Reduction or discontinuation of antipsychotics for challenging behaviour in adults with intellectual disability: a systematic review

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Summary

The use of antipsychotics to manage challenging behaviour in adults with intellectual disability is widespread but controversial and lacking in evidence. There is a perception that antipsychotics used in this context can be reduced or discontinued and this has been a major focus of recent national policy. However, such an intervention risks harm as well as having potential benefits. We reviewed the available evidence and found that antipsychotics can be reduced or discontinued in a significant proportion of adults who use them for challenging behaviour, though not always without adverse reactions. There is a group who display behavioural deterioration on antipsychotic reduction that prevents discontinuation; predictors of poor response could not be reliably identified. Given the relative lack of data and methodological limitations of the available studies, we cannot draw firm conclusions to inform a population level approach to this issue. Antipsychotic medication used for behaviour should be reviewed regularly and an individualised approach taken to treatment.

Introduction

Intellectual disability (ID) is a lifelong condition of impaired cognitive function and deficit in adaptive skills.[1] Antipsychotic medication is often prescribed to adults with ID to manage challenging behaviour in the absence of severe mental illness.[2,3] Challenging behaviour is a non-specific term used to describe any behaviour that may threaten the physical safety of a person with ID or those around them, or that is likely to limit access to ordinary community facilities.[4] It includes presentations such as aggression, self-injury, and property destruction. The prevalence of challenging behaviour in those with ID is typically quoted as 10-15%,[5,6] although that this might be an underestimate.[2,7] Interventions aimed at reducing the frequency or degree of challenging behaviour must recognise the array of biological, psychological, and social factors that can underlie the development and maintenance of behaviour disturbance.[8] There is very limited evidence that antipsychotics are effective in reducing challenging behaviour in adults with ID.[9,10] The NICE guideline on behaviour that challenges recommends a stepped approach to assessment and a central role for psychosocial strategies in management, with antipsychotic medication being used only in certain circumstances and continued only when benefit is clearly demonstrated (panel 1).[11]

There has been longstanding criticism of the use, and perceived over-use of antipsychotic medication in people with ID.[12,13] Professionals and care providers are under close scrutiny following the exposure of systemic abuse of people with ID and complex challenging behaviours at Winterbourne View Hospital, and the prescription of psychotropic medication to people with ID has achieved widespread coverage in the lay and specialist media.[14,15] Transforming Care, the UK Government response to the scandal at Winterbourne View, restated concerns about the inappropriate use of psychotropic medication in this group.[16] These concerns were substantiated by two studies of psychotropic prescribing to people with ID in UK primary care.[2,17] NHS England have issued a 'Call to Action,' (https://www.england.nhs.uk/2015/07/urgent-pledge/), a national drive to reduce antipsychotic prescription rates in people with ID.

Challenging behaviour often persists and those who are prescribed antipsychotic medication tend to remain on it for long periods.[18,19] Reasons might include; favourable drug response; lack of efficacy or availability of alternative (psychosocial) treatments; infrequent or ineffectual medication review; and lack of professional or caregiver confidence in making medication changes for fear of the consequence.

Long-term antipsychotic use is not without risks and adverse effects associated with antipsychotic drugs include movement (extra-pyramidal) side-effects, autonomic disturbance, and endocrine and metabolic disorders.[20] Some can cause sedation and those with a high-degree of anti-cholinergic activity might impair cognition, especially when used in combination with other anti-cholinergic agents.[21,22] People with ID are often considered at greater risk of developing such side-effects[23] although there has been relatively little research on the side-effect profile of psychotropic drugs specifically in people with ID and few studies directly compare side-effect rates in people with and without ID.

It is desirable to reduce antipsychotic medication where possible. There is evidence of the effect of antipsychotic discontinuation in adults with average intelligence who take

antipsychotics for severe mental illness[24,25] and older adults prescribed antipsychotics for neuropsychiatric symptoms in dementia.[26,27] Antipsychotic discontinuation in children with autism spectrum disorders who take antipsychotics for behaviour disorder has also been studied, although primarily with the intention of testing the efficacy of long-term antipsychotic use rather than investigating the consequences of planned reduction.[28-30] As yet there has been no thorough review of the effect of antipsychotic discontinuation in those with ID and the focus of existing discontinuation studies, the participants included, and outcomes measured mean that results might not generalize to those with ID who take antipsychotics.

We conducted a systematic review of the evidence concerning the outcome of reduction or discontinuation of long-term antipsychotic medication used for management of challenging behaviour in adults with ID.

[Panel 1 near here]

Methods

Electronic databases (Medline, EMBASE, PsycINFO, Cochrane, CINAHL Plus) were searched for relevant articles published in any language between 1st January 1990 and 1st March 2016. Search terms for 'intellectual disability', 'antipsychotic medication' and 'reduction/discontinuation' and their synonyms were combined, with relevant MeSH terms also included (appendix A). Reference lists of included studies were checked and their citations were tracked using the Science Citation Index Expanded to supplement the original search. The review protocol was registered with PROSPERO (2015:CRD42015019917).

We included studies published in peer-reviewed journals and all study designs, including individual case studies, but excluded non-peer reviewed articles including letters, meeting abstracts, and dissertations.

Adults (>18 years) with any degree of ID of any aetiology were included. ID was author-defined and expected to conform to ICD/DSM criteria. Participants could have any physical or psychiatric co-morbidity, although those studies where a significant number had psychotic disorders were excluded. Studies conducted in community or institutional settings were included.

Participants must have been taking an antipsychotic regularly for at least 12 weeks before the intervention. Studies reporting reduction or discontinuation of either first- and second-generation antipsychotics were included. The antipsychotic must have been used primarily to manage challenging behaviour, rather than to treat mental illness. Challenging behaviour was author-defined.

The reduction or discontinuation of antipsychotic medication must have been the main intervention. Reduction was defined as a sustained change in antipsychotic to a lower dose and discontinuation as the complete cessation of antipsychotic medication. Any schedule of reduction or discontinuation was permitted. Simultaneous interventions, including

adjustment of other classes of medication and psychotherapeutic interventions, were acceptable but studies that report the substitution of one antipsychotic for another were not included.

The primary outcome was the proportion of participants achieving dose reduction or discontinuation without drop-out or reinstatement of the antipsychotic. Studies that report average dose changes or where change in antipsychotic use could not be differentiated from change in other psychotropic drugs were excluded.

Secondary outcomes measures included change in behaviour, physical health, mental health, cognitive or adaptive functioning, and quality of life in those who reduced or discontinued antipsychotic medication.

All citations were imported into an EndNote library. Duplicates were removed in a two-stage process using the software function and then manually by checking titles. The titles of the remaining citations were screened against the inclusion criteria. Abstracts of the remaining citations were reviewed allowing the exclusion of further studies. When the abstract indicated the paper potentially met inclusion criteria, the full text was reviewed.

Included studies were categorised according to the hierarchy published by the Centre for Evidence-Based Medicine.[31] A separate evaluation of the quality of each study was made focusing on limitations and biases.

Results

Study characteristics

The initial search yielded a total of 1,018 citations and of these twenty-one studies met inclusion criteria (figure 1). Included studies are summarised in table 1. Studies excluded after full-text review are listed in appendix B.

[Figure 1 near here]

We found one (open) RCT, the results of which are reported in two papers;[32,33] one case-series[34]; one single-case report.[35] The remainder of studies were observational studies, some of which included control groups.[36-39]

Fifteen studies were conducted in the USA. Five European studies were included and one from Australasia. Thirteen studies included only participants living in institutions, two studies included only those living in community settings, five studies report on participants living in a range of settings, and in one study the living arrangements of participants are not reported.

Studies reported the outcome of antipsychotic discontinuation or reduction in 1,027 participants in total. Discontinuation practices included dose-reduction programmes and that

were under clinician control. In five studies reduction/discontinuation of antipsychotics was according to formal research protocol.

Details of participants are incompletely reported in several studies. Mean age of participants in studies ranged from 24 to 50 years, with the one case report describing outcome of antipsychotic discontinuation in a 74 year old. There was a predominance of men (approximately 2/3 of those undergoing antipsychotic reduction and discontinuation) and just over 80% had severe-profound ID. Participants were prescribed antipsychotics for challenging behaviour; in almost all cases the nature of the challenging behaviour was not given. A minority in each study had diagnosed co-morbid mental illness. In studies where indication for antipsychotic prescription was not clearly given, the authors clearly allude to challenging behaviour. Most of the antipsychotics were first generation agents.

Outcomes of reduction or discontinuation of antipsychotic medication used for behaviour

Success of attempts to reduce or discontinue antipsychotic medication

Ten studies describe the outcome of reduction or discontinuation of antipsychotic medication as the proportion of the intervention group who were maintained on a lower dose or achieved drug discontinuation at follow-up (ranging from 3 months to over 10 years).[32,38,40-47] The proportion of participants maintained on a reduced dose was between 19% and 83%, discontinuation of antipsychotics ranged from 4% to 74%, the proportion unsuccessful in attempts to reduce or discontinue antipsychotics was between 0% and 96% (table 2). In several cases, reporting of the study is such that it is not possible to distinguish three groups accurately. Due to the study designs we are unable to obtain a summary measure of the successful reduction or discontinuation of antipsychotics, but taken together, these studies have value in providing broad estimates of rates of reduction or discontinuation that might be achieved in a clinical setting.

[Table 2 near here]

Effect of reduction or discontinuation of antipsychotics on behaviour

Six studies report the effect of antipsychotic reduction or discontinuation on participant behaviour.[32,39,43,44,47,48] Behavioural outcome measures ranged from validated instruments to colloquial reports (Appendix C).

[Table 3 near here]

Ahmed and colleagues found no difference in challenging behaviour in the group who discontinued or reduced antipsychotic medication by ≥50% and the control group who underwent no medication change (p>0·05, data not given).[32] They also report behaviour outcomes of the 'failure' group, that is, those who were randomised to the drug reduction arm but who did not discontinue or significantly reduce dose. This group did not demonstrate worsening of overall behaviour and the decision to arrest dose reduction or reinstate medication was found to be related to setting rather than individual variables, including

having fewer full-time and senior staff, lower levels of staff training, and more restrictive environmental features.

deKuijper examined baseline and follow-up differences (12 weeks after planned discontinuation) in carer rated total Aberrant Behaviour Checklist (ABC) score in their cohort.[47] In the group that completed antipsychotic discontinuation, the mean total ABC score reduced from 47 (sd 27) to 37 (sd 29) (p=0·03). Carer ratings of target behaviour on the Visual Analogue Scale (VAS) did not change (mean 6·4 (sd 1·4) vs 6·5 (sd 1·4), p=0·76). The subgroup who reduced antipsychotic dose but did not progress to full discontinuation also showed a statistically significant decline in mean ABC score from baseline to follow-up (62 (sd 27) vs 50 (sd 36), p=0·03), although with a simultaneous increase in severity of challenging behaviour measured by the VAS (6·4 (sd 1·4) vs 5·8 (sd 1·6), p=0·03). Thus, the findings of the VAS potentially contradict the improvement in behaviour measured by the ABC. The authors suggest bias in the VAS scores introduced by caregivers who have the expectation of deterioration following antipsychotic reduction as a possible explanation. A further paradox in this study is that those in the group who reduced but did not discontinue antipsychotics were said not to have progressed to discontinuation "if there was a significant behavioural worsening according to the clinician's judgement", suggesting that this group is, in fact, defined by subjective deterioration in behaviour.

