An open label discontinuation trial of long-term used off-label antipsychotic drugs in people with intellectual disability

de Kuijper, Gerda M.; Hoekstra, Pieter J.

Published in:
Journal of Applied Research in Intellectual Disabilities

DOI:
10.1111/jar.12528

Received: 4 January 2018 | Revised: 12 July 2018 | Accepted: 28 August 2018

DOI: 10.1111/jar.12528

ORIGINAL ARTICLE

WILEY JARID Journal of Applied Research in Intellectual Disabilities bild

An open label discontinuation trial of long-term used off-label antipsychotic drugs in people with intellectual disability: The influence of staff-related factors

Gerda M. de Kuijper[1,2] | Pieter J. Hoekstra[2]

[1]Centre for Intellectual Disabilities and Mental Health/GGZ Drenthe, Assen, The Netherlands

[2]Department of Psychiatry, University of Groningen, University Medical Center Groningen, University Centre Child and Adolescent Psychiatry, Groningen, The Netherlands

Correspondence
Gerda M. de Kuijper, Centre for Intellectual Disabilities and Mental Health/GGZ Drenthe, Assen, The Netherlands.
Email: g.dekuijper@home.nl
and
Pieter J. Hoekstra, University Medical Centre Groningen, University Centre Child and Adolescent Psychiatry, Groningen, The Netherlands.
Email: p.hoekstra@accare.nl

Funding information
The study was funded by Stichting Zorgondersteuning, Soesterberg, the Netherlands (20130022).

Abstract

Background: Results of discontinuation of antipsychotics in people with intellectual disability are variable and may depend on staff factors.

Method: We attempted to taper off antipsychotics in 14 weeks after which participants were free to restart. We investigated the influence of support professionals' feelings towards challenging behaviour, their knowledge of psychotropic drugs and clinicians' judgements of participants' behavioural functioning on whether or not antipsychotics were completely discontinued after 16, 28 and 40 weeks.

Results: Of the 129 participants, 61% achieved discontinuation at 16 weeks; at 28 and 40 weeks, 46% and 40% were completely discontinued. Staff's feelings of Depression/Anger towards their client's behaviour, less knowledge about psychotropic medication and clinicians' judgements of behavioural worsening were negatively associated with achievement of discontinuation.

Conclusions: To enhance discontinuation off-label drug use, staff's feelings should be explored, their knowledge of psychotropic drugs improved and reasons for clinicians' judgements of participants' behavioural worsening investigated.

1 | INTRODUCTION

The use of psychotropic drugs in people with intellectual disability is a point of concern for many clinicians, caregivers, clients' representatives and policymakers. On the one hand, there is need for prescription of this kind of medication, because the incidence and prevalence of mental disorders in people with intellectual disability are high (Cooper, Smiley, Morrison, Williamson, & Allan, 2007; Smiley et al., 2007). On the other hand, there may be overuse of psychotropic drugs, because prescriptions are off-label in a majority and mostly in absence of a diagnosis of a mental disorder (Sheehan et al., 2015). Indeed, the perceived overmedication especially of antipsychotic drugs in people with intellectual disability has been illustrated in a recent study (O'Dwyer et al., 2017). In case psychotropic drugs are off-label prescribed for challenging behaviour, where there is lack of proven effectiveness, prescriptions should be limited to an as short as possible period of time (https://www.nice.org.uk/guidance/ng11; WPA/SPID 2010).

Although guidelines of intellectual disability mental health care recommend to discontinue long-term off-label used antipsychotic drugs, in clinical practice, this is not always possible. In our recent study on reasons for ongoing off-label antipsychotic drug use, physicians indicated that fear for disturbance in clients' behaviour (especially for an increase in symptoms of restlessness, aggression and autism), presence of changes in living situation or the occurrence of life events, and objections against discontinuation of staff members and legal representatives were reasons not to discontinue. In just over half of cases, physicians judged that their clients were eligible to discontinue their long-term off-label antipsychotic use (de Kuijper & Hoekstra, 2017).

In a systematic review of studies on antipsychotic drugs reduction and discontinuation in people with intellectual disability, Sheehan and Hassiotis (2017) concluded that a substantial proportion of clients attempting to discontinue showed behavioural worsening which prevented discontinuation. The causes of such failure were diverse, and predictors could not reliably be identified (Sheehan & Hassiotis, 2017).

Potential causes hindering a discontinuation attempt may lie in unrecognized withdrawal symptoms, which may present as behavioural disturbance. Physicians may then react with changes in medication, most often by increasing dosages and/or addition of new psychotropic medications (Valdovinos, Caruso, Roberts, Kim, & Kennedy, 2005). Furthermore, symptoms of mental or physical disorders, which may come to light during discontinuation, may be mistaken for maladaptive behavioural symptoms. Also staff-related factors may play a role in the results of discontinuation trajectories. Support professionals may have difficulties in managing the behavioural problems of their clients. Staff members may have beliefs that their clients are in need of psychotropic drugs. Indeed, studies have shown a relationship of staff-related factors, that is, staff's knowledge of psychotropic drug use and cognitions and attitude towards challenging behaviour with the likelihood of the use of psychotropic drugs and severity of behavioural symptoms of clients (Hastings, 1997; Lambrechts, Kuppens, & Maes, 2009; Singh et al., 1996). Moreover, studies have shown that support professionals' knowledge of psychotropic drugs is often insufficient, that their expectations towards the effects of antipsychotics are frequently unrealistic, and that they often lack sufficient knowledge regarding the possible side-effects of psychotropic drugs (Fretwell & Felce, 2007; de Kuijper & van der Putten, 2017). Support professionals indicate that they are in need of more knowledge on the effects of psychotropic drug use in clients with intellectual disability (Donley, Chan, & Webber, 2012; de Kuijper & van der Putten, 2017).

Because of the relevance of reducing the overuse of antipsychotic drugs for challenging behaviour, we were interested in factors which may potentially hinder successful discontinuation or predict behavioural worsening during discontinuation trajectories. Therefore, we set up a study on determinants for success or failure of discontinuation of long-term off-label used antipsychotics in people with intellectual disability (de Kuijper & Hoekstra, 2018).

