Antipsychotic drug use in people with intellectual disability and comorbid autism

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Abstract

Objective: To describe antipsychotic (AP) drug use amongst adults with intellectual disability (ID) with and without comorbid autism.

Study design: Cross-sectional study as part of the ‘Challenging Behaviour in adults with Intellectual Disability’ (ChallBe-ID) study.

Methods: From 11 healthcare organisations for people with ID across the Netherlands, 305 adults were included. This group was further divided into two subgroups: an autism ID group (n=86) and a non-autism ID group (n=65). Demographic data, level of ID, the presence of a comorbid diagnosis of autism or a psychotic related disorder and the use of AP drugs was obtained from the medical record and questionnaires. Scores from the subscales irritability and stereotype behaviour were used from the Aberrant Behavioral Checklist (ABC) to measure challenging behaviour. Participant characteristics, prevalence of AP use and off label prescribing was described for the total study group and the two subgroups. Within the autism group characteristics of AP users and non-users were assessed and analysed. Chi square tests were used for categorical variables and independent t-tests for continuous variables.

Results: The prevalence of AP use in the total study group (n=305) was 35.1% (n=107). AP use in the autism ID group was significantly higher (54.7%) than in the non-autism ID group (32.3%), X² (1) = 6.591, p = 0.010. Prevalence of off-label AP prescribing in the autism ID group (83%) and the non-autism ID-group (76.2%) was not significantly different. No significant differences were found in the autism ID group between AP users and non-users regarding sex, age, level of ID and the irritability and stereotype behaviour subscales from the ABC scoring scale.

Conclusion: This study confirmed that the prevalence of AP use in people with ID is still high. In those diagnosed with ID and comorbid autism the prevalence of AP use was significantly higher compared to the non-autism ID group. Off-label prescribing was high in both groups. No significant differences were found within the autism group between AP users and non-users on participant characteristics and challenging behaviour.

Introduction

In people with intellectual disabilities (ID) the use of psychotropic medication, and in particular antipsychotics (AP), is highly prevalent. Since the last decades this has been the topic of much research.1-4 Many people are frequently treated with high doses of multiple psychotropic medications for extended periods of time with little or no data collected to determine treatment efficacy.5 A recurrent finding is the high rate of off-label prescriptions of AP drugs in ID. A recent Dutch study among 3299 people with ID found off-label AP prescribing in 95% of the participants.6 This is in line with the study of Sheehan et al. (2015) in the UK, who found that AP use was disproportionate to the level of recorded mental illnesses and was associated with the presence of challenging behaviour and autism.1 Spreat and Conroy (1998) reported that more than 90% of AP prescriptions for people with ID were issued for regulation of behaviour in residential care settings.7 Use of AP drugs for challenging behaviour is controversial, as placebo-controlled double blind studies are few, often with a short duration and of poor quality.5, 8, 9

The high prevalence of off-label prescriptions is concerning since AP drugs cause several adverse effects that can impair the quality of life and lead to deleterious health outcomes. Some side effects include physical complications such as dry mouth, weight gain, sedation,
constipation, and dizziness. More serious long term changes involve neurological damage resulting in extrapyramidal symptoms. It is generally known that people with ID are more sensitive to AP drug side effects and toxicity, possibly due to less neuronal substrate, qualitative brain differences, or developmental stage. Recently a large cohort study compared AP drug use in adults with and without ID. It showed that AP users with ID were more susceptible to movement side effects including parkinsonism, acute dystonia's and akathisia than those without ID. This supports the view that use of psychotropic medication for challenging behaviour in people with ID should be discouraged and its appropriateness should be reviewed on a regular basis.

Unfortunately a lot of AP withdrawals fail. Two Dutch studies by De Kuijper et al. (2008, 2017) barely found a difference in prevalence of AP use in 2008 and 2017 (respectively 32.2% versus 29.6%), in spite of national and international increasing awareness and initiatives of deprescribing and stimulation of appropriate AP use during that period. Even though two international studies by Tsouris (2013) and Paton et al. (2011) observed an apparent shift away from prescribing AP drugs for challenging behaviour, this tendency was not (yet) found in the Dutch population. Contributing factors to unsuccessful withdrawal may include staff attitudes such as apprehension or fear and environmental characteristics (staff levels, adequate training for staff, living conditions clients) as suggested by Ahmed et al. (2000). Occurrence of withdrawal and rebound syndromes may be misinterpreted as a recurrence of the original challenging behaviour and therefore hinder a successful drug reduction.

De Kuijper et al. (2017, 2018) found that the presence of autism spectrum disorder was an important reason for off-label longstanding AP use not to be discontinued.

As known, autism is a common coexisting condition in the population with ID, with prevalence numbers of 21.7% in the population with ID versus 0.5% in the general population. When autism and ID coexist, challenging behaviour is found to occur up to four times more frequently than in patients with ID alone, which often results in prescribing AP medication. Tsakanikos et al (2007) found that presence of an autism spectrum disorder is the strongest predictor for the use of psychotropic medication for problem behaviours in people with ID. There is limited evidence that AP treatment has positive outcomes on challenging behaviour in autism.