May et al. monitored challenging behaviour of a group of adult men with severe-profound ID over the course of antipsychotic withdrawal to discontinuation using frequency counts.[48] Using a very slow regime of antipsychotic taper and following individuals for at least 3 years, distinct groups became apparent. Five individuals (22%) showed progressive improvement in behaviour coinciding with antipsychotic reduction, 9 (39%) demonstrated transient worsening, and 9 (39%) experienced persistent behavioural worsening requiring prescription of either antipsychotics or other psychotropics. Those who experienced a progressive improvement on antipsychotic withdrawal tended to demonstrate greater baseline frequency of challenging behaviour. However, the study was under-powered for observed differences to reach statistical significance.

Swanson measured total ABC score at baseline, three subsequent time-points during antipsychotic dose reduction, and after discontinuation.[39] Total ABC score increased during withdrawal before falling.

Branford describes the outcome of antipsychotic reduction attempts in 123 patients.[44] One quarter achieved discontinuation without any deterioration in behaviour, 42% experienced deterioration in behaviour necessitating re-prescribing or attenuation of dose reduction. Behaviour change of the remaining individuals (33%) was not reported.

Janowsky et al. report outcome at three months following antipsychotic reduction attempts in a group of 138 participants.[45] Whilst 60% tolerated discontinuation, the remainder had a "significant increase in maladaptive target symptoms" which required antipsychotic re-prescribing or dose increase. The same authors report a follow-up study of 49 of those who failed attempts to discontinue antipsychotic medication; 96% experienced behavioural relapse in future attempts to discontinue medication.[46]

Effect of reduction or discontinuation of antipsychotics on physical health

Ten studies reported physical health outcomes resulting from antipsychotic reduction or discontinuation.[32,35,37-39,47,49-52] Below we report physical health outcome grouped by theme.

Movement effects

Several studies that reported movement effects of antipsychotic reduction or discontinuation used the Dyskinesia Identification System: Condensed User Scale (DISCUS), a scale specifically developed to measure abnormal movements in individuals with ID.[53] Fifteen items relating to movement of different body regions are rated from 0 (not present) to 4 (severe). Categorical definitions for clinically-relevant dyskinesia have been developed based on the total DISCUS score.[54,55]

Wigal et al compared change in DISCUS score at baseline and 10-month follow-up between four groups defined by increase in antipsychotic dose, no change, antipsychotic dose reduction by <25%, and antipsychotic dose reduction ≥25% (but not matched by any other characteristic).[37] Follow-up mean DISCUS score increased in all groups apart from the dose increase group, with the degree of dose reduction being positively correlated with increase in DISCUS score (r=0·506, p<0·001). Employing a categorical definition of dyskinesia (at least a 'mild' rating of abnormal movements in at least two body regions, or at least a 'moderate' rating of abnormal movements in one body region),[55] the authors found the rate of dyskinesia increased from 30% at baseline to 60% at follow-up in the group who reduced medication by >25%, but remained stable in the groups who reduced medication by a lesser percentage or who underwent no dose change.

A later study by the same group reports a small controlled study of 30 individuals with nested controls defined by antipsychotic dose changes.[38] 63% of those who discontinued antipsychotic medication developed tardive dyskinesia compared with 29% of those undergoing dose reduction and none of the controls or those who underwent antipsychotic dose increase or no change.

A third study by this group reports results of antipsychotic discontinuation in 40 people and compare DISCUS scores with a control group at several time-points.[39] The participants are further subdivided by anticonvulsant use, producing 4 groups in total. Mean DISCUS score increased after antipsychotic discontinuation in the group taking antipsychotics alone but not in the group who received concomitant treatment with anticonvulsant medication, raising the possibility of a mitigating effect of anticonvulsants in reducing discontinuation reactions.

Ahmed et al found total DISCUS score was significantly increased at 6 month follow-up in the group who discontinued antipsychotics or underwent ≥50% dose reduction compared with controls (p<0·01).[32] The DISCUS score in the intervention group fell between month 5 and 6, possibly indicating the start of a return to baseline.

The concept of a 'transient withdrawal dyskinesia' is developed in three studies by Newell et al who prospectively monitored individuals undergoing planned antipsychotic dose reduction

to discontinuation.[49-51] The authors investigated change in movement disorder over time with DISCUS rating and by using proxies for movement abnormalities. The first investigated lip movements associated with dyskinesia and demonstrated changes in quality and quantity of resting lip motion over the course of antipsychotic reduction and discontinuation that tended to revert to the pre-reduction state at follow up 6-24 months after discontinuation.[49] In the second study, the authors again report change in DISCUS score; mean total DISCUS score increased from 3·4 at baseline to 10·7 at peak withdrawal (p<0·001), before falling to approximate baseline values at follow-up (mean follow-up DISCUS 3·5, p=NS). Rates of tardive dyskinesia showed a similar pattern, increasing from 31% at baseline to 85% at peak withdrawal, and then dropping to 38% at follow-up.[51] Data presented in the third of these studies reports postural stability as a measure of movement disorder.[50] Indices of postural stability and body motion changed significantly over the course of antipsychotic withdrawal and returned to baseline levels by follow-up. Mean total DISCUS increased from 3·5 at baseline (range 0-11), to 11·1 at peak withdrawal (range 3-22), and 3·8 at follow-up (range 0-11) (p<0·01 for difference over time). This study extends the analysis by reporting a positive association between higher baseline levels of movement symptoms and the degree of withdrawal-associated dyskinesia, thereby giving some indication of people who might be more prone to develop problematic dyskinesia on medication reduction.

deKuijper et al report movement side-effects as a composite of clinician-assessed Parkinsonism, akathisia, and extra-pyramidal side-effect ratings.[47] Reporting of this outcome is incomplete but there was little change in average movement side-effect score between baseline and at the point of antipsychotic discontinuation in those who completed withdrawal (baseline score 2·8, follow-up 3·0, p not given).

Autonomic function

Despite disturbance of autonomic function being a known side-effect of antipsychotic drugs, only two studies reported the autonomic effects of their reduction or discontinuation.[35,47] deKuijper[47] used the Scale Outcomes Parkinson's disease-Autonomic symptoms (SCOPA-AUT) to assess autonomic adverse events at baseline and following reduction or discontinuation of antipsychotics.[56] Both the group achieving discontinuation and the group who underwent dose reduction short of complete discontinuation showed significantly decreased SCOPA-AUT scores at 12 week follow-up (in the discontinuation group mean SCOPA-AUT changed from 6·0 to 3·6, p<0·01; in the dose reduction group mean SCOPA-AUT changed from 6·0 to 4·9, p<0·01) indicating a lower burden of autonomic symptoms and a dose-response relationship.

In a case report, Orfan and Kolski describe the outcome of fluphenazine withdrawal in a 74 year old woman with ID who received the drug for behaviour control.[35] The patient developed "severe and debilitating" rhinorrhoea following antipsychotic discontinuation.

Weight / metabolic parameters

Ahmed et al compared weight change between a group who discontinued or reduced antipsychotic dose by ≥50% and a control group who underwent no medication change.[32] Those in the intervention group lost an average of 2·3kg at 6 months, although this was not statistically different from weight change observed in controls (data not given, p>0·05).

deKuijper reports change in weight, BMI, and several metabolic parameters in a subgroup of participants who achieved antipsychotic discontinuation and remained antipsychotic free at 12 weeks.[52] Waist circumference, weight, and BMI were all significantly reduced at follow-up compared with baseline (waist circumference 93·2cm vs 88·8cm, p<0·001; weight 68·7kg vs 65·2kg, p=0·02; BMI 25kg/m^2 vs 23·66kg/m^2, p=0·006). Systolic, but not diastolic blood pressure also showed a significant fall (systolic 129mmHg vs 122mmHg, p=0·02; diastolic 80mmgHg vs 75mmHg, p=NS). Laboratory markers of the metabolic syndrome (plasma triglycerides, HDL, and fasting glucose) did not change significantly, although this might be a reflection of the relatively short duration of follow-up.

Effect of reduction or discontinuation of antipsychotics on mental health

No studies reported the effect of reduction or discontinuation of antipsychotics on the mental health of participants.

Effect of reduction or discontinuation of antipsychotics on cognitive/adaptive functioning

Four studies reported impact of reduction or discontinuation of antipsychotics on cognitive or adaptive function. In a small controlled study, Carpenter and colleagues report the effect on performance in a standardised computer-based cognitive test in which participants are required to match colours.[36] All of those undergoing antipsychotic dose reduction or discontinuation demonstrated improved performance on the test compared with none of those with no medication change or not on an antipsychotic drug (number of attempts to reach 4 consecutive correct responses reduced by average of 29% in withdrawal group (range 13·8-53·5%) and by 0.4% in control group (range 0·3% – 0·7%); percentage of correct responses increased by average of 10% in withdrawal group (range 2·7% – 19·7%) but declined by 1·5% in controls (range 1·3% – -4·9%); statistical tests not performed).

Gedye reports the results of a small case series (n=4).[34] All had demonstrated cognitive decline and been diagnosed clinically with dementia, at an average age of 42 years. Reduction and later discontinuation of antipsychotic medication resulted in substantial and sustained clinician-rated improvement in overall cognitive and adaptive function such that the diagnosis of dementia was no longer applicable.

Ahmed et al[32] directly observed participant behaviour for a random 1·5 hour period three times a month during their 6 month study and collated the amount of time participants spent in each of several pre-defined activities, including a measure of engagement in the activity. Full results are not reported but the authors state that the group who discontinued antipsychotics or had at least 50% dose reduction spent significantly more time engaged in activity than controls (p<0·05). Additional data obtained in the same study focus specifically on responsiveness to staff interaction.[33] No difference in likelihood of response to staff interaction was found between the groups, probably as a high baseline response was recorded.

