responsible clinicians to be eligible for a trial of withdrawal trial of their long-term off-label antipsychotic drugs were able to discontinue in a time frame of approximately four to seven months with on average no behavioral worsening.

We identified some a number determinants, which may explaining the failure of to achieve complete discontinuation of long-term off-label used antipsychotics in people with intellectual disability and these findings should havewith clear clinical implications. Especially worsening in chronic medical conditions or temporary ill-health conditions in clients, which were negatively associated with successful discontinuation should be addressed appropriately and should be no reason to stop the discontinuation trajectory. Also, the presence of neurological side-effect symptoms should be carefully examined and appropriately managed, since these symptoms were associated with higher severity of maladaptive behavior, which in turn was associated with more a higher chance of failure failedin discontinuation of antipsychotics. Finally, the presence of autism spectrum disorder, which was also associated with failure in discontinuation, should be a reason to carefully look for comorbid psychosis or symptoms of other mental disorders, since comorbidity of mental disorders is common in this group of patients, perhaps indicating that antipsychotics are more effective in those with autism spectrum disorder.
Because just over 25% of eligible participants took part in the study, we ought to be cautious in drawing final conclusions as results may not be generalizable to the whole population using long-term antipsychotics; however, this low percentage of those willing to attempt discontinuation reflects clinical reality. Larger scale studies in various settings of intellectual disability care are needed to confirm our results and to investigate which treatments should be offered in case of unsuccessful attempts to discontinue off-label antipsychotics.

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AUTHOR DISCLOSURE INFORMATION
The authors declare no conflict of interest

DATA SHARING STATEMENT
No additional data are available

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REFERENCES


Figure legend

Figure 1

Figure 1: Flow chart of the study
*according to physicians judgement; *main reasons for non-inclusion were clinicians’ concerns that discontinuation might be harmful due to changes in the clients’ environment

Figure 2

Figure 2: Flow chart of antipsychotic drugs discontinuation trajectory of participants
*16 weeks: one participant had died; 28 weeks: two participants had died; 40 weeks: two participants had died and of eight participants clinicians failed to provide data
Figure 2: Flow chart of antipsychotic drugs discontinuation trajectory of participants

#16 weeks: one participant had died; 28 weeks: two participants had died; 40 weeks: two participants had died and of eight participants clinicians failed to provide data
Table 1a Characteristics of participants (n=129) with intellectual disability who will discontinue long-term use of antipsychotics for behavioral symptoms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median, mean (SD)</td>
<td>51.3, 49.2 (16.0); (range 11.5-84.2)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>66.7%</td>
</tr>
</tbody>
</table>
| Severity of intellectual disability                  | Profound: 15.9%  
Severe: 44.4%  
Moderate: 23.9%  
Mild: 13.4%                                                                 |
| Living situation                                    | Congregated centre: 70.9%  
Community centre: 22.2%  
Community living facility: 6.8%                                                                 |
| Living situation, group size                         | 1-4 persons: 18.5%  
4-8 persons: 55.6%  
8-12 persons: 22.2%  
Independently: 3.7%                                                                 |
| Presence of comorbid physical conditions             | Internal condition: 42%  
Neurological condition: 41%  
Musculoskeletal: 18%                                                                 |
| Presence of comorbid non-psychotic mental conditions| Autism spectrum disorder: 67.4%  
ADHD: 3.6%  
Mood disorder: 7.3%  
Post-Traumatic Stress Disorder: 0.9%  
Anxiety disorder: 5.5%  
Obsessive compulsive disorder: 0.9%  
Attachment disorder: 3.6%                                                                 |
| Presence of extrapyramidal symptoms (EPS)           | Dyskinesia: 45.2%  
Akathisia: 30.0%  
Parkinsonism: 23.8%                                                                 |
| Mean scores of those with EPS symptoms (n=60) (SD)   | 9.2 (5.7), minimum 3, maximum 28                                                                 |
| Presence of autonomic symptoms                       | Dysphagia: 36.3%  
Defecation problems: 33.3%  
Urinary problems: 79.8%  
Dizziness: 2.5%  
Temperature dysregulation: 37.5%                                                                 |
| Mean scores of those with autonomic symptoms (n=87) (SD) | 13.5 (8.4), minimum 3, maximum 35                                                                 |