In the present study, we report on the influence of staff-related factors on results of discontinuation trajectories and the behaviour of their clients. We hypothesized that more negative feelings towards challenging behaviour of clients and less knowledge towards effects of psychotropic drug use of support professionals, and higher severity of behavioural symptoms as assessed by clinicians predicted less chance of successful discontinuation. Other questions were whether there was a relationship between support professionals' feelings and participants' behaviour, and whether we could identify factors which were related to clinicians' judgements of worsening of behaviour during discontinuation.

2 | METHODS

2.1 | Design and setting

In this open label discontinuation trial, we prospectively investigated the influence of staff-related factors that were potentially associated with successful discontinuation of long-term used antipsychotics for challenging behaviour in people with intellectual disability. Study settings were living facilities of six care providing organizations.

2.2 | 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 behaviour. All legal representatives had provided written informed consent. 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. Use of other psychotropic drugs was not an exclusion criterion.

2.3 | Procedures

Potential participants received a treatment proposal from their physician involving an attempt to discontinue antipsychotics. Discontinuation was guided 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 off antipsychotic drugs in a relatively short time frame was done safely (de Kuijper, Evenhuis, Minderaa, & Hoekstra, 2014). The study was performed as part of regular clinical care. This meant 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, should use a higher dose or restart the antipsychotic drug use.

Participants were included from 1st of January 2015 till 1st 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. We also collected baseline participant characteristics, that is, age, gender, severity of intellectual disability, the presence of autism spectrum disorder and living situation. Furthermore, we collected baseline support professionals' characteristics, that is, age, gender, education and years of working experience, and agreement in staff members on the decision to discontinue participants' long-term use.

We asked the main support professional of the participant whether he or she was willing to provide information with regard to his or her reactions towards challenging behaviour of the participant and with regard to his or her knowledge of use of psychotropic agents. The measurements of support professional related factors took take place twice, at baseline and at 16 weeks after the first dose reduction.

We used three time points to assess achievement of complete discontinuation, that is, 16, 28 and 40 weeks after the first dose reduction, reflecting the time points shortly after the scheduled discontinuation and at 3 and 6 months follow-up, respectively.

The study had been approved by the Medical Ethical Committee University Groningen, METc 2014/402 and is registered in the Netherlands National Trial Register, NTR 5519 to which we added data on open label discontinuation of risperidone (NTR5519 excludes use of risperidone).

2.4 | Outcomes

The primary outcome was achievement of complete discontinuation at 16 weeks. Secondary outcomes were achievement of complete discontinuation at 28 and 40 weeks, the Aberrant Behaviour Checklist (ABC) and its five subscales, that is, irritability, lethargy, stereotypic behaviour, hyperactivity and inadequate speech, the Clinical Global Impression scale-severity (CGI-S) and the Clinical Global Impression scale-Improvement (CGI-I) with regard to severity of psychiatric symptoms and challenging behaviour. The ABC is a standardized, validated scale developed to measure severity of challenging behaviours and effects of treatment on the behaviour (Aman, Burrow, & Wolford, 1995; Aman, Singh, Stewart, & Field, 1985). The ABC was completed by the main caregiver. We defined changes of >8 points in ABC total scores (0.33 *SD*) as clinically relevant. The CGI-S and CGI-I are frequently used instruments to assess the severity and effects of treatment on a seven-point scale (1 = absent to 7 = very severe and 1 = very much improved to 7 = very much worse, respectively). The CGI-S and CGI-I were completed by the main clinician, that is, the behavioural scientist or the intellectual disability physician.

2.5 | Determinants

Possible determinants of successful discontinuation at 16 weeks were baseline severity of participants' behavioural symptoms as assessed with the CGI-S, and support professionals' baseline confidence and feelings towards challenging behaviour of their clients, their knowledge of psychotropic drug use, expectations towards effects of antipsychotic drugs and agreement of staff members concerning clients' eligibility to discontinue.

To assess feelings and knowledge towards challenging behaviour and psychotropic drug use of the direct support professionals of participants, we used translated and validated versions of the Challenging Behavior Self Efficacy Scale (CBSES; Hastings & Brown, 2002) and the Emotional Reactions to Challenging Behavior (ERCB) scale (Mitchell & Hastings, 1998). Both have been translated and validated in the Netherlands. In the ERCB, four profiles of staff characteristics are distinguished: Confident–Relaxed, Cheerful–Excited, Fear–Anxiety and Depression–Anger. We also used two self-designed questionnaires with adequate psychometric properties (de Kuijper & van der Putten, 2017). One questionnaire rates support professionals' knowledge of psychotropic drugs, consisting of 12 questions regarding indications, effects and side-effects and 3 additional questions on the psychotropic drug use of professionals' own clients. The other questionnaire comprises 26 questions on expectations of support professionals towards potential physical, psychological and behavioural effects of antipsychotic drug use in people with intellectual disabilities, and a question whether professionals felt they had enough information regarding effects and side-effects of psychotropic drugs. To assess whether the expectations were more or less realistic, we recoded responses to this latter questionnaire into three categories of realistic, less realistic and unrealistic. We removed the questions on comparisons of effects of antipsychotic drugs with behavioural interventions (i.e., questions 11 and 12) and those on effects of antipsychotics on daily functioning (questions 12, 14, 15, 20 and 21).

Possible determinants of successful discontinuation at 28 and 40 weeks were the severity of behavioural symptoms as assessed with the CGI-S and the CGI-I at the time points 16, 28 and 40 weeks and agreement of staff members concerning clients' eligibility for ongoing discontinuation and support professional related factors as measured at 16 weeks.

2.6 | Sample size

The sample size calculation was based on potential associations of support professional-related determinants with achievement of complete discontinuation by means of multivariate logistic regression analyses. With a total of 6 variables, a medium effect size of 0.15, a power of 0.80 and a probability level of 0.05 a sample size of 97 participants was required.

2.7 | Statistical analyses

The main study parameter was achievement of complete discontinuation by participants at 16 weeks (i.e., 2 weeks after the scheduled complete discontinuation) and at two follow-up time points, 28 and 40 weeks after the first dose reduction. We used outcomes at baseline and at these three points for comparisons within and between groups. Paired sample *t* tests were used for comparisons of continuous variables within groups, that is, baseline with 16 weeks, with 28 and with 40 weeks, respectively. Independent sample *t* tests were used for comparisons of continuous variables and Pearson's chi-squared tests for comparisons of categorical variables between groups. In case of non-normal distribution of continuous variables, we used nonparametric tests, that is, Wilcoxon signed rank test for paired samples and Mann–Whitney *U* test for independent sample testing.