Predictors of successful antipsychotic reduction or discontinuation

As part of a separate search, we identified studies that report factors associated with success of attempts to reduce or discontinue antipsychotic reduction (table 3). Relatively good evidence shows that those who have previously failed attempts to reduce antipsychotic medication are poor candidates for further attempts to stop medication.[46] Studies tend to be in agreement that those on a lower baseline antipsychotic dose are more likely to have successful withdrawal.[47,48,57,58] Other predictors of successful withdrawal attempts are less clear and are sometimes conflicting between studies (e.g. gender). Those with a high level of psychopathology (whether psychotic or not) seem to be more likely to relapse when an antipsychotic is withdrawn;[57,59] these may be people with co-morbid mental illness which deteriorates when an their medication is reduced. The use of concomitant psychotropics (including antiepileptic drugs) has been shown to be of benefit in facilitating antipsychotic withdrawal attempts,[59] although this is not a consistent finding.[48,57]

Discussion

A significant proportion of individuals in whom a concerted effort was made to reduce antipsychotic drugs achieved discontinuation or dose reduction. This suggests that clinicians can reasonably attempt to reduce antipsychotics in patients who are prescribed them for challenging behavioural. However, it is also the case that many of those in whom attempts were made to reduce or discontinue antipsychotic medication could not tolerate reduction and required re-prescribing. Stevenson and colleagues, writing in the aftermath of the restrictions imposed on the use of the first-generation agent thioridazine in 2000, contested that wide-scale antipsychotic withdrawal in this group is likely to cause serious harm, including precipitating increases in behaviour problems and mental ill-health.[60]

Overall results from studies that report behavioural outcomes are inconclusive. Both deKuijper et al[47] and Ahmed et al[32] report no change, or even improvement in behaviour after antipsychotic discontinuation, although those whose behaviour deteriorated did not complete the withdrawal programme. Other studies report between 40% and 96% of those undergoing dose reduction experience significant behavioural deterioration which could persist for several years.[44-46,48]

None of the included studies investigated mechanisms underlying behavioural deterioration following antipsychotic reduction or discontinuation. Hypotheses related to a pathophysiological discontinuation syndrome include; onset of super-sensitivity psychosis; cholinergic and/or adrenergic rebound; and emergence of movement side-effects such as withdrawal dyskinesia or tardive akathisia.[61] In all cases, the impact of symptoms may be greater in people with ID due to limitations in understanding and communicating distress verbally, which may then find expression as challenging behaviour. Slow taper of antipsychotic medication has been advocated in order to minimise the risk of these discontinuation effects[62] although the only study that compared rates of antipsychotic taper did not find any advantage in stopping the medication over a period of longer than 14 weeks.[47]

One of the most consistent findings of the review is the transient increase in dyskinesia that accompanied antipsychotic reduction or discontinuation associated with the use of both first-

and second-generation agents.[63] Dyskinesia on antipsychotic reduction appears to be proportionate to the degree of dose reduction and may persist for several months. A return to baseline measures of dyskinesia was noted in studies employing longer follow-up periods, suggesting that it remits over time.

Weight loss and some improved markers of the metabolic syndrome were noted when antipsychotics were reduced or discontinued.[32,52] This is an important consideration in adults with ID who are more likely to be obese than peers of average intelligence[64], and less likely to eat a balanced diet or achieve minimum recommended physical activity targets.[65]

Antipsychotic medication may reduce cognitive ability in people with ID, either due to increased somnolence and sedation[66,67] or their anti-cholinergic properties. Where change in cognition was investigated there was some evidence of improvement in those who reduced or discontinued antipsychotics. This warrants further attention given that reductions in cognitive capacity might negatively impact the success of psychosocial management of challenging behaviour and interfere with habilitation programmes.

Limitations of existing research and directions for future research

A major finding of the review is that current literature on the feasibility and outcome of antipsychotic withdrawal in people with ID is lacking in volume, quality and scope. Critical appraisal (table 1) revealed trials including small numbers of participants, selection bias and use of convenience samples, lack of control groups and of blinding, lack of standardised or validated outcome measures, and incomplete outcome reporting or statistical testing. The studies were often naturalistic and the intervention to reduce or discontinue antipsychotics was not well described. The length of follow-up was often short and may have been insufficient to capture some important outcomes. Studies may have included other simultaneous interventions that were not reported and could have confounded the results. No studies addressed the effect of reduction or discontinuation of antipsychotics on participant's mental health, despite withdrawal of antipsychotics having been associated with new-onset psychotic symptoms even in those without previous psychosis.[68] These significant methodological shortcomings limit the internal and external validity of the results and the strength of conclusions we are able to draw.

[Panel 2 near here]

Systematic review – strengths and limitations

This is the first study of which we are aware that has attempted to consolidate current knowledge on this topic. Our search strategy was comprehensive, conducted according to a pre-defined protocol, and undertaken in several databases. We included all types of outcome measure in order to present a broad analysis.

There are some limitations of our review. We chose to exclude studies published before 1990 as we felt that the relatively rapid changes in understanding and care of people with ID make it difficult to generalise results of earlier studies to current practice. Despite this date limit, a

number of studies that we included were conducted in large residential institutions for people with ID. Most studies include a high proportion of people with severe-profound ID who constitute only a minority of the total intellectually disabled population.

Most people in included studies were taking a first-generation antipsychotic drug. This might limit the relevance of the review findings although there is evidence that a significant proportion of people taking antipsychotics still receive first-generation agents.[69]

Conclusions and implications for practice

Antipsychotics are likely to have a role in the multi-modal management of certain cases of challenging behaviour in people with ID but clinicians must respond to the prevailing attitude that these drugs have too often been used indiscriminately and for too long. Evidence-based practice guidelines and quality indicators have been developed to improve antipsychotic prescribing for challenging behaviour.[11,70-72] These focus on the holistic assessment and management of challenging behaviour and the initiation of antipsychotic medication, rather than addressing antipsychotic discontinuation. There remains relatively little information to guide practice in reducing or discontinuing antipsychotics in the cohort who are already taking these drugs.

In terms of predictors of successful or unsuccessful reduction or discontinuation of antipsychotics, setting and carer characteristics (as well as some individual traits) were shown to be important consistent with previous research. Working conditions, staff experience, and attributions about challenging behaviour can influence how behaviour is reported and how it is managed.[73-75] Where psychotropic medication is used, carers often report inadequate training and a desire for more information.[76,77] These deficiencies in knowledge and skills can act as a barrier to appropriate monitoring of antipsychotics in this group, particularly as clinicians are often heavily reliant on third-party reports of drug effects.[78] Living environment is similarly important in influencing prescribing; a four-fold difference in rates of antipsychotic prescription for behaviour has been demonstrated between those living in institutions and those residing in family homes, despite no underlying difference in the rates of behaviour disorder.[79] Clearly, any attempt to transform antipsychotic prescribing to people with ID must recognise the wider elements that may directly influence drug use and which individual clinicians have little power to change.[80]

This review exposes a gap between the available evidence and the national policy drive to reduce antipsychotic prescribing to people with ID. We are not able to recommend a routine programme of antipsychotic discontinuation in people with ID who use the drugs for challenging behaviour and advocate a measured response according to published guidelines.[72] As contextual factors are important, commissioning of appropriate provider services and support for carers is paramount. No amount of goodwill will be sufficient to drive a change in the current status quo unless a systems approach to prescribing is considered.[80]

Contributors

RS and AH designed the protocol. RS completed the literature search and data synthesis. RS and AH interpreted the results. RS and AH wrote the manuscript.

Declaration of interests

RS declares no competing interests.
AH was a member of the NICE Guideline 'Challenging behaviour and learning disabilities: prevention and interventions for people with learning disabilities whose behaviour challenges' (NG11).

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Arlington, VA: American Psychiatric Publishing; 2013.
2. Sheehan R, Hassiotis A, Walters K, Osborn D, Strydom A, Horsfall L. Mental illness, challenging behaviour, and psychotropic drug prescribing in people with intellectual disability: UK population based cohort study. *BMJ* 2015; **351**: h4326.
3. Holden B, Gitlesen JP. Psychotropic medication in adults with mental retardation: prevalence, and prescription practices. *Res Dev Disabil* 2004; **25**: 509-21.
4. Emerson E. Challenging Behaviour: Analysis and Intervention in People with Severe Intellectual Disabilities. 2nd ed. Cambridge: Cambridge University Press; 2001.
5. Emerson E, Kiernan C, Alborz A, et al. The prevalence of challenging behaviors: a total population study. *Res Dev Disabil* 2001; **22**: 77-93.
6. Holden B, Gitlesen JP. A total population study of challenging behaviour in the county of Hedmark, Norway: Prevalence, and risk markers. *Res Dev Disabil* 2006; **27**: 456-65.
7. Cooper S-A, Smiley E, Morrison J, Williamson A, Allan L. Mental ill-health in adults with intellectual disabilities: prevalence and associated factors. *Br J Psychiatry* 2007; **190**: 27-35.
8. Royal College of Psychiatrists, British Psychological Society, Royal College of Speech and Language Therapists. Challenging behaviour: a unified approach. Royal College of Psychiatrists. London: 2007.
9. Deb S, Sohanpal S, Soni R, Lentre L, Unwin G. The effectiveness of antipsychotic medication in the management of behaviour problems in adults with intellectual disabilities. *J Intellect Disabil Res* 2007; **51**: 766-77.
10. Matson JL, Neal D. Psychotropic medication use for challenging behaviors in persons with intellectual disabilities: An overview. *Res Dev Disabil* 2009; **30**: 572-86.
11. National Institute for Health and Care Excellence. Challenging Behaviour and Learning Disabilities: Prevention and Interventions for People with Learning Disabilities Whose Behaviour Challenges (NICE Guideline NG11). NICE. 2015.
12. Matson JL, Bamburg JW, Mayville EA, et al. Psychopharmacology and mental retardation: a 10 year review (1990–1999). *Res Dev Disabil* 2000; **21**: 263-96.
13. Tsiouris J. Pharmacotherapy for aggressive behaviours in persons with intellectual disabilities: treatment or mistreatment? *J Intellect Disabil Res* 2010; **54**: 1-16.
14. Tyrer P, Cooper S-A, Hassiotis A. Drug treatments in people with intellectual disability and challenging behaviour. *BMJ* 2014; **349**: g4323.
15. Glover G, Bernard S, Branford D, Holland A, Strydom A. Use of medication for challenging behaviour in people with intellectual disability. *Br J Psychiatry* 2014; **205**: 6-7.
16. Department of Health. Transforming care: A national response to Winterbourne View Hospital: Department of Health Review Final Report. Department of Health. London: 2012.
17. Public Health England. Prescribing of psychotropic drugs to people with learning disabilities and/or autism by general practitioners in England. Public Health England. London: 2015.
18. Marshall T. Audit of the use of psychotropic medication for challenging behaviour in a community learning disability service. *The Psychiatrist* 2004; **28**: 447-50.
19. Deb S, Unwin G, Deb T. Characteristics and the trajectory of psychotropic medication use in general and antipsychotics in particular among adults with an intellectual disability who exhibit aggressive behaviour. *J Intellect Disabil Res* 2015; **59**: 11-25.
20. de Leon J, Greenlee B, Barber J, Sabaawi M, Singh NN. Practical guidelines for the use of new generation antipsychotic drugs (except clozapine) in adult individuals with intellectual disabilities. *Res Dev Disabil* 2009; **30**: 613-69.
21. Campbell N, Boustani M, Limbil T, et al. The cognitive impact of anticholinergics: a clinical review. *Clinical Interventions in Aging* 2009; **4**: 225-33.