* including three adolescents

1 as noted in the medical record; 2 including sensory impairments; 3 score > 1; 4 total score > 2; 5 incontinence not included; 6 EPS: as measured with the Abnormal Involuntary Movement Scale items 1 through 9, BARS akathisia objective symptoms, subjective symptoms and burden scale and Unified Parkinson Disorder Rating Scale motor items 20, 21, 22 and 31 (maximum scale score=41); 7 autonomic symptoms: as measured with the adapted Scale Outcomes Parkinson-autonomic symptoms (maximum scale score=61)
Table 1b Psychotropic drug use of participants (n=129) with intellectual disability who will discontinue long-term use of antipsychotics for behavioral symptoms

<table>
<thead>
<tr>
<th>Defined Daily Dose of total antipsychotic drug use, mean (SD)</th>
<th>0.60 (0.48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defined Daily Dose of users of atypical antipsychotics, mean (SD)</td>
<td>0.67 (0.46)</td>
</tr>
<tr>
<td>Defined Daily Dose of users of typical antipsychotics, mean (SD)</td>
<td>0.55 (0.48)</td>
</tr>
<tr>
<td>Type of antipsychotropic drug (%)</td>
<td></td>
</tr>
<tr>
<td>Atypical:</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>15.6</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10.9</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>2.3</td>
</tr>
<tr>
<td>Clozapine</td>
<td>4.7</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>0.8</td>
</tr>
<tr>
<td>Typical:</td>
<td></td>
</tr>
<tr>
<td>Pipamperone</td>
<td>44.1</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>10.2</td>
</tr>
<tr>
<td>Pericyazine</td>
<td>5.5</td>
</tr>
<tr>
<td>Zuclopentixol</td>
<td>6.2</td>
</tr>
<tr>
<td>Levomepromazine</td>
<td>3.9</td>
</tr>
<tr>
<td>Pimozide</td>
<td>6.3</td>
</tr>
<tr>
<td>Use of &gt;1 antipsychotic drug simultaneously (%)</td>
<td>7.4</td>
</tr>
<tr>
<td>Use of other psychotropic drugs (%)</td>
<td>31.1</td>
</tr>
<tr>
<td>Use of anticonvulsive drugs (%)</td>
<td>36.1</td>
</tr>
</tbody>
</table>
Table 2

Differences in scores of Aberrant Behavior Checklist (ABC) between participants who had completely (n=79) and who had incompletely (n=49) discontinued long-term off-label use of antipsychotics at the time point of 16 weeks after the first dose-reduction

<table>
<thead>
<tr>
<th></th>
<th>Mean Completely/incompletely</th>
<th>Median Completely/incompletely</th>
<th>Confidence interval of Mean Completely/incompletely</th>
<th>Significant difference of Mean; p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC total</td>
<td>33.6/52.7</td>
<td>29.0/43.0</td>
<td>27.5-39.7/41.2-64.2</td>
<td>p=0.01</td>
</tr>
<tr>
<td>ABC subscale irritability</td>
<td>10.9/16.85</td>
<td>8.0/14.0</td>
<td>8.6-13.1/13.1-20.6</td>
<td>p=0.02</td>
</tr>
<tr>
<td>ABC subscale lethargy</td>
<td>6.6/9.3</td>
<td>4.0/7.5</td>
<td>4.8-8.3/6.8-11.8</td>
<td></td>
</tr>
<tr>
<td>ABC subscale stereotypy</td>
<td>4.5/6.5</td>
<td>3.0/5.5</td>
<td>3.3-5.7/4.7-8.3</td>
<td>p=0.04</td>
</tr>
<tr>
<td>ABC subscale hyperactivity</td>
<td>9.1/15.9</td>
<td>7.0/12.5</td>
<td>7.2-11.0/12.1-19.7</td>
<td>p=0.005</td>
</tr>
<tr>
<td>ABC subscale inadequate speech</td>
<td>2.6/4.2</td>
<td>2.2/4.0</td>
<td>1.8-3.3/3.0-5.5</td>
<td></td>
</tr>
</tbody>
</table>