Univariate and multivariate logistic regression analyses were used to analyse associations of outcome measures and of participant and support professionals characteristics with odds for complete discontinuation at the time points 16, 28 and 40 weeks, and odds for worsening in behaviour as assessed with the CGI-I at 16 weeks.

The variables with a p-value < 0.2 in univariate analyses were used in multivariate stepwise logistic regression analyses. We adjusted for differences in participants' characteristics between those who had and who had not successfully discontinued by adding the relevant variables in the stepwise regression analyses. Ratings at previous time points were used as baseline for later time points, that is, baseline ratings with odds for successful discontinuation at 16 weeks, 16 week ratings with odds at 28 weeks and 28 weeks ratings with odds at 40 weeks.

Pearson Correlation tests were used to analyse potential correlations of support professional characteristics with behavioural symptoms of participants as measured with ABC subscales, and for potential correlations of differences in ABC (subscale) scores between baseline and 16, 28 and 40 weeks, respectively, with CGI-I outcomes at these three time points. We defined a weak correlation as a Pearson Correlation (r) $0.30 < r < 0.50$, a moderate correlation as $0.50 < r < 0.70$ and a strong correlation as $<0.70 < r < 0.90$.

As there were very few participants who had shown very much improvement or very much worsening according to the CGI-I, we merged CGI-I results of changes in severity of behavioural symptoms into three categories, that is, improvement, no or minimal change and worsening. A p-value of <0.05 was used to indicate significant differences.

3 | RESULTS

3.1 | Sample characteristics

Of the 997 persons in the living facilities of service providers who used antipsychotics, 499 were eligible to discontinue their long-term use according to clinicians' judgement. For 134 persons of those the legal representative had provided informed consent for clients' participation in the study, of which five participants withdrew before study entrance. The mean age of participants was 49 years, 67% were male, 16% had a profound, 44% a severe, 24% a moderate and 13% a mild intellectual disability (3% missing) and 67% had a comorbid diagnosis of autism spectrum disorder.

3.2 | Achievement of discontinuation

At 16 weeks 61% of participants, at 28 weeks 46% and at 40 weeks 40% of participants were completely off antipsychotic drug use. Two participants died of cancer at 16 and 28 weeks, respectively. There were significant differences in participants' characteristics between those who had and those who had not completely discontinued at 16 weeks (higher severity of intellectual disability in those who had not discontinued), and at 28 weeks and 40 weeks (more often presence of autism spectrum disorder in those who had not discontinued).

3.3 | Behavioural outcomes

With paired sample testing, we found that the mean total ABC scores were similar at 16 weeks in those who had completely discontinued and had decreased significantly at the time points of 28 weeks (38.5 vs. 30.1, $t = 2.62$, $p = 0.01$) and 40 weeks (37.4 vs. 27.5, $t = 2.93$, $p = 0.005$) compared to baseline. In those who had incompletely discontinued mean total ABC scores had slightly increased at the time points 28 and 40 weeks, but this difference was not significant; yet, we found a not significant but clinically relevant difference at the time point of 16 weeks (43.6 vs. 52.5).

Mean scores of ABC total and of ABC subscales were significantly lower in those with complete discontinuation compared to those with incomplete discontinuation at the time points 16 weeks (ABC total,- subscales 1, 3 and 4), 28 weeks (ABC total, -subscales 1, 2, 3, 4 and 5) and 40 weeks (ABC total, -subscales 2, 4 and 5).

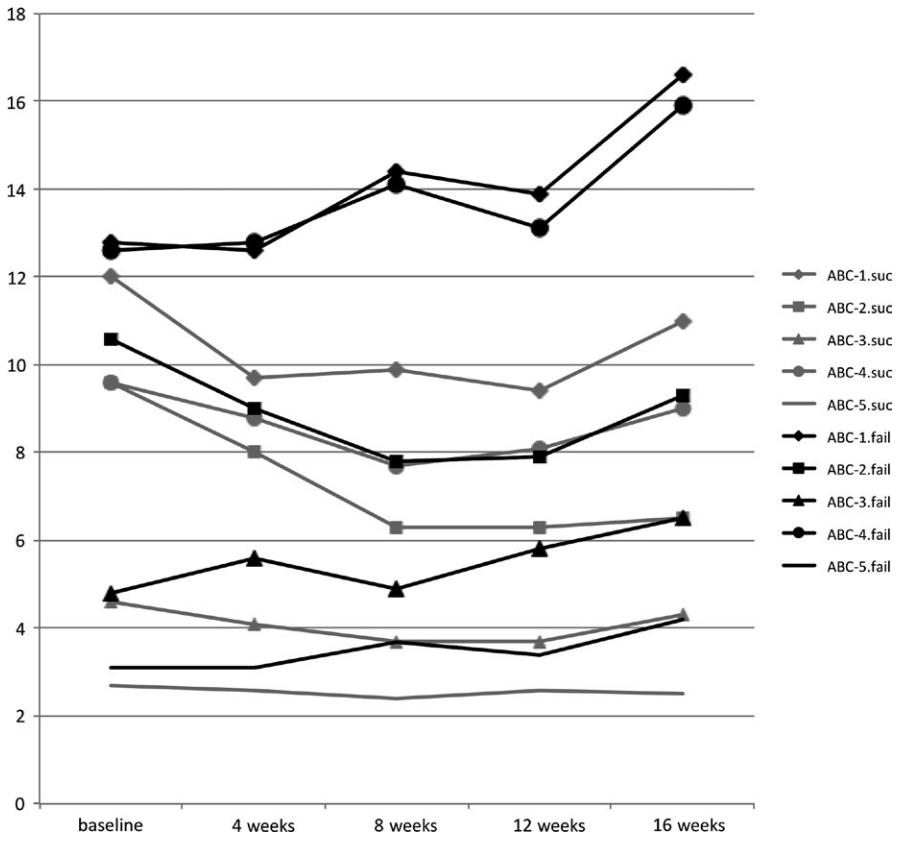

FIGURE 1 Course of ABC subscale scores in a sample of 127 participants who had completely (.suc/grey lines) and incompletely (.fail/black lines) discontinued off-label long-term use of antipsychotics for behavioural symptoms at the time point after the scheduled discontinuation, that is, 16 weeks after the first dose reduction. ABC: Aberrant Behaviour Checklist; ABC-1: irritability scale; ABC-2: lethargy scale; ABC-3: stereotypic behaviour scale; ABC-4: hyperactivity scale; ABC-5: inadequate speech scale