22. Fox C, Smith T, Maidment I, et al. Effect of medications with anti-cholinergic properties on cognitive function, delirium, physical function and mortality: a systematic review. *Age Ageing* 2014; **43**: 604-15.
23. Arnold LE. Clinical pharmacological issues in treating psychiatric disorders of patients with mental retardation. *Ann Clin Psychiatry* 1993; **5**: 189-97.
24. Wyatt RJ. Research in schizophrenia and the discontinuation of antipsychotic medications. *Schizophr Bull* 1997; **23**: 3-9.
25. Jeste DV, Palmer BW, Harris MJ. Neuroleptic discontinuation in clinical and research settings: scientific issues and ethical dilemmas. *Biol Psychiatry* 1999; **46**: 1050-9.
26. Pan YJ, Wu CS, Gau SSF, Chan HY, Banerjee S. Antipsychotic Discontinuation in Patients with Dementia: A Systematic Review and Meta-Analysis of Published Randomized Controlled Studies. *Dement Geriatr Cogn Disord* 2014; **37**: 125-40.
27. Declercq T, Petrovic M, Azermai M, et al. Withdrawal versus continuation of chronic antipsychotic drugs for behavioural and psychological symptoms in older people with dementia. *Cochrane Database Syst Rev* 2013.
28. Troost PW, Lahuis BE, Steenhuis M-P, et al. Long-term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. *J Am Acad Child Adolesc Psychiatry* 2005; **44**: 1137-44.
29. Reyes M, Buitelaar J, Toren P, Augustyns I, Eerdekens M. A randomized, double-blind, placebo-controlled study of risperidone maintenance treatment in children and adolescents with disruptive behavior disorders. *AJ Psychiatry* 2006; **163**: 402-10.
30. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. *AJ Psychiatry* 2005.
31. Howick J, Chalmers, I., Glasziou, P., Greenhalgh, T., Heneghan, C., Liberati, A., Moschetti, I., Phillips, B., Thornton, H. Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document). Oxford Centre for Evidence-Based Medicine.
32. Ahmed Z, Fraser W, Kerr MP, et al. Reducing antipsychotic medication in people with a learning disability. *Br J Psychiatry* 2000; **176**: 42-6.
33. Smith C, Felce D, Ahmed Z, et al. Sedation effects on responsiveness: Evaluating the reduction of antipsychotic medication in people with intellectual disability using a conditional probability approach. *J Intellect Disabil Res* 2002; **46**: 464-71.
34. Gedye A. Neuroleptic-induced dementia documented in four adults with mental retardation.[Erratum appears in Ment Retard 1999 Apr;37(2):138]. *Ment Retard* 1998; **36**: 182-6.
35. Orfan NA, Kolski GB. Rhinorrhea related to antipsychotic drug therapy. *J Allergy Clin Immunol* 1993; **91**: 681-2.
36. Carpenter M, Cowart CA, McCallum R, Bell SM. Effects of antipsychotic medication on discrimination learning for institutionalized adults who have mental retardation. *Behavioral Residential Treatment* 1990; **5**: 105-20.
37. Wigal T, Christian DL, Wigal SB, et al. Classification of types of tardive dyskinesia in a developmentally disabled population at a public residential facility. *J Dev Phys Disabil* 1993; **5**: 55-69.
38. Wigal T, Swanson JM, Christian DL, et al. Admissions to a public residential facility for individuals with developmental disabilities: Change in neuroleptic drug use and tardive dykinesia. *J Dev Phys Disabil* 1994; **6**: 115-24.
39. Swanson JM, Christian DL, Wigal T, et al. Tardive dyskinesia in a developmentally disabled population: Manifestation during the initial stage of a minimal effective dose program. *Exp Clin Psychopharmacol* 1996; **4**: 218-23.
40. Hancock RD, Weber SL, Kaza R, Her KS. Changes in psychotropic drug use in long-term residents of an ICF/MR facility. *Am J Ment Retard* 1991; **96**: 137-41.
41. Lepler S, Hodas A, Cotter-Mack A. Implementation of an interdisciplinary psychotropic drug review process for community-based facilities. *Ment Retard* 1993; **31**: 307.

42. Spreat S, Serafin C, Behar D, Leiman S. Tranquilizer reduction trials in a residential program for persons with mental retardation. *Hosp Community Psychiatry* 1993; **44**: 1100-2.
43. Jauernig R, Hudson A. Evaluation of an Interdisciplinary Review Committee managing the use of psychotropic medication with people with intellectual disabilities. *Australia and New Zealand Journal of Developmental Disabilities* 1995; **20**: 51-61.
44. Branford D. A review of antipsychotic drugs prescribed for people with learning disabilities who live in Leicestershire. *J Intellect Disabil Res* 1996; **40**: 358-68.
45. Janowsky DS, Barnhill L, Khalid AS, Davis JM. Relapse of Aggressive and Disruptive Behavior in Mentally Retarded Adults Following Antipsychotic Drug Withdrawal Predicts Psychotropic Drug Use a Decade Later. *J Clin Psychiatry* 2006; **67**: 1272-7.
46. Janowsky DS, Barnhill LJ, Khalid AS, Davis JM. Antipsychotic withdrawal-induced relapse predicts future relapses in institutionalized adults with severe intellectual disability. *J Clin Psychopharmacol* 2008; **28**: 401-5.
47. de Kuijper G, Evenhuis H, Minderaa R, Hoekstra P. Effects of controlled discontinuation of long-term used antipsychotics for behavioural symptoms in individuals with intellectual disability. *J Intellect Disabil Res* 2014; **58**: 71-83.
48. May P, London EB, Zimmerman T, Thompson R, Mento T, Spreat S. A study of the clinical outcome of patients with profound mental retardation gradually withdrawn from chronic neuroleptic medication. *Ann Clin Psychiatry* 1995; **7**: 155-60.
49. Newell KM, Bodfish JW, Mahorney SL, Sprague RL. Dynamics of lip dyskinesia associated with neuroleptic withdrawal. *Am J Ment Retard* 2000; **105**: 260-8.
50. Newell KM, Ko YG, Sprague RL, Mahorney SL, Bodfish JW. Onset of dyskinesia and changes in postural task performance during the course of neuroleptic withdrawal. *Am J Ment Retard* 2002; **107**: 270-7.
51. Newell KM, Wszola B, Sprague RL, Mahorney SL, Bodfish JW. The changing effector pattern of tardive dyskinesia during the course of neuroleptic withdrawal. *Exp Clin Psychopharmacol* 2001; **9**: 262-8.
52. de Kuijper G, Mulder H, Evenhuis H, Visser F, Hoekstra PJ. Effects of controlled discontinuation of long-term used antipsychotics on weight and metabolic parameters in individuals with intellectual disability. *J Clin Psychopharmacol* 2013; **33**: 520-4.
53. Sprague RL, Kalachnik JE, Slaw KM. Psychometric properties of the dyskinesia identification system: Condensed user scale (DISCUS). *Ment Retard* 1989; **27**: 141.
54. Kalachnik JE, Sprague RL. The Dyskinesia Identification System Condensed User Scale (DISCUS): reliability, validity, and a total score cut-off for mentally ill and mentally retarded populations. *J Clin Psychol* 1993; **49**: 177-89.
55. Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia. *Arch Gen Psychiatry* 1982; **39**: 486-7.
56. Visser M, Marinus J, Stiggelbout AM, Van Hilten JJ. Assessment of autonomic dysfunction in Parkinson's disease: The SCOPA-AUT. *Mov Disord* 2004; **19**: 1306-12.
57. Branford D. Factors associated with the successful or unsuccessful withdrawal of antipsychotic drug therapy prescribed for people with learning disabilities. *J Intellect Disabil Res* 1996; **40**: 322-9.
58. Matthews T, Weston SN. Experience of thioridazine use before and after the Committee on Safety of Medicines warning. *The Psychiatrist* 2003; **27**: 87-9.
59. Luchins DJ, Dojka D, Hanrahan P. Factors associated with reduction in antipsychotic medication dosage in adults with mental retardation. *Am J Ment Retard* 1993; **98**: 165-72.
60. Stevenson C, Rajan L, Reid G, Melville C, McGilp R, Cooper S-A. Withdrawal of antipsychotic drugs from adults with intellectual disabilities. *Ir J Psychol Med* 2004; **21**: 85-90.
61. Salomon C, Hamilton B. Antipsychotic discontinuation syndromes: A narrative review of the evidence and its integration into Australian mental health nursing textbooks. *Int J Ment Health Nurs* 2014; **23**: 69-78.

62. Verghese C, DeLeon J, Nair C, Simpson GM. Clozapine withdrawal effects and receptor profiles of typical and atypical neuroleptics. *Biol Psychiatry* 1996; **39**: 135-8.
63. Urbano M, Spiegel D, Rai A. Atypical antipsychotic withdrawal dyskinesia in 4 patients with mood disorders. *J Clin Psychopharmacol* 2007; **27**: 705-7.
64. Samele C, Seymour L, Morris B. A formal investigation into health inequalities experienced by people with learning difficulties and people with mental health problems-Area Studies Report. Disability Rights Commission. London: 2006.
65. Robertson J, Emerson E, Gregory N, et al. Lifestyle related risk factors for poor health in residential settings for people with intellectual disabilities. *Res Dev Disabil* 2000; **21**: 469-86.
66. Aman M, Singh, N. Pharmacological intervention. In: Matson JL, Mulick, J. , ed. Handbook of Mental Retardation. New York: Pergamon; 1991.
67. Wysocki T, Fuqua RW, Davis VJ, Breuning SE. Effects of thioridazine (Mellaril) on titrating delayed matching-to-sample performance of mentally retarded adults. *Am J Ment Defic* 1981; **85**: 539-47.
68. Moncrieff J. Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse. *Acta Psychiatr Scand* 2006; **114**: 3-13.
69. Marston L, Nazareth I, Petersen I, Walters K, Osborn DP. Prescribing of antipsychotics in UK primary care: a cohort study. *BMJ Open* 2014; **4**: e006135.
70. Deb S, Kwok H, Bertelli M, et al. International guide to prescribing psychotropic medication for the management of problem behaviours in adults with intellectual disabilities. *World Psychiatry* 2009; **8**: 181-6.
71. Flood B, Henman MC. Building quality indicators for medication use in people aging with intellectual disabilities and behaviour disorders. *Int J Dev Disabil* 2015.
72. Royal College of Psychiatrists. Psychotropic drug prescribing for people with intellectual disability, mental health problems and/or behaviours that challenge: practice guidelines. Royal College of Psychiatrists. London: 2016.
73. Bromley J, Emerson E. Beliefs and emotional reactions of care staff working with people with challenging behaviour. *J Intellect Disabil Res* 1995; **39**: 341-52.
74. Dagnan D, Cairns M. Staff judgements of responsibility for the challenging behaviour of adults with intellectual disabilities. *J Intellect Disabil Res* 2005; **49**: 95-101.
75. Lambrechts G, Maes B. Analysis of staff reports on the frequency of challenging behaviour in people with severe or profound intellectual disabilities. *Res Dev Disabil* 2009; **30**: 863-72.
76. Singh N, Ellis CR, Donatelli LS, et al. Professionals perceptions of psychotropic medication in residential facilities for individuals with mental retardation. *J Intellect Disabil Res* 1996; **40**: 1-7.
77. Donley M, Chan J, Webber L. Disability support workers' knowledge and education needs about psychotropic medication. *Br J Learn Disabil* 2012; **40**: 286-91.
78. Christian L, Snycerski S, Singh N, Poling A. Direct service staff and their perceptions of psychotropic medication in non-institutional settings for people with intellectual disability. *J Intellect Disabil Res* 1999; **43**: 88-93.
79. Clarke DJ, Kelley S, Thinn K, Corbett JA. Psychotropic drugs and mental retardation: 1. Disabilities and the prescription of drugs for behaviour and for epilepsy in three residential settings. *J Intellect Disabil Res* 1990; **34**: 385-95.
80. Bamidele K, Hall I. The place of medication for challenging behaviour: a whole system perspective. *Advances in Mental Health and Intellectual Disabilities* 2013; **7**: 325-32.
81. Findholt NE, Emmett CG. Impact of interdisciplinary team review on psychotropic drug use with persons who have mental retardation. *Ment Retard* 1990; **28**: 41.
82. Bisconer SW, Zhang X, Sine LF. Impact of a psychotropic medication and physical restraint review process on adults with mental retardation, psychiatric diagnoses, and challenging behaviors. *J Dev Phys Disabil* 1995; **7**: 123-35.