* Subscale 1=irritability, - 2= lethargy, - 3= stereotypy; - 4= hyperactivity, -5= inadequate speech
Table 3  
Odds* of achievement of complete discontinuation of long-term off-label used antipsychotics in people with intellectual disability (n=129) at the time point of 16 weeks (discontinuation per protocol), 28, and 40 weeks after the first dose reduction

<table>
<thead>
<tr>
<th>Detemrants</th>
<th>Odds Ratio (OR) (95% Confidence Interval)</th>
<th>Goodness-of fit of model*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete discontinuation 16 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>OR=0.15 (0.03-0.8)</td>
<td>55%/90% Overall: 79%</td>
</tr>
<tr>
<td>No recent hospitalization</td>
<td>OR=20.8 (1.9-230.1)</td>
<td></td>
</tr>
<tr>
<td>Complete discontinuation 28 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABC total score at 16 weeks</td>
<td>OR=0.97 (0.95-0.99)</td>
<td>68%/82% Overall: 76%</td>
</tr>
<tr>
<td>Complete discontinuation 40 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>OR=1.06 (1.01-1.11)</td>
<td>77%/82% Overall: 79%</td>
</tr>
<tr>
<td>No history of surgical conditions</td>
<td>OR=0.14 (0.03-0.69)</td>
<td></td>
</tr>
<tr>
<td>Akathisia at 28 weeks</td>
<td>OR=0.62 (0.41-0.95)</td>
<td></td>
</tr>
<tr>
<td>More often worsening in health 28-40 weeks</td>
<td>OR=0.46 (0.22-0.95)</td>
<td></td>
</tr>
</tbody>
</table>

* In multivariate logistic regression analyses  
* Hosmer and Lemeshow Test; percentage of correct prediction of “no achievement of complete discontinuation”/percentage of correct prediction of “achievement of complete discontinuation”, and percentage of overall correct prediction
Table 4
Associations of neurological extrapyramidal and autonomic symptoms\(^1\) with behavioral symptoms as measured with the Aberrant Behavior Checklist at different time points during and after discontinuation trajectories

<table>
<thead>
<tr>
<th>ABC subscale</th>
<th>baseline</th>
<th>16 weeks</th>
<th>28 weeks</th>
<th>40 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>irritability</td>
<td>Autonomic</td>
<td>Autonomic</td>
<td>Autonomic</td>
<td></td>
</tr>
<tr>
<td>symptoms</td>
<td>symptoms</td>
<td>symptoms</td>
<td>symptoms</td>
<td></td>
</tr>
<tr>
<td>(\beta=0.26; p=0.01; )</td>
<td>(R^2=0.06)</td>
<td>(\beta=0.21; p=0.02; )</td>
<td>(R^2=0.04)</td>
<td></td>
</tr>
<tr>
<td>lethargy</td>
<td>Dyskinesia</td>
<td>Autonomic</td>
<td>Akathisia</td>
<td>Autonomic</td>
</tr>
<tr>
<td>(\beta=0.28; p=0.002; )</td>
<td>(R^2=0.07)</td>
<td>symptoms</td>
<td>(\beta=0.24; p=0.02; )</td>
<td>(R^2=0.11)</td>
</tr>
<tr>
<td>Akathisia</td>
<td>(\beta=0.25; p=0.01; )</td>
<td>(R^2=0.05)</td>
<td>(\beta=0.24; p=0.02; )</td>
<td>(R^2=0.05)</td>
</tr>
<tr>
<td>stereotypy</td>
<td>Akathisia</td>
<td>Autonomic</td>
<td>Akathisia</td>
<td>Autonomic</td>
</tr>
<tr>
<td>(\beta=0.30; p=0.002; )</td>
<td>(R^2=0.08)</td>
<td>symptoms</td>
<td>(\beta=0.26; p=0.01; )</td>
<td>(R^2=0.06)</td>
</tr>
<tr>
<td>hyperactivity</td>
<td></td>
<td>Autonomic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>inadequate speech</td>
<td></td>
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</tr>
</tbody>
</table>

\(^1\) Dyskinesia as measured with the Abnormal Involuntary Movement Scale items 1 through 9; akathisia with the Barnes akathisia objective symptoms, subjective symptoms and burden scale; parkinsonism with the Unified Parkinson Disorder Rating Scale motor items 20, 21, 22 and 31; autonomic symptoms with the adapted Scale Outcomes Parkinson-autonomic symptoms

ABC= Aberrant Behavior Checklist
\(\beta\): standardized regression coefficient
\(R^2\): adjusted R square; explained variance
Supplemental Table 1
Comparisons of severity of behavioral and physical symptoms associated with use of antipsychotic drugs in people with intellectual disability (n=129) for groups of participants who had completely and incompletely discontinued their long-term off-label use between baseline and 16 weeks (discontinuation as per protocol), 28 and 40 weeks after the first dose reduction.