TABLE 1 Clinical Global Impression Scale-Severity (CGI-S) and Clinical Global Impression Scale-Improvement (CGI-I) in people with intellectual disability (n = 129) who discontinued long-term off-label used antipsychotic drugs

	Baseline vs. 16 weeks[a] (mean/*SD*)	Baseline vs. 28 weeks[b] (mean/*SD*)	Baseline vs. 40 weeks[b] (mean/*SD*)
CGI-S/paired samples			
Participants completely discontinued	2.6* (1.6)/2.6 (1.5)	2.4 (1.5)/2.6 (1.5)	2.5* (1.6)/2.5 (1.5)
Participants incompletely discontinued	1.9* (1.5)/2.4 (1.7)[c]	2.4 (1.7)/2.7 (1.6)	2.6* (1.7)/3.1 (1.5)[c]
CGI-I/improvement/no change/worse			
Participants completely discontinued	6 (7.5%)/63 (80%)/4 (5%) Missing: 6 (7.5%)	4 (7%)/44 (73%)**/3 (5%)** Missing: 9 (15%)	12 (23%)/30 (59%)/1 (2%) Missing: 8 (16%)
Participants incompletely discontinued	1 (2%)/31 (63%)/6 (12%) Missing: 11 (23%)	1 (6%)/32 (48%)**/12 (18%)** Missing: 17 (25%)	7 (10%)/36 (53%)/5 (7%) Missing: 20 (30%)

[a]Discontinuation per-protocol. [b]Follow-up 28 and 40 weeks after the first dose reduction. [c]Paired samples within groups: Significant difference according to paired T test.
*Significant difference ($p < 0.05$) between groups according to independent samples T test. **Significant difference ($p < 0.05$) between groups according to Pearson's chi-squared test.

TABLE 2 Characteristics and ratings at questionnaires of main support professionals of 129 participants with intellectual disability who discontinued long-term off-label used antipsychotic drugs

Age in years (mean, *SD*)	37.3 (10.6) missing 10%	
Gender, male/female, (number, %)	16 (12.4%)/91 (70.5%) missing 17%	
Type of education[a]	1: 50 (38.8%) 2: 36 (27.9%) 3: 7 (5.4%) missing 30%	
Level of education[b] (number, %)	1: 4 (3.1%) 2: 60 (46.5%) 3: 30 (23.3%) missing 27%	
Education on psychotropic drugs[c] (mean/*SD*, range)	3.25 (1.9), 0–6 missing 13%	
Working experience in the field in years (mean, *SD*)	13.4 (8.3) missing 12%	
Ratings at questionnaires	**Baseline (mean/*SD*)**	**16 weeks[d] (mean/*SD*)**
ERCB[f]/CR	9.3 (2.6); missing 9%	9.4 (2.4); missing 47%
ERCB[f]/CE	5.3 (3.0); missing 22%	4.8 (3.0); missing 52%
ERCB[f]/FA	1.5 (2.0); missing 10%	1.0 (1.2); missing 47%
ERCB[f]/DA	4.0 (3.0); missing 9%	3.9 (3.0); missing 47%
CBSE[g]	28.6 (3.9); missing 9%	28.3 (4.5); missing 46%
Knowledge[e,h]	74.6 (13.7); missing 63%	70.2 (13.0); missing 50%
Expectations[i]	35.6 (5.1); missing 34%	36.3 (5.6); missing 34%
Information[j]	0.9 (0.9); missing 14%	1.2 (1); missing 18%

[a]1 = educational background (social work), 2 = medical (nursing) background, 3 = other. [b]1 = Higher educational level or university of applied sciences, 2 = senior secondary vocational education, 3 = lower vocational education. [c]0–8 max. [d]16 weeks after first dose reduction. [e]Percentile score. [f]Emotional Reactions to Challenging Behaviour scale; four profiles CR = Confident–Relaxed (0–12)/CE = Cheerful-Excited (0–12)/FA = Fear-Anxiety (0–15)/DA = Depression–Anger (0–30). [g]Challenging Behavior Self Efficacy Scale (0–35). [h]Knowledge on indications and effects of psychotropic drug use. [i]Expectations towards physical, behavioural and psychological effects of antipsychotic drug use in people with intellectual disability; range 0–57; lower ratings represent more realistic expectations. [j]Support professionals' feelings regarding being informed on psychotropic drug use of their clients; range 0–2; higher ratings means better informed.

TABLE 3 Differences in staff-related factors between participants (n = 129) with intellectual disability who discontinued long-term off-label used antipsychotic drugs

	Complete[a] (n = 79)/incomplete (n = 49) discontinuation 16 weeks	Complete[b] (n = 60)/incomplete (n = 67) discontinuation 28 weeks	Complete[b] (n = 51)/incomplete (n = 68) discontinuation 40 weeks
Support professionals characteristics			
Gender of support professional (% male)		4/24 Pearson χ^2 = 9.74; p = 0.01	4/23 Pearson χ^2 = 7.55; p = 0.02
ERCB[d] Baseline Confident–Relaxed (mean/*SD*)	8.9(2.8)/10.2(1.9) t = −2.95[c]; p = 0.004		
ERCB Baseline Cheerful–Excited (mean/*SD*)	4.9(3.1)/6.2(2.5) t = −2.13[c]; p = 0.04		
ERCB 16 weeks Depression–Anger (mean/*SD*)	3.3(2.5)/5.0(3.6) t = −1.90[c]; p = 0.06*	3.0(2.4)/4.6(3.3) t = −2.27[c]; p = 0.03	2.4(1.7)/4.9(3.3) t = −3.95[c]; p < 0.001
CBSES[e] 16 weeks (mean/*SD*)		29.4(3.6)/27.5(5.0) t = +1.86[c]; p = 0.07*	30.2(3.0)/27.3(5.1) t = +2.62[c]; p = 0.01
Knowledge Psychotropic drugs[f] 16 weeks (mean/*SD*)			74.3(9.6)/67.2(15.1) t = +2.12[c]; p = 0.04
Clinicians' judgements of participants' behaviour as assessed with CGI			
CGI-S[g] baseline (mean/*SD*)	2.7(1.6)/1.8(1.5) t = +2.57[c]; p = 0.01		
CGI-S 40 weeks (mean/*SD*)			2.6(1.4)/3.1(1.5) t = −1.98[c]; p = 0.05
CGI-I[h] worse 16 weeks (number/percentage)	4(6%)/6(16%), p = 0.07* Pearson χ^2 = 3.24		
CGI-I worse 28 weeks (number/percentage)		3(6%)/12(24%), p = 0.01 Pearson χ^2 = 6.55	