83. Howerton K, Fernandez G, Touchette P, et al. Psychotropic medications in community based individuals with developmental disabilities: observations of an interdisciplinary team. *Mental Health Aspects of Developmental Disabilities* 2002; **5**: 78-86.
84. Ruggerini C, Guaraldi GP, Russo A, Neviani V, Castagnini A. Integration of a psychiatric service in a long-term charitable facility for people with intellectual disabilities: a 5-year medication survey. *Res Dev Disabil* 2004; **25**: 431-41.
85. Lim WWC. Use of psychoactive medications in Hong Kong institutions for adults with severe to profound learning disabilities: a retrospective study (1988–2003) and economic analysis. *Journal of Applied Research in Intellectual Disabilities* 2007; **20**: 529-38.
86. Wressell SE, Tyrer SP, Berney TP. Reduction in antipsychotic drug dosage in mentally handicapped patients. A hospital study. *Br J Psychiatry* 1990; **157**: 101-6.
87. Etherington J, Sheppard L, Ballinger B, Fenton G. Psychotropic drugs in a hospital for intellectual disability: the story of 18 years. *Mental Handicap Research* 1995; **8**: 184-93.
88. Gravestock S. Regional audit of depot neuroleptic usage in adults with learning disabilities. *The Psychiatrist* 1996; **20**: 289-91.
89. Branford D. A follow-up study of prescribing for people with learning disabilities previously in National Health Service care in Leicestershire, England. *J Intellect Disabil Res* 1997; **41**: 339-45.
90. Branford D, Hutchins D. Tardive akathisia in people with mental retardation. *J Dev Phys Disabil* 1996; **8**: 117-32.
91. Pary RJ. Discontinuation of neuroleptics in community-dwelling individuals with mental retardation and mental illness. *Am J Ment Retard* 1995; **100**: 207-12.
92. Sovner R. Thioridazine Withdrawal-Induced Behavioral Deteriration Treated With Clonidine: Two Case Reports. *Ment Retard* 1995; **33**: 221.
93. Davies SJ, Cooke LB, Moore AG, Potokar J. Discontinuation of thioridazine in patients with learning disabilities: balancing cardiovascular toxicity with adverse consequences of changing drugs. *BMJ* 2002; **324**: 1519.
94. Margetić B, Aukst-Margetić B. Neuroleptic malignant syndrome and clozapine withdrawal at the same time? *Prog Neuropsychopharmacol Bol Psychiatry* 2005; **29**: 145-7.
95. Stonecipher A, Galang R, Black J. Psychotropic discontinuation symptoms: a case of withdrawal neuroleptic malignant syndrome. *Gen Hosp Psychiatry* 2006; **28**: 541-3.
96. Janowsky DS, Barnhill LJ, Shetty M, Davis JM. Minimally effective doses of conventional antipsychotic medications used to treat aggression, self-injurious and destructive behaviors in mentally retarded adults. *J Clin Psychopharmacol* 2005; **25**: 19-25.
97. Haessler F, Glaser T, Pap A, Beneke M, Diefenbacher A, Reis O. A double-blind placebo-controlled discontinuation study of zuclopenthixol for the treatment of aggressive disruptive behaviours in adults with mental retardation-secondary parameter analyses. *Pharmacopsychiatry* 2008; **41**: 232-9.
98. Häßler F, Glaser T, Reis O. Effects of zuclopenthixol on aggressive disruptive behavior in adults with mental retardation--a 2-year follow-up on a withdrawal study. *Pharmacopsychiatry* 2011; **44**: 339-43.
99. Rapp JT, Swanson G, Dornbusch K. Temporary Increases in Problem Behavior and Sleep Disruption Following Decreases in Medication A Descriptive Analysis of Conditional Rates. *Behav Modif* 2007; **31**: 825-46.
100. Levitas AS, Turk J, Bramble D, Hurley AD. Antipsychotics for aggression unrelated to a psychiatric diagnosis. *Mental Health Aspects of Developmental Disabilities* 2008; **11**: 65.

Consider antipsychotic medication in the management of challenging behaviour only when:

- Psychological or other interventions alone are not effective
- Treatment for co-morbid physical or mental disorders has been given
- The risk to the person or others is high

Only offer antipsychotic medication in combination with psychological or other interventions

Antipsychotic medication should be prescribed and initially monitored by a psychiatrist who should:

- Document the rationale for the medication
- Prescribe the lowest dose necessary
- Review the effectiveness and any side-effects after 3-4 weeks
- Develop a strategy for stopping the medication
- Stop the medication if there is no indication of response at 6 weeks

Antipsychotic medication should continue to be prescribed past 6 weeks only when supported by:

- Proven continued benefit of the drug
- Full multidisciplinary review at 3 months and every 6 months thereafter

Panel 1 Summary of guidelines on the use of antipsychotic medication to manage challenging behaviour, adapted from NICE NG11[11]

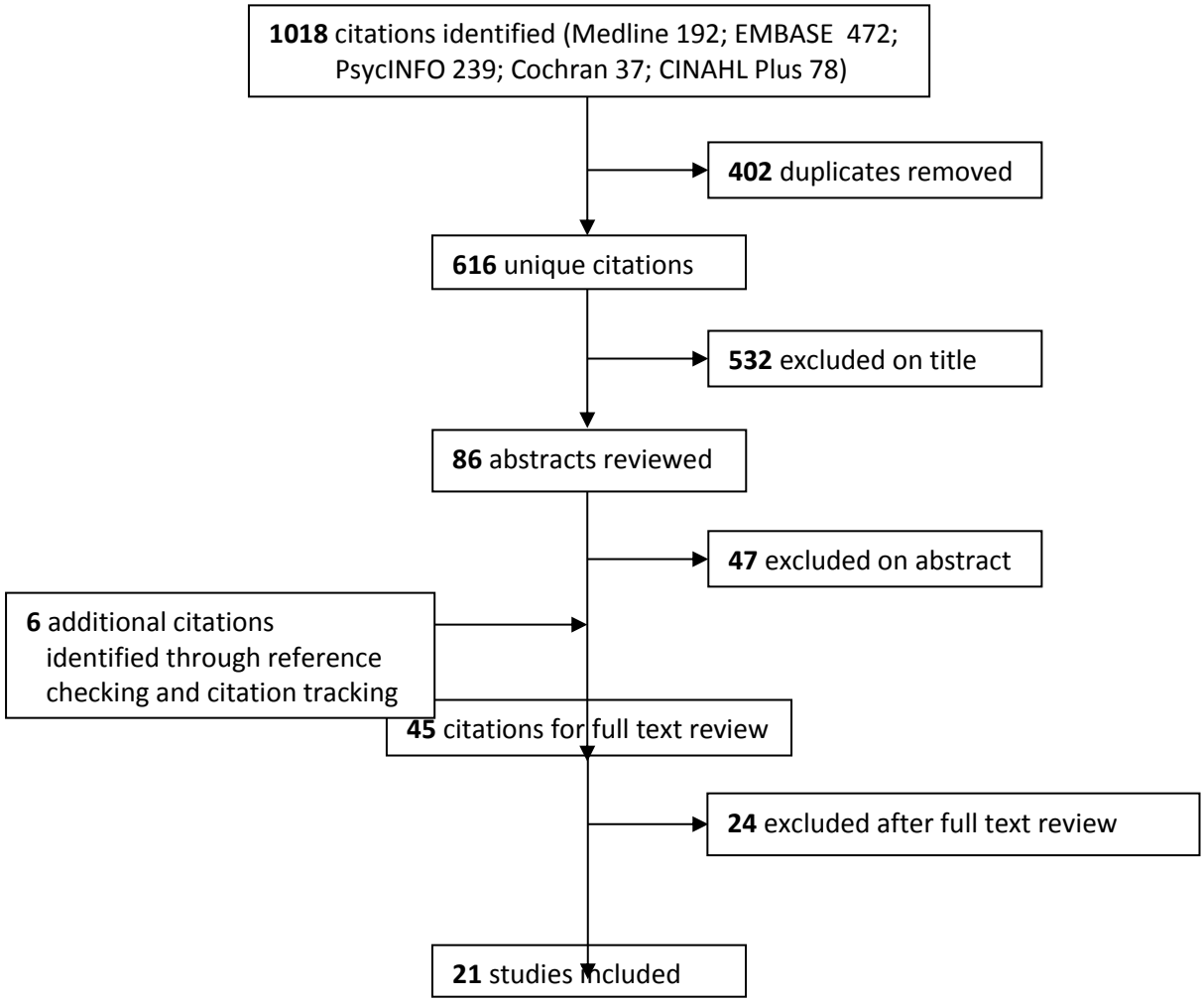

Figure 1 – study selection

Study and level of evidence (LE)	Participants	Setting	Intervention	Follow-up	Outcome	Results	Bias and limitations
Carpenter et al, 1990 LE: 3	*n*=10 90% ♂ Mean age 30 yrs ID: borderline 10%, mild 50%, moderate 10%, severe 30% Intervention group (*n*=7) taking antipsychotic for challenging behaviour. Control group (*n*=3) taking antipsychotic for behaviour or no antipsychotic medication. One control diagnosed with schizophrenia.	State institution USA	Reduction of antipsychotic medication by 25-100%, not according to a pre-defined schedule. No medication changes in controls.	After medication reduction or discontinuation	Performance on a discrimination task requiring matching of colours presented sequentially on a computer screen; an initial colour is presented, followed by a delay, and then two colours – the participant must move a joystick in the direction of the matching colour for a correct response. Performance measured by a) trials needed to achieve 4 consecutive correct responses and b) overall percentage of correct responses	Intervention group improved in both measures of performance (trials to 4 consecutive correct responses – mean improvement 28.7% reduction group vs. 0.4% for controls; percentage of correct responses mean improvement 10.2% reduction group vs. -1.5% control group)	(1) (2) (3) (4) (5) (6) (7) (8)
Hancock et al, 1991 LE: 4	*n*=42 42% ♂ Mean age at entry 28 yrs ID: mild 5%, moderate 5%, severe 7%, profound 83% 5% psychiatric co-morbidity (details not given) Antipsychotics: Thioridazine (*n*=36), chlorpromazine (*n*=1), haloperidol (*n*=3), mesoridazine (*n*=3) (one participant on 2 drugs)	State institution USA	Interdisciplinary team programme to review psychotropic medication with a view to reduction or discontinuation (not according to a pre-defined schedule)	5 years 10 years	Number discontinuing antipsychotics Number discontinuing antipsychotics	10/42 (24%) discontinued antipsychotics 31/42 (74%) discontinued antipsychotics	(8) (9) (10)