<table>
<thead>
<tr>
<th></th>
<th>Baseline versus 16 weeks (mean/SD)</th>
<th>Baseline versus 28 weeks (mean/SD)</th>
<th>Baseline versus 40 weeks (mean/SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete (n=79)/incomplete (n=49)</td>
<td>Complete (n=60)/incomplete (n=67)</td>
<td>Complete (n=51)/incomplete (n=68)</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs 16 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total:</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ABC</td>
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</tr>
<tr>
<td>Subscale 1</td>
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<tr>
<td>Participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>completely</td>
<td>38.2 (23.3)/33.3 (26.7)</td>
<td>38.3 (22.6)/30.3 (25.9)</td>
<td>38.6 (24.2)/27.5 (21.5)</td>
</tr>
<tr>
<td>discontinued</td>
<td>43.3 (25.4)/52.7 (38.8)</td>
<td>42.5 (25.2)/49.7 (35.1)</td>
<td>40.7 (24.8)/42.2 (32.3)</td>
</tr>
<tr>
<td>vs 28 weeks</td>
<td></td>
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</tr>
<tr>
<td>Subscale 2</td>
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<td></td>
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<tr>
<td>Participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>completely</td>
<td>12.0 (8.6)/11.0 (9.8)</td>
<td>12.6 (8.7)/10.4 (9.4)</td>
<td>13.0 (9.4)/9.5 (8.6)</td>
</tr>
<tr>
<td>discontinued</td>
<td>12.8 (9.8)/16.6 (12.7)</td>
<td>12.5 (9.4)/15.4 (12.0)</td>
<td>12.0 (9.2)/12.6 (10.8)</td>
</tr>
<tr>
<td>vs 40 weeks</td>
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<tr>
<td>Subscale 3</td>
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<tr>
<td>Participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>completely</td>
<td>9.6 (8.0)/6.5 (7.7)</td>
<td>9.4 (7.0)/5.4 (6.4)</td>
<td>9.1 (6.9)/5.5 (6.9)</td>
</tr>
<tr>
<td>discontinued</td>
<td>10.6 (7.4)/9.3 (8.5)</td>
<td>10.4 (8.3)/9.3 (8.6)</td>
<td>10.2 (8.2)/8.9 (8.9)</td>
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<tr>
<td>Subscale 4</td>
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<tr>
<td>Participants</td>
<td></td>
<td></td>
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<tr>
<td>completely</td>
<td>4.6 (4.5)/4.3 (5.2)</td>
<td>4.4 (4.8)/3.4 (4.5)</td>
<td>4.5 (5.0)/3.9 (4.5)</td>
</tr>
<tr>
<td>discontinued</td>
<td>4.8 (4.2)/6.5 (6.0)</td>
<td>5.2 (4.2)/6.2 (5.5)</td>
<td>5.0 (4.3)/5.0 (4.8)</td>
</tr>
<tr>
<td>Subscale 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>completely</td>
<td>9.6 (7.3)/9.0 (8.3)</td>
<td>10.0 (7.4)/8.6 (8.3)</td>
<td>10.2 (7.7)/6.7 (6.3)</td>
</tr>
<tr>
<td>discontinued</td>
<td>12.6 (8.6)/15.9 (12.8)</td>
<td>11.5 (8.2)/14.3 (12.2)</td>
<td>10.9 (8.2)/12.3 (10.1)</td>
</tr>
<tr>
<td>AIMS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>completely</td>
<td>2.7 (3.1)/2.5 (3.2)</td>
<td>2.5 (3.2)/2.5 (3.4)</td>
<td>2.4 (3.3)/1.8 (2.7)</td>
</tr>
<tr>
<td>discontinued</td>
<td>3.1 (3.5)/4.2 (4.2)</td>
<td>3.4 (3.3)/4.5 (3.8)</td>
<td>3.2 (3.2)/3.4 (3.2)</td>
</tr>
<tr>
<td>BARS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>completely</td>
<td>3.6 (5.1)/3.8 (5.0)</td>
<td>3.4 (4.9)/3.4 (5.0)</td>
<td>4.2 (6.0)/3.7 (5.3)</td>
</tr>
<tr>
<td>discontinued</td>
<td>3.1 (5.1)/3.7 (6.0)</td>
<td>3.6 (5.3)/3.4 (4.9)</td>
<td>3.1 (4.4)/3.1 (4.7)</td>
</tr>
<tr>
<td>UPDRS</td>
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<td></td>
</tr>
<tr>
<td>Participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>completely</td>
<td>1.0 (1.6)/1.1 (1.9)</td>
<td>0.9 (1.2)/0.7 (1.2)</td>
<td>0.9 (1.3)/0.8 (1.3)</td>
</tr>
<tr>
<td>discontinued</td>
<td>1.1 (2.0)/1.1 (1.6)</td>
<td>1.3 (2.1)/1.4 (1.9)</td>
<td>1.3 (2.1)/0.8 (1.3)</td>
</tr>
</tbody>
</table>
## Table 1