[a]Discontinuation per-protocol. [b]Follow-up 28 and 40 weeks after the first dose reduction. [c]t test; a negative value of t relates to incomplete discontinuation. [d]Emotional reactions to challenging behaviour scale/subscales Confident–Relaxed (0–12), Cheerful–Excited (0–12), Fear-Anxiety (0–15), Depression–Anger (0–30); completed by the main caregiver at baseline and at 16 weeks. [e]Challenging Behavior Self Efficacy Scale (0–35); completed by the main caregiver at baseline and at 16 weeks. [f]Questionnaire Knowledge Psychotropic drugs (0–100); completed by the main caregiver at baseline and at 16 weeks. [g]Clinical Global Impression-Severity Scale: severity of behavioural symptoms of clients as judged by their main clinician. [h]Clinical Global Impression-Improvement Scale: improvement, no change or worsening of behavioural symptoms of clients as compared to baseline as judged by their main clinician.
Significant difference is defined for p-values of <0.05. *Near significant difference.

Figure 1 shows the course of ABC subscales from baseline to the time point of 16 weeks for participants who had succeeded and who had failed to completely discontinue at that time point.

Table 1 shows comparisons of CGI-S ratings at 16, 28 and 40 weeks with the baseline CGI-S as well as CGI-I outcomes at 16, 28 and 40 weeks for groups of participants who had and who had not completely discontinued their antipsychotic drug use at these time points. In the total group of participants, according to the CGI-I, at 16 weeks 6% of participants had shown improvement and 9% worsening in behaviour; at 28 weeks, these percentages were 9% and 15%, and at 40 weeks 21% and 7%, respectively. Only at 28 weeks did we find that those who had not achieved complete discontinuation had significantly more often worsening in behaviour according to the CGI-I than those who had successfully discontinued (18% vs. 5%, Pearson's chi-square = 6.55, p = 0.01).

3.4 | Support professionals characteristics

Table 2 shows characteristics of main support professionals and their questionnaire ratings at baseline and 16 weeks. With paired sample testing we found no significant differences between baseline and 16 weeks ERCBS and CBSES ratings. Unfortunately, a substantial part of support professionals had not provided all the data requested as shown by the percentage of missing data for all support professional-related variables.

3.5 | Differences between groups of participants of complete versus incomplete discontinuation

Table 3 shows differences in staff-related variables (support professionals' variables and CGI outcomes as assessed by the main clinician) between groups of participants who had and who had not achieved complete discontinuation at the time points 16, 28 and 40 weeks.

3.6 | Determinants for successful discontinuation

Table 4 shows associations with a p-value < 0.2 of support professional related determinants and of clinicians' assessments (CGI) with odds for complete discontinuation at 16, 28 and 40 weeks in univariate regression analyses.

In stepwise multivariate logistic regression analyses for odds of complete discontinuation at the different time points, we adjusted for differences in severity of intellectual disability (odds at 16 weeks) and prevalence of autism spectrum disorder (odds at 28 and 40 weeks). Complete discontinuation at 16 weeks was negatively associated with male gender of support professional and positively with less severe intellectual disability (OR = 0.17 [C.I. = 0.03–0.92], $p = 0.03$ and OR = 3.14 [CI = 1.41–7.0], $p = 0.005$, respectively). Complete discontinuation at 28 weeks was at trend level negatively associated with male gender of support professional and with higher ratings of ERCBS Depression/Anger (OR = 0.13 [CI = 0.01–1.20], $p = 0.07$ and OR = 0.79 [CI = 0.61–1.03], $p = 0.08$, respectively). We

TABLE 4 Staff-related determinants in univariate regression analyses for successful discontinuation of long-term off-label used antipsychotic drugs in people with intellectual disability ($n = 129$)

Support professionals characteristics	16 weeks[h]	28 weeks[i]	40 weeks[i]
Male gender of support professional	OR[a] = 0.41 (0.14–1.24)[b] 0.1 < p < 0.2	OR = 0.13 (0.03–0.60)[b] p* < 0.01**	OR = 0.16 (0.03–0.77)[b] p < 0.05**
Confident–relaxed at baseline[c]	OR = 0.79 (0.66–095)[b] p = 0.01**		
Cheerfull–Excited at baseline[c]	OR = 0.86 (0.74–1.01)[b] 0.05 < p < 1.0		
Cheerfull–Excited at 16 weeks[c]	OR = 0.87 (0.73–1.05)[b] 0.1 < p < 0.2		
Depression–Anger at 16 weeks[c]	OR = 0.83 (0.70–0.99)[b] p < 0.05**	OR = 0.82 (0.68–0.99)[b] p < 0.05**	OR = 0.71 (0.56–0.89)[b] p < 0.01**
CBSE scale at 16 weeks[d]		OR = 1.13 (0.99–1.29)[b] 0.05 < p < 0.1	OR = 1.23 (1.05–1.45)[b] p < 0.05**
Education on psychotropic drugs			
Baseline	OR = 1.16 (0.94–1.44)[b] 0.1 < p < 0.2		
At 16 weeks	OR = 1.04 (0.99–1.08)[b] 0.1 < p < 0.2		
Q. Knowledge at 16 weeks[e]	OR = 1.03 (0.99–1.07)[b] 0.1 < p < 0.2		OR = 1.05 (1.00–1.10)[b] p < 0.05**
Agreement in staff baseline	OR = 1.15 (0.95–1.38)[b] 0.1 < p < 0.2		
Clinicians' judgements of participants' behaviour as assessed with CGI			
CGI-S[f]			
Baseline	OR = 1.48 (1.01–2.06)[b] p < 0.05**		
CGI-S			
40 weeks			OR = 0.75 (0.56–1.00)[b] p = 0.05**
CGI-I[g] worse			
16 weeks	OR = 3.23 (0.85–12.26)[b] 0.05 < p < 0.1	OR = 4.33 (0.88–21.43)[b] 0.05 < p < 0.1	
28 weeks		OR = 5.06 (1.33–19.20)[b] p < 0.05**	OR = 13.26 (1.65–106.87)[b] p < 0.05**
40 weeks			OR = 4.88 (0.55–43.58)[b] 0.1 < p < 0.2
CGI-I better			
40 weeks			OR = 0.44 (0.16–1.25)[b] 0.1 < p < 0.2