Orfan et al, 1993 LE: 5	*n*=1 ♀ 74 yrs Degree of ID not given Antipsychotic for challenging behaviour Psychiatric diagnosis not given Antipsychotic: Fluphenazine	Private home USA	Single-case report Antipsychotic reduced to discontinuation over 3 months	4 year	ENT symptoms	Debilitating and persistent rhinorrhoea on fluphenazine (and benztropine) discontinuation	(1) (4) (5) (9) (11)
Lepler et al, 1993 LE: 4	*n*=6 on antipsychotic medication from larger cohort: 60% ♂ Mean age 34 years ID: mild 4%, moderate 23%, severe 46%, profound 31% Comorbidities not reported Antipsychotics: Trifluoperazine (*n*=2), thioridazine (*n*=2), haloperidol (*n*=1), thiothixene (*n*=1)	Supported community homes USA	Interdisciplinary team programme to review psychotropic medication with a view to reduction or discontinuation (not according to a pre-defined schedule)	4 year	Number discontinuing antipsychotics Number on reduced dose of antipsychotic	1/6 (17%) discontinued antipsychotics 5/6 (83%) maintained on reduced dose	(5) (9) (10)
Spreat et al, 1993 LE: 4	*n*=86 From a larger cohort (*n*=284): 67% ♂ Mean age 31 yrs ID severe/profound 80% Comorbidities not reported	State institution USA	Medication reduction trial (not according to a pre-defined schedule)	1 year	Change in antipsychotic use	14/86 (16%) >50% dose reduction or discontinuation 26/86 (30%) dose reduction ≤50% 46/86 (53%) same or increased dose	(1) (8) (9) (10)

	Antipsychotics (in overall group): Haloperidol 36%, mesoridazine 27%, thioridazine 15%, thioxanthene 6%, chlorpromazine 5%, trifluoperazine 4%, molindone 4%, fluphenazine 2%, chlorprothixene 2%						
Wigal et al, 1993 LE: 3	n=56 64% ♂ Mean age 33 yrs ID: severe-profound 96% Comorbidities not reported Antipsychotics not reported by type	State institution USA	Medication review and dose reduction programme (not according to a pre-defined schedule) Comparison of 4 unmatched groups: Increase in antipsychotic dose (IN, *n*=5) No change in antipsychotic dose (NC, *n*=14) Reduction in antipsychotic dose of <25% (SD, *n*=21) Reduction in antipsychotic dose of ≥25% (25D, *n*=16)	10 months	DISCUS score compared between groups undergoing at baseline (T1) and follow-up (T2) Proportion with dyskinesia (Schooler & Kane categorical definition[55])	No difference in DISCUS score between groups at T1. DISCUS score at T2 was increased in NC, SD, and 25D groups – greatest increase observed in 25D group. DISCUS score at T2 decreased in the IN group. Significant correlation demonstrated between degree of dose reduction and DISCUS score (r=0.506, p<0.001) Proportion with dyskinesia increased from 30% at T1 to 60% at T2 in the 25D group, did not change in the SD or NC groups, and fell from 60% to 20% in the IN group.	(1) (2) (3) (7) (8) (9) (10)
Wigal et al, 1994 LE: 4	*n*=245 From a larger cohort (*n*=636): 67% ♂ Mean age 24 yrs ID: severe-profound 96%	State institution USA	Medication review and dose reduction programme (not according to a pre-defined schedule)	1 year	Number discontinuing antipsychotics	141/245 (58%) discontinued antipsychotic medication	(1) (2) (3) (7) (8) (9) (10)

	Comorbidities not reported Antipsychotics not reported by type						
	n=30 From a larger cohort (*n*=43): 61% ♂ Mean age 31 yrs ID: severe-profound 86% Comorbidities not reported Antipsychotics not reported by type		Medication review and dose reduction programme (not according to a pre-defined schedule). Comparison of groups defined by antipsychotic discontinuation (not otherwise matched) (*n*=8), dose reduction (*n*=7), no change/increase (*n*=5) and control group not on antipsychotics (*n*=10)	10 months	Rates of dyskinesia (Schooler & Kane categorical definition[55])	5/8 (63%) in discontinuation group developed dyskinesia 2/7 (29%) in dose reduction group developed dyskinesia None in the no change/increase or unmedicated group developed dyskinesia	
Jauernig et al, 1994 LE: 4	*n*=25 Demographic characteristics not reported 6 with co-morbid mental illness (detail not given) Antipsychotics: Thioridazine (*n*=11) Chlorpromazine (*n*=10) Haloperidol (*n*=3) Fluphenazine (*n*=2) Trifluoperazine (*n*=1) (some took more than one antipsychotic drug)	State institution Australia	Medication review and dose reduction programme (not according to a pre-defined schedule, but slow titrations preferred and maximum monthly dose decrease was 25% initial dose or 100mg chlorpromazine equivalents)	2 years	Number reducing or discontinuing antipsychotic medication Challenging behaviour (frequency count of target behaviours)	3/25 (12%) discontinued antipsychotic medication 19/25 (86%) underwent dose reduction 3/25 (12%) no change in dose. Challenging behaviour frequency at follow-up lower than baseline in all 3 (100%) whose antipsychotic had been discontinued and in 15 (79%) of those who underwent dose reduction.	(1) (3) (4) (8) (9) (10) (12)
May et al, 1995 LE: 4	*n*=23 100% ♂ Mean age 42 yrs	State institution USA	Antipsychotic reduction by 10% original dose every 3 months to discontinuation. All	3-4 years (incl. at least 1 year after discontinuation)	Challenging behaviour (frequency counts)	Three groups described on basis of change in challenging behaviour: transient worsening (*n*=9, 39%), progressive improvement (*n*=5, 22%), persistent worsening (*n*=9, 39%)	(1) (4) (7) (8)

	ID: severe-profound 100% Comorbidities not reported Thioridazine used in all participants		completed discontinuation.			Those in the progressive improvement group tended to receive lower initial doses of antipsychotic and have higher baseline levels of challenging behaviour (differences between groups not statistically significant, data not given).	(9) (11)
Branford, 1996 LE: 4	*n*=123 From a larger cohort (*n*=198): 66% ♂ Mean age 43 yrs ID: borderline 1%, mild 13%, moderate 30%, severe 56% Psychiatric comorbidity: Schizophrenia 4%, affective disorder 7%, anxiety disorder 16%, personality disorder 8% Antipsychotics: Thioridazine (*n*=98), chlorpromazine (*n*=52), zuclopenthixol (*n*=34), haloperidol (*n*=15), other (*n*=15) (some took more than one antipsychotic drug)	47% hospital, 53% community UK	Medication review and dose reduction programme (not according to a pre-defined schedule, most dose reduction was over a 3 month period)	12 months	Number reducing or discontinuing antipsychotic medication Challenging behaviour (anecdotal report)	31/123 (25%) discontinued antipsychotic 56/123 (46%) reduced dose 27/123 (22%) same dose 9/123 (7%) higher dose 31/123 (25%) no deterioration 52/123 (42%) deterioration in behaviour 40/123 (33%) not reported	(1) (4) (9) (10) (13)
Swanson et al, 1996 LE: 3	*n*=80 61% ♂ Mean age 38 yrs ID: moderate 1%, severe 16%, profound 80%, unknown 3% 1% diagnosed mental illness	State institution USA	Medication review and dose reduction programme to discontinuation (not according to a pre-defined schedule) Four groups compared (unmatched)	3 monthly intervals to 6 months after antipsychotic discontinuation	Dyskinesia (DISCUS score)	Transient increase in average DISCUS score in antipsychotic-only group after withdrawal with return to baseline 6 months after discontinuation. No consistent change in those withdrawn from antipsychotics who were also taking anti-convulsants. No change in control groups (no medication and anti-convulsant medication only)	(1) (2) (3) (7) (8) (10)

	Antipsychotics: Thioridazine (*n*=18), haloperidol (*n*=7), loxapine (*n*=6) chlorpromazine (*n*=5), other (*n*=4)		Intervention groups: antipsychotics only (*n*=19), antipsychotics + anti-convulsants (*n*=21) Control groups: no medication (*n*=19), anti-convulsants only (*n*=21)		Challenging behaviour (ABC)	No consistent change in antipsychotic only group over course of withdrawal. Transient increase in average ABC during antipsychotic withdrawal in those also prescribed anti-convulsants. No change in control groups.	
Gedye, 1998 LE: 4	*n*=4 75% ♂ Mean age 42 yrs Degree of ID not given Comorbidities not reported Antipsychotics: Thioridazine (*n*=1), haloperidol (*n*=1), pimozide (*n*=1), loxapine (*n*=1)	Not known USA	Case series Antipsychotic discontinuation (not according to a pre-defined schedule)	Not specified	Clinical assessment	Antipsychotic discontinuation associated with improvement in cognitive function and revocation of previous diagnosis of dementia in all cases	(1) (3) (4) (5) (9) (11)
Ahmed et al, 2000 LE: 2	*n*=56 48% ♂ Mean age 43 yrs ID: mild 7%, moderate 30%, severe 26%, profound 35% Comorbidities not reported but none had psychosis Antipsychotics: Thioridazine (*n*=18), haloperidol (*n*=13), chlorpromazine (*n*=8), other (*n*=17)	45% hospital 55% community UK	RCT – participants randomly assigned to intervention or control groups. Intervention group (*n*=36): reduction of antipsychotic by 25% monthly to discontinuation Control group (*n*=20): no medication changes	6 months (1 month after planned discontinuation)	Number reducing or discontinuing antipsychotic medication (intervention group) Challenging behaviour (ABC) Observed behaviour DISCUS Weight	12/36 (33%) discontinued medication 7/36 (19%) ≥50% reduction in dose 17/36 (48%) unable to tolerate reduction No difference between group who discontinued or achieved ≥50% reduction and controls Higher engagement activity in discontinuation/reduction group compared with controls ($p<0.05$). No difference in maladaptive behaviour among groups DISCUS score increased in group who discontinued or achieved ≥50% dose reduction compared with controls ($p<0.01$) Average weight loss of 2.3kg in group who discontinued or achieved ≥50% dose	(1) (2) (3) (7) (13)

						reduction but no statistically significant difference from controls	
Newell et al, 2000 LE: 4	*n*=6 67% ♂ Mean age 37 yrs ID: moderate 50%, severe 33%, profound 17% No comorbidities Antipsychotics: haloperidol (*n*=3) thioridazine (*n*=2) Mesoridazine (*n*=1)	State institution USA	Antipsychotic dose reduction by approx. 25% every 3 mths to discontinuation	Post-discontinuation follow-up of 6months-2years	Video analysis of lip movement (as proxy of TD) DISCUS score	Dyskinetic movements increased during antipsychotic withdrawal followed by a reduction post-discontinuation, although not to baseline levels Results not given	(1) (3) (4) (5) (7) (8) (9) (12) (13)
Newell et al, 2001 LE: 4	*n*=26 69% ♂ Mean age 35 yrs ID: mild 4%, moderate 20%, severe 46%, profound 31% No psychiatric comorbidities Antipsychotics: haloperidol (*n*=9) thioridazine (*n*=9) chlorpromazine (*n*=3) mosoridazine (*n*=3) loxapine (*n*=1) trifluperazine (*n*=1)	State institution USA	Antipsychotic dose reduction by approx.. 25% every 2-4 mths to discontinuation	Post-discontinuation follow-up of 12 months	DISCUS score Tardive dyskinesia (Kalachnik & Sprague categorical definition)	Mean total DISCUS increased significantly from baseline during antipsychotic withdrawal (3.423 to 10.731, p<0.001), before returning to baseline levels at follow-up (3.462). Prevalence in group increased from 31% at baseline to 85% during antipsychotic withdrawal, and fell to 38% at follow-up	(1) (3) (8) (12)
Newell et al, 2002 LE: 4	*n*=20 75% ♂ Mean age 37 yrs ID: severe-profound 100% No comorbidities	State institution USA	Antipsychotic dose reduction by approx.. 25% every 3 mths to discontinuation	Post-discontinuation follow-up of 12 months	Postural stability DISCUS	Indices of postural stability changed significantly over the course of medication withdrawal and tended to return to baseline levels at follow-up Mean total DISCUS increased significantly from baseline during antipsychotic withdrawal (3.52 to 11.10, *p*<0.01), before	(1) (3) (4) (7) (8) (9) (12)