<table>
<thead>
<tr>
<th>Condition</th>
<th>Completely Discontinued</th>
<th>Incompletely Discontinued</th>
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<td><strong>EPS total</strong></td>
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<td></td>
</tr>
<tr>
<td>Participants completely</td>
<td>1.8 (2.3)/1.4 (2.0)</td>
<td>1.7 (2.4)/1.1 (1.8)</td>
</tr>
<tr>
<td>discontinued</td>
<td>1.1 (1.7)/1.2 (1.7)</td>
<td>1.5 (1.9)/1.1 (1.5)</td>
</tr>
<tr>
<td>Participants incompletely</td>
<td>1.6 (1.9)/1.5 (2.0)</td>
<td></td>
</tr>
<tr>
<td>discontinued</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SCOPA-AUT total</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants completely</td>
<td>4.9 (5.3)/5.7 (7.0)</td>
<td>4.8 (5.4)/4.4 (5.5)</td>
</tr>
<tr>
<td>discontinued</td>
<td>5.4 (7.2)/6.0 (7.8)</td>
<td>5.8 (6.7)/6.1 (7.1)</td>
</tr>
<tr>
<td>Participants incompletely</td>
<td>5.1 (5.9)/11.3 (8.4)</td>
<td>5.6 (6.4)/7.4 (4.7)</td>
</tr>
<tr>
<td>discontinued</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Aberrant behavior Checklist; total and subscales 1 (irritability), - 2 (lethargy), - 3 Stereotypy, - 4 (hyperactivity) and - 5 (inadequate speech); 2 Abnormal Involuntary Movement Scale items 1 through 9; 3 Barnes akathisia objective symptoms, subjective symptoms and burden scale; 4 Unified Parkinson Disorder Rating Scale motor items 20, 21, 22 and 31; 5 Total of scores of extrapyramidal symptoms as measured with the AIMS, BARS and UPDRS; 6 total of autonomic symptoms as measured with the adapted Scale Outcomes Parkinson-autonomic symptoms

* Paired samples within groups: Significant difference according to Wilcoxon Signed rank test (hyperactivity) and - 5 (inadequate speech)

† one participant had died; †† two participants had died; ††† two participants had died and data of ten participants missing due to clinicians failing to provide data
Supplemental Table 2: Differences between groups of participants with intellectual disability who had completely and incompletely discontinued their long-term off-label use of antipsychotics at 16 weeks (discontinuation as per protocol), 28 and 40 weeks (follow-up) after the first dose reduction.