[a]Odds ratio. [b]CI = Confidence Interval of OR [Exp(B)]. [c]Emotional reactions to challenging behaviour scale/subscales Confident–Relaxed; range 0–12, Cheerful–Excited; range 0–12, Fear-Anxiety; range 0–15, Depression–Anger; range 0–30. [d]Challenging Behaviour Self Efficacy Scale; range 0–35. [e]Questionnaire Knowledge of psychotropic drugs; % scores 0%–100%. [f]Clinical Global Impression-Severity (CGI-S); range 1–7. [g]Clinical Global Impression-Improvement (improved/no change/worse compared to baseline). [h]Discontinuation per-protocol. [i]Follow-up 28 and 40 weeks after the first dose reduction.

*Significance level p-value < 0.05. **Significant association.

found no associations of any variable with odds of complete discontinuation at 40 weeks; probably due to too much missing data which limited the number of cases included in this analysis.

With regard to the influence of clinicians judgements as assessed with the CGI-S, we found that higher severity of behavioural symptoms was associated with higher odds of complete discontinuation at 16 weeks (OR = 1.42 [CI = 1.01–1.92], $p = 0.02$). No worsening in CGI-I and absence of autism spectrum disorder were positively associated with complete discontinuation at 40 weeks (OR = 10.4 [CI = 1.23–87.92], $p = 0.03$ and OR = 2.77 [CI = 1.08–7.13], $p = 0.04$, respectively].

3.7 | Predictors for CGI-I worsening at 16 weeks (the time point of scheduled discontinuation)

In univariate analyses, there were no associations of participants' characteristics age, gender, severity of intellectual disability and the presence of autism with worsening according to the CGI-I. Less agreement in staff members with regard to participants' eligibility to discontinue the antipsychotic drug use at baseline and higher scores of ABC subscale 1, 4 and 5 at 16 weeks were associated with higher odds of worsening in behaviour at 16 weeks (OR = 0.65[0.45–0.95], $p = 0.03$; OR = 1.10[1.02–1.15], $p = 0.02$; OR = 1.10[1.02–1.15], $p = 0.008$ and OR = 1.24[1.04–1.48], $p = 0.02$, respectively).

In multivariate logistic regression analysis, adjusting for participants' baseline ABC scores, we found less agreement in staff members was associated with higher odds of worsening in behaviour (OR = 0.43[0.20–0.92, $p = 0.03$).

3.8 | Correlations of staff-related variables with behavioural symptoms as measured with the ABC

We found a number of weak correlations and no moderate and strong correlations between support professionals-related questionnaires and ABC scales at baseline and at 16 weeks:

Baseline: Positive correlations of ERCB-depression/anger with ABC subscale-irritability ($r = 0.33$) and -hyperactivity ($r = 0.30$). Negative correlation of ERCB-confident/relaxed with ABC subscale irritability ($r = 0.33$).

At 16 weeks: Positive correlations of ERCB-depression/anger with ABC subscale-irritability ($r = 0.58$), -lethargy ($r = 0.43$), -stereotypy ($r = 0.54$) and -hyperactivity ($r = 0.57$). Negative correlations of CBSES with ABC subscale-irritability ($r = 0.32$), -lethargy ($r = 0.32$), -stereotypy ($r = 0.44$) and -hyperactivity ($r = 0.40$).

We found no correlations of clinicians' judgements of the severity of behavioural symptoms as assessed with CGI-S and change in behaviour as assessed with CGI-I, with any of ABC scales at baseline and 16 weeks.

For CGI-I based worsening at the time points 28 and 40 weeks, we distinguished between participants who had completely tapered off their antipsychotic drug use and those who had not. In both groups, we found no correlations of CGI-based worsening with an increase in ABC scores at 28 weeks, nor at 40 weeks.

4 | DISCUSSION

In this prospective open label study, we hypothesized that staff's feelings and subjective judgements towards challenging behaviour, and their knowledge of antipsychotic drugs were related to success or failure in discontinuation of participants' off-label long-term antipsychotic drug use.

We indeed found significant differences in staff-related variables between those participants who succeeded and those who failed in complete discontinuation. Also, we found a number of staff-related factors that were associated with the chance of complete discontinuation. Male gender and feelings of depression/anger of support professionals, and clinicians' judgements of worsening in behaviour during the discontinuation trajectory were associated with a lesser chance of complete discontinuation, and clinicians' judgements of no worsening in behaviour with a higher likelihood. Furthermore, we found support professionals' education and knowledge of psychotropic drug use, and agreement in staff with regard to participants' eligibility to discontinue the antipsychotic drug use were positively associated with successful discontinuation. Remarkable findings were the association of support professionals' feelings of "cheerful/excited" and "confident/relaxed" with failure and the association of clinicians' judgement of higher baseline severity of maladaptive behaviour with success in discontinuation at 16 weeks.

The percentage of participants who achieved complete discontinuation is in line with figures of 4%–74% reported by Sheehan et al. (2017) in their systematic review of discontinuation studies, with studies using reduction programmes or scheduled discontinuation reporting the highest percentages. Of note, there was a fall in percentages of participants with complete discontinuation from 61% at the 16 weeks' time point of scheduled discontinuation to 46% at 28- and 40% at 40 weeks' follow-up. Thus, a substantial proportion of participants restarted the use of antipsychotics. Besides the influence of staff-related factors in sustaining the termination of antipsychotic drug use, this may also be related to participant factors like the presence of autism or worse health conditions (de Kuijper & Hoekstra, 2018). Also, symptoms of mental disorders which may emerge during discontinuation may be wrongly attributed to symptoms of challenging behaviours as were suggested by Perry et al. (2018) (Perry et al., 2018).