	Antipsychotics: thioridazline (*n*=7) haloperidol (*n*=5) trifluoperazine (*n*=3) loxapine (*n*=3) chlorpromazine (*n*=2)					returning to baseline levels at follow-up (3.75).	
Smith et al, 2002 LE: 2 Additional reporting of Ahmed et al, 2000	*n*=56 48% ♂ Mean age 43 yrs ID: mild 7%, moderate 30%, severe 26%, profound 35% Comorbidities not reported but none had psychosis Antipsychotics: Thioridazine (*n*=18), haloperidol (*n*=13), chlorpromazine (*n*=8), other (*n*=17)	45% hospital 55% community UK	RCT Intervention group (*n*=36): reduction of antipsychotic by 25% monthly to discontinuation Control group (*n*=20): no medication changes	6 months (1 month after planned discontinuation)	Responsiveness to staff interaction	No difference between group undergoing antipsychotic reduction/discontinuation and control group	(1) (2) (3) (7)
Janowsky et al, 2006 LE: 4	*n*=138 from a larger cohort (*n*=151): 60% ♂ Mean age 48 yrs ID: severe-profound 100% Psychiatric comorbidities incl. bipolar disorder, autism, stereotyped movements with self-injury, intermittent explosive disorder, mood disorder, obsessive-compulsive	State institution USA	Medication review and dose reduction programme (not according to a pre-defined schedule)	3 months Ave 10 years	Number discontinuing antipsychotic medication Number discontinuing antipsychotic medication	83/138 (60%) discontinued antipsychotic medication 55/138 (40%) experienced behavioural disturbance requiring re-prescribing 74/138 (54%) discontinued antipsychotic medication 64/138 (46%) could not discontinue antipsychotic medication	(1) (8) (9) (10)

	disorder, psychotic disorder, anxiety disorder, behaviour disorder, oppositional defiant disorder (percentages not given) but antipsychotics given to manage behaviour Antipsychotics not given by type						
Janowsky et al, 2008 LE:	*n*=49 from a larger cohort (*n*=57): 65% ♂ Mean age 52 yrs ID: severe-profound 100% All had experienced behavioural worsening on a previous attempt to reduce or discontinue antipsychotics Psychiatric comorbidities incl. bipolar disorder, autism, stereotyped movements with self-injury, intermittent explosive disorder, mood disorder, obsessive-compulsive disorder, psychotic disorder, anxiety disorder, behaviour disorder, oppositional defiant disorder	State institution USA	Medication review and dose reduction programme (not according to a pre-defined schedule but most were reduced at ≤10% per month)	Up to 15 years (average follow-up not given)	Number discontinuing antipsychotic medication Challenging behaviour (anecdotal report)	4/49 (8%) discontinued antipsychotic medication 45/49 (92%) could not discontinue antipsychotic medication 2/49 (4%) no deterioration in maladaptive behaviour 47/49 (96%) experienced relapse in maladaptive behaviour on antipsychotic reduction	(1) (8) (9) (10)

	(percentages not given) but antipsychotics given to manage behaviour Antipsychotics (larger group): haloperidol (*n*=24), thioridazine (*n*=20), chlorpromazine (*n*=7), thiothixine (*n*=5), loxapine (*n*=1)						
deKuijper et al, 2013 LE: 4 Additional reporting of deKuijper et al, 2014	*n*=36 from a larger cohort (*n*=98): 64% ♂ Mean age 50 yrs ID: mild 7%, moderate 30%, severe 26%, profound 35% 54% had co-morbid mental illness (autism spectrum condition 45%, ADHD 3%, mood disorder 4%, other 4%, none had schizophrenia or bipolar disorder) Antipsychotics: Pipamperone (*n*=64), haloperidol (*n*=18), levomepromazine (*n*=7), pimozide (*n*=1), risperidone (*n*=15), olanzapine (*n*=8) (some took more than one antipsychotic drug)	Residential care centres (74%) and community settings (26%) Netherlands	Planned reduction of antipsychotic by 12.5% every 2 or 4 weeks (random allocation to reduction schedule in 1:1 ratio) Results of those achieving antipsychotic discontinuation (*n*=36)	26 or 40 weeks (12 weeks after discontinuation, depending on reduction schedule (*n*=21 on faster reduction schedule, *n*=15 on slower reduction schedule)	Waist circumference Weight BMI Systolic BP Diastolic BP Plasma triglycerides Plasma HDL Plasma glucose	Mean change -4.4cm ($p<0.001$) Mean change -3.5kg ($p=0.02$) Mean change -1.41kg/m^2 ($p=0.006$) Mean change -7.1mmHg ($p=0.02$) Mean change -4.3mmHg (p=NS) Mean change +0.05mmol/L (p=NS) Mean change +0.04mmol/L (p=NS) Mean change -0.09mmol/L (p=NS)	(1) (3) (7) (8) (12)

deKuijper et al, 2014 LE: 4	*n*=98 64% ♂ Mean age 50 yrs ID: mild 7%, moderate 30%, severe 26%, profound 35% 54% had co-morbid mental illness (autism spectrum condition 45%, ADHD 3%, mood disorder 4%, other 4%, none had schizophrenia or bipolar disorder) Antipsychotics: Pipamperone (*n*=64), haloperidol (*n*=18), levomepromazine (*n*=7), pimozide (*n*=1), risperidone (*n*=15), olanzapine (*n*=8) (some took more than one antipsychotic drug)	Residential care centres (74%) and community settings (26%) Netherlands	Reduction of antipsychotic by 12.5% every 2 or 4 weeks (random allocation to reduction schedule in 1:1 ratio) but under clinician control	Planned discontinuation: 14 or 28 weeks after initiation of dose reduction, depending on reduction schedule	Number reducing or discontinuing antipsychotic medication	43/98 (44%) discontinued antipsychotics. 55/98 (56%) could not discontinue medication but achieved average dose reduction of 41-48% compared with baseline.	(1) (3) (7) (8) (12)
					ABC	Significant improvement from baseline in group who achieved discontinuation (47 to 32, $p<0.01$).	
					VAS	No change from baseline in group who discontinued antipsychotics (mean 6.4 to 6.5, $p=0.76$)	
					CGI-I	14% improved, 83% no change, 2% worse compared with baseline in group discontinuing antipsychotics	
					SCOPA-AUT (autonomic symptoms)	Significant decrease in those achieving discontinuation (mean 6.0 to 3.0, $p<0.01$).	
					EPS (composite of scores on akathisia scale, parkinsonism scale and AIMS)	No change in those who achieved antipsychotic discontinuation (mean 2.8 to 2.8, statistical test not reported)	
				Follow-up: 26 or 40 weeks, depending on reduction schedule (i.e. 12 weeks after planned discontinuation)	Number reducing or discontinuing antipsychotic medication	36/98 (37%) remained off antipsychotics. 62/98 (56%) who did not discontinue or who were re-prescribed medication after discontinuation received average doses 15-20% lower that baseline.	
					ABC	Significant improvement from baseline in group who achieved discontinuation (mean 47 to 37, $p=0.03$).	

	VAS	No change from baseline in group who discontinued antipsychotics (mean 6.4 to 6.5, *p*=0.76)
	CGI-I	31% improved, 64% no change, 5% worse compared with baseline in group discontinuing antipsychotics
	SCOPA-AUT (autonomic symptoms)	Significant decrease in those who achieved discontinuation (mean 6.0 to 3.6, *p*=0.01).
	EPS (composite of scores on akathisia scale, parkinsonism scale and AIMS)	Slight increase in those who achieved antipsychotic discontinuation (mean 2.8 to 3.0, statistical test not reported).

ABC, aberrant behaviour checklist; AIMS, abnormal involuntary movement scale; BMI, body mass index; BP, blood pressure; DISCUS, dyskinesia identification system: condensed user scale; CGI-I, clinical global impression-improvement scale; ENT, ear, nose and throat; EPS, extrapyramidal symptoms; HDL, high density lipoprotein; ID, intellectual disability; RCT, randomised controlled trial; SCOPA-AUT, scale outcomes Parkinson's disease – automonic symptoms; TD, tardive dyskinesia; VAS, visual analogue scale

Table 1 Summary of included studies

Key to biases and limitations (in order of appearance in table):

(1) Selection bias
(2) Control group inadequately matched
(3) Lack of blinding
(4) Use of unvalidated measures/non-standard assessment tools
(5) Small sample size (<10 undergoing intervention)
(6) Possible practise effect
(7) Statistics or statistical tests inadequately reported or inappropriate
(8) Institutional setting
(9) Missing baseline information
(10) Intervention poorly defined
(11) Retrospective report/possible recall bias
(12) Lack of control group
(13) Selective reporting/incomplete outcome data

Study	*n*	Follow-up	Antipsychotic discontinued at follow-up	Antipsychotic discontinued or reduced at follow-up	Antipsychotic reduced at follow-up	Antipsychotic reduced or no change at follow-up	Antipsychotic no change or increased at follow-up
Hancock[40]	42	5 yrs	10/42 (24%)	-	-	32/42 (76%)	-
		10 yrs	31/42 (74%)	-	-	11/42 (26%)	-
Lepler[41]	6	4 yrs	1/6 (17%)	-	5/6 (83%)	-	-
Spreat[42]	86	1 yr	-	40 (47%)	-	46/86 (53%)	-
Wigal[38]	245	1 yr	141/245 (58%)	-	-	104/245 (42%)	-
Jauernig[43]	25	2 yrs	3/25 (12%)	-	19/25 (76%)	-	3/25 (12%)
Branford[44]	123	1 yr	31/123 (25%)	-	56/123 (46%)	-	36/123 (29%)
Ahmed[32]	56	6 mths	12/36 (33%)	-	7/36 (19%)	-	17/36 (47%)
Janowsky[45]	138	3 mths	83/138 (60%)	-	-	55/138 (40%)	-
		10 yrs	74/138 (54%)	-	-	64/138 (46%)	-
Janowsky[46]	49	Up to 15 yrs	2/49 (4%)			47/49 (96%)	
deKuijper[47]	51	26 wks	21/51 (41%)	-	-	30/51 (59%)	-
	47	40 wks	15/47 (32%)	-	-	32/47 (68%)	-

Table 2 – Outcome of interventions to reduce or discontinue antipsychotic medication

Demographic factors
Male sex[47]
Female sex[40]
Clinical factors
Higher baseline antipsychotic dose[47,48,57,58]
Higher baseline behavioural symptoms[47,48,57]
Lower baseline behavioural symptoms[48]
Higher baseline extrapyramidal symptoms[47]
Higher baseline psychopathology[57,59]
Previous unsuccessful antipsychotic withdrawal attempt[46]
Absence of co-administration of other psychoactive medication[39, 59]
Setting/environmental factors
More restrictive environments[32]
Lower staffing levels and training[32]

Table 3 Factors shown to be associated with unsuccessful attempts to reduce or discontinue antipsychotic medication in people with ID taking antipsychotics for challenging behaviour

- High quality studies that investigate the feasibility of reduction or discontinuation of antipsychotics used for challenging behaviour in people with intellectual disability are needed.
- Baseline characteristics of study participants should be well-defined and include screening for co-morbid mental illness using standardised instruments (such as the PAS-ADD) or adapted diagnostic criterial (such as the DC-LD).
- To be useful in guiding management decisions, studies should be adequately powered to elucidate environmental and individual characteristics that are associated with successful and unsuccessful attempts to reduce or discontinue antipsychotic medication.
- Although patient and caregiver attitude towards antipsychotic medication for challenging behaviour and concordance with treatment plans quite clearly influence their success, these were not mentioned in included studies, and should be investigated further.
- The economic impact and change in resource use resulting from antipsychotic reduction or discontinuation for challenging behaviour is likely to be complex and will require the balancing of short-term risks (e.g. management of behavioural deterioration) against potential longer-term savings (e.g. in prescription costs and managing long-term adverse side-effects).
- Novel or pragmatic study designs, possibly using routinely-collected health data, might be appropriate for further investigating this topic.