<table>
<thead>
<tr>
<th></th>
<th>Complete (n=79)/incomplete (n=49)*</th>
<th>Complete (n=60)/incomplete (n=67) *</th>
<th>Complete (n=51)/incomplete (n=68) *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity of intellectual disability</strong></td>
<td>2.5(0.9)/2.2(0.9) t=+0.38; p&lt;0.05</td>
<td>2.5(0.9)/2.2(0.9) t=+0.38; p&lt;0.05</td>
<td>2.5(0.9)/2.2(0.9) t=+0.38; p&lt;0.05</td>
</tr>
<tr>
<td><strong>History of surgical conditions (%)</strong></td>
<td>35/16 Pearson Chi²=3.78; p=0.05</td>
<td>43/16 Pearson Chi²=9.93; p=0.002</td>
<td>44/14 Pearson Chi²=11.60; p=0.001</td>
</tr>
<tr>
<td><strong>History of dermatoses (%)</strong></td>
<td>19/4 Pearson Chi²=5.47; p=0.02</td>
<td>33/55 Pearson Chi²=4.34; p=0.04</td>
<td>33/55 Pearson Chi²=4.34; p=0.04</td>
</tr>
<tr>
<td><strong>Presence of neurological conditions (including sensory impairment) (%)</strong></td>
<td>35/61 Pearson Chi²=7.34; p=0.007</td>
<td>35/60 Pearson Chi²=6.32; p=0.01</td>
<td>35/60 Pearson Chi²=6.32; p=0.01</td>
</tr>
<tr>
<td><strong>Dose of antipsychotic drugs (Defined Daily Dose) (mean/SD)</strong></td>
<td>0.48(0.50)/0.69(0.50) t=-2.61; p=0.01</td>
<td>0.48(0.50)/0.69(0.50) t=-2.61; p=0.01</td>
<td>0.48(0.50)/0.69(0.50) t=-2.61; p=0.01</td>
</tr>
<tr>
<td><strong>Use of &gt;1 antipsychotic drug simultaneously (%)</strong></td>
<td>2/13 Pearson Chi²=5.16; p=0.02</td>
<td>2/13 Pearson Chi²=4.02; p=0.05</td>
<td>2/13 Pearson Chi²=4.02; p=0.05</td>
</tr>
<tr>
<td><strong>Severity of symptoms of side-effects: UPDRS² (mean/SD) 40 weeks</strong></td>
<td>2.3(0.9)/3.7(3.1) p=0.02*</td>
<td>2.3(0.9)/3.7(3.1) p=0.02*</td>
<td>2.3(0.9)/3.7(3.1) p=0.02*</td>
</tr>
<tr>
<td><strong>Event of worsening in health (range 0-6/4 weeks)</strong></td>
<td>1.3(1.7)/2.5(2.1) t=3.43; p=0.001</td>
<td>1.3(1.7)/2.5(2.1) t=3.43; p=0.001</td>
<td>1.3(1.7)/2.5(2.1) t=3.43; p=0.001</td>
</tr>
<tr>
<td><strong>Baseline-16 weeks 16-28 weeks (mean/SD)</strong></td>
<td>33.3(26.7)/52.7(38.8) p=0.01*</td>
<td>33.3(26.7)/52.7(38.8) p=0.01*</td>
<td>33.3(26.7)/52.7(38.8) p=0.01*</td>
</tr>
<tr>
<td><strong>28-40 weeks (mean/SD)</strong></td>
<td>30.3(25.9)/49.7(35.1) p=0.003*</td>
<td>30.3(25.9)/49.7(35.1) p=0.003*</td>
<td>30.3(25.9)/49.7(35.1) p=0.003*</td>
</tr>
<tr>
<td><strong>Baseline-40 weeks (mean/SD)</strong></td>
<td>27.5(21.5)/42.2(32.3) p=0.02*</td>
<td>27.5(21.5)/42.2(32.3) p=0.02*</td>
<td>27.5(21.5)/42.2(32.3) p=0.02*</td>
</tr>
<tr>
<td><strong>ABC² total (mean/SD) 16 weeks</strong></td>
<td>10.1(9.8)/16.9(12.7)</td>
<td>10.1(9.8)/16.9(12.7)</td>
<td>10.1(9.8)/16.9(12.7)</td>
</tr>
<tr>
<td><strong>28 weeks</strong></td>
<td>10.1(9.8)/16.9(12.7)</td>
<td>10.1(9.8)/16.9(12.7)</td>
<td>10.1(9.8)/16.9(12.7)</td>
</tr>
<tr>
<td><strong>40 weeks</strong></td>
<td>10.1(9.8)/16.9(12.7)</td>
<td>10.1(9.8)/16.9(12.7)</td>
<td>10.1(9.8)/16.9(12.7)</td>
</tr>
</tbody>
</table>