As far as we know, this study was the first investigating the relationship of staffs' feelings and knowledge with success or failure of off-label antipsychotic drug discontinuation in people with intellectual disability. Ahmed et al. (2000) investigated the influence of setting related factors; in their study, an association of more restrictive environments, lower staffing levels and less training of staff with failure in discontinuation has been shown (Ahmed et al., 2000).

The result of the present study, a positive association of more information and knowledge on psychotropic drug use in support professionals with successful discontinuation, is in line with this previous study.

Other previous studies had shown a relationship between higher severity of behavioural symptoms and failure to achieve discontinuation or reduction of antipsychotic drug use (Branford, 1996; de Kuijper & Hoekstra, 2018; de Kuijper et al., 2014; May et al., 1995). Therefore, we also investigated potential relationships of staff-related factors and severity of behavioural symptoms as measured with the ABC. We found weak correlations of higher ABC scores with more negative feelings of support professionals at baseline, and at 16 weeks, that is, the time point of (whether or not successful) scheduled discontinuation. Correlations between staffs' feeling and behaviour of their clients were also found in the study of Lambrechts et al. (2009) (Lambrechts et al., 2009). The present study also confirms results of this study with regard to the more frequent ratings of positive feelings of support professionals' characteristics compared to negative feelings, which was explained by the self-report nature of the questionnaires possibly leading to more social desirable answers. The mean ratings on knowledge of psychotropic drugs of support professionals were higher and unrealistic expectations towards effects of antipsychotic drug use on clients with intellectual disabilities of support professionals were lower than those found in a previous study (de Kuijper & van der Putten, 2017). This may be explained by the fact that support professionals in the present study were all main caregivers of clients with antipsychotic drug use participating in the study. They all had received comprehensive information on the rationale and background of discontinuation off-label antipsychotic drugs.

Clinicians' judgements of severity of maladaptive behaviour as assessed with CGI-S were not correlated with ABC scores, nor were those of worsening in behaviour during discontinuation as assessed with CGI-I with changes in ABC scores. We also found that worsening as per CGI-I was predicted by less agreement in staff on the decision of participants' antipsychotic drug discontinuation. This may suggest that staff-related factors also play a role in clinicians' subjective judgements of severity of challenging behaviour.

This study had some limitations which should be acknowledged. A major limitation was the missing data of support professionals, which we could not overcome, because we had to rely on their willingness to complete the questionnaires. Approximately just over half of professionals completed all questionnaires. This lack of data limited the possibilities to identify determinants of successful discontinuation.

Another limitation was that we did not investigate clinicians' characteristics.

A strength of the study is the prospective design in a clinical setting, the naturalistic nature and the relatively long follow-up period of six months. We were thus able to identify staff-related determinants for successful discontinuation at the short-term and at a longer term, while accounting for participants' characteristics.

5 | CONCLUSIONS/CLINICAL IMPLICATIONS

The present study showed that discontinuation of long-term antipsychotic drug use is often possible without behavioural deterioration as measured with a standardized scale and 40% of participants completely off antipsychotics at 40 weeks follow-up. Overall, during the study period, the percentage of worsening in behaviour of participants according to clinicians' judgements varied from 15% at short-term follow-up to 7% at long-term follow-up; improvement varied from 6% shortly after the scheduled discontinuation to 21% at long-term follow-up.

This study provides worthful information on factors which should be taken into account when a discontinuation trajectory of long-term antipsychotic drug use for challenging behaviour will be started. Support professionals should be educated in effects of psychotropic drugs, including management of side-effects and withdrawal symptoms, and receive training and support in understanding and management of challenging behaviour of clients with intellectual disability. Negative feelings of support professionals before and during discontinuation trajectories of clients should be recognized and addressed. Agreement in staff (caregivers, professionals, clinicians, managers) on policies regarding the need for psychotropic drug use in clients and decision making in discontinuation trajectories is of major importance. Clients themselves and legal representatives should be involved in decisions and policies.

Assessments of clinicians regarding behavioural deterioration during discontinuation or reducing antipsychotics in their clients may not depend solely on severity of behavioural symptoms, since their judgements did not parallel the standardized behavioural outcome measure. Possibly, other clients' characteristics like mental and physical ill health, the influence of setting characteristics or clinicians' own subjective opinions also determined their judgements.

5.1 | Research and policy implications

The issue of psychotropic drug use in clients with challenging behaviour has been a topic on research agenda's for more than twenty years, and this has resulted in evidence based advices to reduce inappropriate use. However, implementation of these recommendations differs within and between countries and policies regarding appropriate management and treatment of challenging behaviour often lack clear visions and targets. Lack of resources, insufficient collaboration of professionals and management and other organizational factors will likely play a role. Implementation studies are clearly needed.

Furthermore, more and larger scale studies on predictors of success or failure of off-label psychotropic drug discontinuation are needed, leading to evidence based knowledge how to prevent behavioural worsening during discontinuation.

ACKNOWLEDGMENTS

Herman de Waal, Janneke Saalmink, Lenneke van Loo, Lotte Ramerman, Frank Visser, Josien Jonker, Jeroen Auener, Hans

Steegemans, Pete de Jager, Ed Klapwijk and Anja van de Heide contributed to data collection. Nicole Damen contributed to and was responsible for the data management.

COMPETING INTERESTS

None declared.

ORCID

Gerda M. Kuijper http://orcid.org/0000-0001-5315-2110

REFERENCES

Ahmed, Z., Fraser, W., Kerr, M. P., Kiernan, C., Emerson, E., Robertson, J., … Thomas, J. (2000). Reducing antipsychotic medication in people with a learning disability. *The British Journal of Psychiatry: The Journal of Mental Science*, *176*, 42–46. https://doi.org/10.1192/bjp.176.1.42

Aman, M., Burrow, W., & Wolford, P. (1995). The aberrant behavior checklist-community: Factor validity and effect of subject variables for adults in group homes. *American Journal of Mental Retardation*, *100*, 283–292.

Aman, M. G., Singh, N. N., Stewart, A. W., & Field, C. J. (1985). Psychometric characteristics of the aberrant behavior checklist. *American Journal of Mental Deficiency*, *89*, 492–502.