Panel 2 Future research directions

Appendix A – full list of search terms

Medline search terms (conducted on 27/03/2016)

Terms for intellectual disability (title or abstract)	Terms for anti-psychotic (title or abstract)	Terms for reduction or discontinuation (title or abstract)
Intellectual* disab*	Anti$psychotic*	Withdraw*
Intellectual* impair*	Neuroleptic*	Discontinu*
Intellectual* retard*	Major tranquil*i*er*	Stop*
Intellectual* handicap*	Dopamine antagonist	Remov*
Intellectual* subnormal*	Phenothiazine*	Reduc*
Intellectual* deficien*	Butyrophenone*	Minimi*
Learning disab*	Thioxanthene*	Cessation
Learning impair*	Diphenylbutylpiperidine*	Taper*
Learning retard*	Benperidol	
Learning handicap*	Chlorpromazine	
Learning subnormal*	Droperidol	
Learning deficien*	Flupent*ixol	
Mental* disab*	Haloperidol	
Mental* impair*	Levomepromazine	
Mental* retard*	Peric*azine	
Mental* handicap*	Perphenazine	
Mental* subnormal*	Pimozide	
Mental* deficien*	Prochlorperazine	
Developmental* disab*	Promazine	
Developmental* impair*	Sulpiride	
Developmental* retard*	Trifluoperazine	
Developmental* handicap*	Zuclopent*ixol	
Developmental* subnormal*	Amisulp*ride	
Developmental* deficien*	Aripiprazole	
Neurodevelopmental* disab*	Asenapine	
Neurodevelopmental* impair*	Clozapine	
Neurodevelopmental* retard*	Lurasidone	
Neurodevelopmental* handicap*	Olanzapine	
Neurodevelopmental* subnormal*	Paliperidone	
Neurodevelopmental* deficien*	Quetiapine	
	Risperidone	
	Thioridazine	
MeSH headings		
Intellectual Disability	Antipsychotic Agents	Substance Withdrawal Syndrome
Mentally Disabled Persons	Dopamine Antagonists	

PsycINFO search terms (conducted on 27/03/2016)

Terms for intellectual disability (title or abstract)	Terms for anti-psychotic (title or abstract)	Terms for reduction or discontinuation (title or abstract)
Intellectual* disab*	Anti-psychotic*	Withdraw*
Intellectual* impair*	Antipsychotic*	Discontinu*
Intellectual* retard*	Neuroleptic*	Stop*
Intellectual* handicap*	Major tranquil*i*er*	Remov*
Intellectual* subnormal*	Dopamine antagonist	Reduc*
Intellectual* deficien*	Phenothiazine*	Minimi*
Learning disab*	Butyrophenone*	Cessation
Learning impair*	Thioxanthene*	Taper*
Learning retard*	Diphenylbutylpiperidine*	
Learning handicap*	Benperidol	
Learning subnormal*	Chlorpromazine	
Learning deficien*	Droperidol	
Mental* disab*	Flupent*ixol	
Mental* impair*	Haloperidol	
Mental* retard*	Levomepromazine	
Mental* handicap*	Peric*azine	
Mental* subnormal*	Perphenazine	
Mental* deficien*	Pimozide	
Developmental* disab*	Prochlorperazine	
Developmental* impair*	Promazine	
Developmental* retard*	Sulpiride	
Developmental* handicap*	Trifluoperazine	
Developmental* subnormal*	Zuclopent*ixol	
Developmental* deficien*	Amisulp*ride	
Neurodevelopmental* disab*	Aripiprazole	
Neurodevelopmental* impair*	Asenapine	
Neurodevelopmental* retard*	Clozapine	
Neurodevelopmental* handicap*	Lurasidone	
Neurodevelopmental* subnormal*	Olanzapine	
Neurodevelopmental* deficien*	Paliperidone	
	Quetiapine	
	Risperidone	
	Thioridazine	
MeSH headings		
Intellectual development disorder	Neuroleptic drugs	Drug withdrawal
Developmental disabilities	Dopamine antagonists	

EMBASE search terms (conducted on 28/03/2016)

Terms for intellectual disability (title or abstract)	Terms for anti-psychotic (title or abstract)	Terms for reduction or discontinuation (title or abstract)
Intellectual* disab*	Anti-psychotic*	Withdraw*
Intellectual* impair*	Antipsychotic*	Discontinu*
Intellectual* retard*	Neuroleptic*	Stop*
Intellectual* handicap*	Major tranquil*i*er*	Remov*
Intellectual* subnormal*	Dopamine antagonist	Reduc*
Intellectual* deficien*	Phenothiazine*	Minimi*
Learning disab*	Butyrophenone*	Cessation
Learning impair*	Thioxanthene*	Taper*
Learning retard*	Diphenylbutylpiperidine*	
Learning handicap*	Benperidol	
Learning subnormal*	Chlorpromazine	
Learning deficien*	Droperidol	
Mental* disab*	Flupent*ixol	
Mental* impair*	Haloperidol	
Mental* retard*	Levomepromazine	
Mental* handicap*	Peric*azine	
Mental* subnormal*	Perphenazine	
Mental* deficien*	Pimozide	
Developmental* disab*	Prochlorperazine	
Developmental* impair*	Promazine	
Developmental* retard*	Sulpiride	
Developmental* handicap*	Trifluoperazine	
Developmental* subnormal*	Zuclopent*ixol	
Developmental* deficien*	Amisulp*ride	
Neurodevelopmental* disab*	Aripiprazole	
Neurodevelopmental* impair*	Asenapine	
Neurodevelopmental* retard*	Clozapine	
Neurodevelopmental* handicap*	Lurasidone	
Neurodevelopmental* subnormal*	Olanzapine	
Neurodevelopmental* deficien*	Paliperidone	
	Quetiapine	
	Risperidone	
	Thioridazine	
MeSH headings		
intellectual impairment	neuroleptic agent	drug withdrawal
mental deficiency	dopamine receptor blocking agent	

CINAHL Plus search terms (conducted on 28/03/2016)

Terms for intellectual disability	Terms for anti-psychotic	Terms for reduction or discontinuation
Intellectual* disab*	Anti-psychotic*	Withdraw*
Intellectual* impair*	Antipsychotic*	Discontinu*
Intellectual* retard*	Neuroleptic*	Stop*
Intellectual* handicap*	Major tranquiliser*	Remov*
Intellectual* subnormal*	Major tranquilliser*	Reduc*
Intellectual* deficien*	Major tranquilizer*	Cessation
Learning disab*	Major tranqillizer*	Taper*
Learning impair*	Dopamine antagonist*	
Learning retard*	Phenothiazine*	
Learning handicap*	Butyrophenone*	
Learning subnormal*	Thioxanthene*	
Learning deficien*	Diphenylbutylpiperidine*	
Mental* disab*	Benperidol	
Mental* impair*	Chlorpromazine	
Mental* retard*	Droperidol	
Mental* handicap*	Flupenthixol	
Mental* subnormal*	Flupentixol	
Mental* deficien*	Haloperidol	
Developmental* disab*	Levomepromazine	
Developmental* impair*	Periciazine	
Developmental* retard*	Pericyazine	
Developmental* handicap*	Perphenazine	
Developmental* subnormal*	Pimozide	
Developmental* deficien*	Prochlorperazine	
Neurodevelopmental* disab*	Promazine	
Neurodevelopmental* impair*	Sulpiride	
Neurodevelopmental* retard*	Trifluoperazine	
Neurodevelopmental* handicap*	Zuclopenthixol	
Neurodevelopmental* subnormal*	Zuclopentixol	
Neurodevelopmental* deficien*	Amisulpride	
	Amisulpiride	
	Aripiprazole	
	Asenapine	
	Clozapine	
	Lurasidone	
	Olanzapine	
	Paliperidone	
	Quetiapine	
	Risperidone	

	Thioridazine	
CINAHL headings		
Intellectual disability	Dopamine antagonists	Substance withdrawal syndrome
Mentally disabled persons	Antipsychotic agents	Substance withdrawal, controlled
	Antipsychotic agents, phenothiazine	
	Antipsychotic agents, butyrophenone	

Systematic review – Cochrane (conducted on 28/03/16)

Terms for intellectual disability	Terms for anti-psychotic	Terms for reduction or discontinuation
(Intellectual* OR learning* OR mental* OR developmental* OR neurodevelopmental*) NEXT (disab* OR impair* OR retard* OR handicap* OR subnormal* OR deficien*)	Anti-psychotic*	Withdraw*
	Neuroleptic*	Discontinu*
	“major tranquiliser”	Stop*
	“Dopamine antagonist”	Remov*
		Reduc*
		Minimi*
		Cessation
		Taper*
MeSH terms		
Intellectual disability	Dopamine antagonists	Substance withdrawal syndrome
Mentally disabled persons	Antipsychotic agents	

Appendix B – studies excluded after full-text review

Studies with no individual outcomes reported, including those reporting average changes in medication use only
Findholt and Emmett[81]
Luchins et al[59]
Bisconer et al[82]
Branford[57]
Howerton et al[83]
Ruggerini et al[84]
Lim[85]
Observational studies with no active intervention to reduce or discontinue antipsychotic drugs
Wressell et al[86]
Etherington et al[87]
Gravestock[88]
Branford[89]
Studies reporting no new suitable information
Branford[90]
Studies where most or all participants were taking antipsychotic for mental illness
Pary et al[91]
Sovner[92]
Davies et al[93]
Margetić and Aukst- Margetić[94]
Stonecipler et al[95]
Janowsky et al[96]
Studies describing switch of antipsychotics
Matthews and Weston[58]
Stevenson et al[60]
Studies evaluating efficacy of antipsychotics in managing challenging behaviour
Haessler et al[97]
Haßler et al[98]
Studies including children/adolescents only
Rapp et al[99]
Review articles/expert opinion
Levitas et al[100]

Appendix C – Behavioural outcome measures used in included studies

Method/instrument	Description
Aberrant behaviour checklist (ABC)	58 item carer-rated scale measuring range of behavioural disturbances in 5 sub-scales. Sensitive to changes in behaviour secondary to medication change
Visual analogue scale (VAS)	Target behaviour(s) rated by caregiver between 0 (severe) and 10 (mild) on a generic scale used to quantify subjective experience
Direct observation	Formal categorisation of behaviour according to pre-defined groups in discrete time periods during which the behaviour of the participant is observed
Descriptive report	Any statement(s) where any aspect of the behaviour of individuals or of the group is described