*Significance level: p<0.05

**Table footnote:**
1. Defined as an IQ score between 1 and 70.
2. UPDRS²: Unified Parkinson's Disease Rating Scale Part II.
3. ABC²: activities of daily living scale.
4. *Significance level: p<0.01
<table>
<thead>
<tr>
<th></th>
<th>p-value</th>
<th>[Mean/SD]</th>
<th>p-value</th>
<th>[Mean/SD]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC subscale 2</td>
<td>p=0.02</td>
<td>10.4(9.4)/15.4(11.9)</td>
<td>p=0.03</td>
<td>10.4(9.4)/15.4(11.9)</td>
</tr>
<tr>
<td>(mean/SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 weeks</td>
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<tr>
<td>40 weeks</td>
<td></td>
<td></td>
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<tr>
<td>ABC subscale 3</td>
<td>p=0.04</td>
<td>4.3(5.2)/6.5(6.0)</td>
<td>p=0.05</td>
<td>4.3(5.2)/6.5(6.0)</td>
</tr>
<tr>
<td>(mean/SD)</td>
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<td></td>
</tr>
<tr>
<td>16 weeks</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>28 weeks</td>
<td></td>
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</tr>
<tr>
<td>ABC subscale 4</td>
<td>p=0.02</td>
<td>2.5(3.4)/4.5(3.8)</td>
<td>p=0.004</td>
<td>2.5(3.4)/4.5(3.8)</td>
</tr>
<tr>
<td>(mean/SD)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 weeks</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>40 weeks</td>
<td></td>
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</tr>
</tbody>
</table>

1-4: profound=1, severe=2, moderate=3, mild=4; \(^2\) Unified Parkinson Disorder rating Scale; motor items 20, 21, 22 and 31; \(^3\) Aberrant Behavior Checklist; total and subscales 1 (irritability), 2 (laziness), 3 Stereotypy, 4 (hyperactivity) and 5 (inadequate speech).

\(^*\) one participant had died; \(^*\) two participants had died; \(^*\) two participants had died and data of ten participants missing due to clinicians failing to provide data.

\(^\&\) Independent samples Mann-Whitney U test. \(^\#\) t-test; a negative value of t relates to incomplete discontinuation.

Significant difference is defined for p-values of <0.05.
Supplemental Table 3: Determinants/baseline characteristics in univariate regression analyses for successful discontinuation of long-term off-label used antipsychotic drugs in people with intellectual disability (n=129) at 16 weeks (per protocol), 28 and 40 weeks (follow-up) after the first dose reduction.

<table>
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<tr>
<th>Determinants</th>
<th>16 weeks</th>
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</thead>
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<td>Age</td>
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</tr>
<tr>
<td>Male sex</td>
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<tr>
<td>Less severe intellectual disability</td>
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<tr>
<td>No history of surgical conditions</td>
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</tr>
<tr>
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</tr>
<tr>
<td>No autism spectrum disorder</td>
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<tr>
<td>No recent life-event/hospitalization</td>
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<tr>
<td>No stressful family conditions</td>
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<tr>
<td>Worsening in health /16-28 weeks</td>
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<tr>
<td>Worsening in health /28-40 weeks</td>
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</tr>
<tr>
<td>Worsening in health /0-40 weeks</td>
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<td></td>
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<tr>
<td>No use of&gt; 1 antipsychotic drug simultaneously</td>
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</tr>
<tr>
<td>Higher dose of antipsychotic drug</td>
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<tr>
<td>Larger living group size</td>
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<tr>
<td>ABC at 16 weeks</td>
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<tr>
<td>ABC at 28 weeks</td>
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<tr>
<td>ABC at 40 weeks</td>
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<tr>
<td>BARS at 16 weeks</td>
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<td>BARS at 28 weeks</td>
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<td>UPDRS at 40 weeks</td>
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1 Odds ratio
2 significance level p-value <0.05; 3 Significant association
3 Aberrant Behavior Checklist (ABC); range 0-174
4 Barnes akathisia objective symptoms, subjective symptoms and burden scale; range 0-9.
5 Unified Parkinson Disorder Rating Scale motor items 20,21,22 and 31; range 0-16