Branford, D. (1996). Factors associated with the successful or unsuccessful withdrawal of antipsychotic drug therapy prescribed for people with learning disabilities. *Journal of Intellectual Disability Research*, *40*, 322–329. https://doi.org/10.1111/j.1365-2788.1996.tb00637.x

Cooper, S. A., Smiley, E., Morrison, J., Williamson, A., & Allan, L. (2007). Mental ill-health in adults with intellectual disabilities: Prevalence and associated factors. *The British Journal of Psychiatry: The Journal of Mental Science*, *190*, 27–35. https://doi.org/10.1192/bjp.bp.106.022483

Donley, M., Chan, J., & Webber, L. (2012). Disability support workers' knowledge and education needs about psychotropic medication. *British Journal of Learning Disabilities*, *40*, 286–291. https://doi.org/10.1111/j.1468-3156.2011.00707.x

Fretwell, C., & Felce, D. (2007). Staff knowledge of the side effects of antipsychoticmedication.*JournalofAppliedResearchinIntellectualDisabilities*, *20*, 580–585. https://doi.org/10.1111/j.1468-3148.2006.00356.x

Hastings, R. P. (1997). Staff beliefs about the challenging behaviors of children and adults with mental retardation. *Clinical Psychology Review*, *17*, 775–790. https://doi.org/10.1016/S0272-7358(97)00050-0

Hastings, R. P., & Brown, T. (2002). Behavioural knowledge, causal beliefs and self-efficacy as predictors of special educators' emotional reactions to challenging behaviours. *Journal of Intellectual Disability Research*, *46*, 144–150. https://doi.org/10.1046/j.1365-2788.2002.00378.x

de Kuijper, G., Evenhuis, H., Minderaa, R., & Hoekstra, P. (2014). Effects of controlled discontinuation of long-term used antipsychotics for behavioural symptoms in individuals with intellectual disability. *Journal of Intellectual Disability Research*, *58*, 71–83. https://doi.org/10.1111/j.1365-2788.2012.01631.x

de Kuijper, G. M., & Hoekstra, P. J. (2017). Physicians' reasons not to discontinue long-term used off-label antipsychotic drugs in people with intellectual disability. *Journal of Intellectual Disability Research*, *61*, 899–908. https://doi.org/10.1111/jir.12385

de Kuijper, G. M., & Hoekstra, P. J. (2018). An open label discontinuation trial of long-term used off-label antipsychotic medication in people with intellectual disability; determinants of success and failure. *Journal of Clinical Psychopharmacology*. https://doi.org/10.1002/jcph.1271

de Kuijper, G., & van der Putten, A. A. J. (2017). Knowledge and expectations of direct support professionals towards effects of psychotropic drug use in people with intellectual disabilities. *Journal of Applied Research in Intellectual Disabilities*, *30*, 1–9. https://doi.org/10.1111/jar.12357

Lambrechts, G., Kuppens, S., & Maes, B. (2009). Staff variables associated with the challenging behaviour of clients with severe or profound intellectual disabilities. *Journal of Intellectual Disability Research*, *53*, 620–632. https://doi.org/10.1111/j.1365-2788.2009.01162.x

May, P., London, E. B., Zimmerman, T., Thompson, R., Mento, T., & Spreat, S. (1995). A study of the clinical outcome of patients with profound mental retardation gradually withdrawn from chronic neuroleptic medication. *Annals of Clinical Psychiatry: Official Journal of the American Academy of Clinical Psychiatrists*, *7*, 155–160. https://doi.org/10.3109/10401239509149620

Mitchell, G., & Hastings, R. P. (1998). Learning disability care staff's emotional reactions to aggressive challenging behaviours: Development of a measurement tool. *The British Journal of Clinical Psychology/the British Psychological Society*, *37*, 441–449. https://doi.org/10.1111/j.2044-8260.1998.tb01401.x

O'Dwyer, M., Peklar, J., Mulryan, N., McCallion, P., McCarron, M., & Henman, M. C. (2017). Prevalence, patterns and factors associated with psychotropic use in older adults with intellectual disabilities in ireland. *Journal of Intellectual Disability Research*, *61*, 969–983. https://doi.org/10.1111/jir.12391

Perry, B. I., Cooray, S. E., Mendis, J., Purandare, K., Wijeratne, A., Manjubhashini, S., … Kwok, H. F. (2018). Problem behaviours and psychotropic medication use in intellectual disability: A multinational cross-sectional survey. *Journal of Intellectual Disability Research*, *62*, 140–149. https://doi.org/10.1111/jir.12471

Sheehan, R., & Hassiotis, A. (2017). Reduction or discontinuation of antipsychotics for challenging behaviour in adults with intellectual disability: A systematic review. *The Lancet Psychiatry*, *4*, 238–256. https://doi.org/S2215-0366(16)30191-2

Sheehan, R., Hassiotis, A., Walters, K., Osborn, D., Strydom, A., & Horsfall, L. (2015). Mental illness, challenging behaviour, and psychotropic drug prescribing in people with intellectual disability: UK population based cohort study. *BMJ*, *351*, h4326. https://doi.org/10.1136/bmj.h4326 [doi]

Singh, N. N., Ellis, C. R., Donatelli, L. S., Williams, D. E., Ricketts, R. W., Goza, A. B., … Singh, Y. N. (1996). Professionals' perceptions of psychotropic medication in residential facilities for individuals with mental retardation. *Journal of Intellectual Disability Research*, *40*, 1–7. https://doi.org/10.1111/j.1365-2788.1996.tb00596.x

Smiley, E., Cooper, S. A., Finlayson, J., Jackson, A., Allan, L., Mantry, D., … Morrison, J. (2007). Incidence and predictors of mental ill-health in adults with intellectual disabilities: Prospective study. *The British Journal of Psychiatry: The Journal of Mental Science*, *191*, 313–319. https://doi.org/10.1192/bjp.bp.106.031104

Valdovinos, M. G., Caruso, M., Roberts, C., Kim, G., & Kennedy, C. H. (2005). Medical and behavioral symptoms as potential medication side effects in adults with developmental disabilities. *American Journal of Mental Retardation*, *110*, 164–170. https://doi.org/10.1352/0895-8017(2005)110<164:MABSAP>2.0.CO;2

How to cite this article: de Kuijper GM, Hoekstra PJ. An open label discontinuation trial of long-term used off-label antipsychotic drugs in people with intellectual disability: The influence of staff-related factors. *J Appl Res Intellect Disabil*. 2019;32:313–322. https://doi.org/10.1111/jar.12528