As a starting point we have studied AP use in people with ID with and without comorbid autism. Data were extracted from the ‘Challenging Behaviour in adults with Intellectual Disability (ChallBe-ID) study’. This study will focus on the following questions:

1. What is the current prevalence of AP drug use in people with ID?
2. What is the difference in prevalence of AP drug use in people with ID with autism compared to people with ID without autism?
3. What is the difference in prevalence of AP off-label drug use in people with ID with autism compared people with ID without autism?
4. Within the group diagnosed with autism, are there differences in sex, age, level of ID and challenging behaviour between the AP drug users and non-users?

Methods

Study design and participants

This study is a cross-sectional study and part of the ChallBe-ID study. The ChallBe-ID study, an ongoing observational cohort study, started in 2015 and is conducted by the Erasmus MC, University Medical Centre Rotterdam. Approval was granted by the medical ethical committee of the Erasmus MC, University Medical Centre Rotterdam. To be eligible for inclusion in the study people had to receive care from one of the participating care organisations providing specialised care for people with ID, and had to be 18 years or over. Initially 4798 people of the participating organisations were eligible to participate of which a random selection of 932 participants were invited to participate. Of this group, 317 people with ID or their legal representatives provided informed consent. However, 12 of the latter group either did not consent in time for data collection or their data were incomplete. Ultimately, the final study sample consisted of 305 participants. This group was further divided into two subgroups, depending whether a diagnosis of autism was given (autism ID group, n=86) or not (non-autism ID group, n=65). People were excluded from further analyses when a diagnosis of autism was suspected, but not confirmed (n=20), or when it was unknown whether there was a diagnosis of autism (n=134) (figure 1).

Procedures

Data was collected through questionnaires completed by professional caregivers and behavioural experts involved in the care of the participants. Additionally data were retrieved from the medical records by the researchers, who were all physicians following training to become specialized in providing care for people with ID.

Measurements

Age, sex, and level of ID were obtained from the medical
records. For the level of ID the classification of ID as reported in the medical records was used, based on IQ tests or on clinical experience of the medical professionals. The following five categories were distinguished: profound ID (IQ < 20), severe ID (IQ 20-34), moderate ID (IQ 35-49), mild ID (IQ 50-69), borderline intellectual functioning (IQ 70-84).

Presence of the diagnosis autism and of a psychosis, past or present, was collected from the medical records, and categorised into yes, no, suspicion, or unknown. Other AP drug use related conditions such as bipolar disorder, schizophrenia and Gilles de la Tourette syndrome were also recorded.

Data on current use of AP drugs was collected from the medical files. The list of AP drugs of the Anatomical Therapeutic Chemical Classification System, developed by the WHO (ATC code N05A) was used as a guide to classify the psychotropic medication. Lithium (ATC code N05AN) however, is not classified as an AP within the Dutch formulary and was therefore not taken into account in this study.

In this study we have considered AP prescribing as off-label when it was prescribed for challenging behaviour or when a diagnosis of a psychosis or a psychosis related disorder was lacking in the medical files. AP prescribing for comorbid conditions such as bipolar disorder, schizophrenia and Gilles de la Tourette syndrome was not seen as off-label use.

Challenging behaviour of each participant was assessed with the Aberrant Behaviour Checklist (ABC). This is a 58-item questionnaire for caregivers that originally was designed to monitor treatment effects in problem behaviour in ID. It is also tested to assess the presence and severity of various problem behaviours commonly observed in people with ID. An extensive psychometric assessment of the ABC has indicated that the test has high internal consistency, good reliability and validity. The ABC has five subscales; irritability, lethargy, stereotype behaviour, hyperactivity and inadequate speech. As AP use in autism could be related to irritability and/or stereotype behaviour, the mean scores of these two subscales were used. The checklist was completed by the professional caregiver of the participant, and was based on the behaviour of the client in the previous week.

Statistical Analyses
Firstly, a descriptive analysis of the demographic data was carried out. This included age, sex, level of ID, the presence of a psychotic disorder and the prevalence of AP use of the total study group and of the subgroups autism and non-autism. Also included were the mean scores of the subscales irritability and stereotype behaviour. Subsequently we described the prevalence of off-label use of AP drugs in the total study group and the two subgroups. Chi square tests were used to identify whether there was a difference between the autism and non-autism groups in the prevalence of AP use and the prevalence of off-label AP use. Within the group diagnosed with autism, differences in age, sex, level of ID, and challenging behaviour (subscales irritability and stereotype behaviour of the ABC scale) were assessed between AP-users and non-users. Chi square tests were used for categorical variables and independent t-tests for continuous variables.

For the primary question regarding the difference in prevalence of AP drug use between people with autism and people without autism a p-value of 0.05 was considered
to be statistically significant (two tailed). The Bonferroni correction was used to reduce the chances of obtaining false positive results by performing multiple tests in the analysis for our sub questions: hence the p-value was adjusted to 0.01 (0.05/5). SPSS version 25.0 was used for all analyses.

**Results**
As shown in figure 1, the total study group consisted of 305 participants, of whom 86 (28.2%) had a diagnosis of autism, and 65 (21.3%) had no autism. The remaining group with a suspected or unconfirmed diagnosis of autism (n=154, 50.5%) was excluded from further analysis. (See figure 1 on page 25.)

**Prevalence of AP drug use and differences between the autism ID group and the non-autism ID group**
As shown in table 1, the prevalence of AP use was 35.1% in the total study group, 54.7% in the group with autism, and 32.3% in the group without autism.

AP use in the autism ID group was significantly higher (54.7%) than in the non-autism ID group (32.3%), \(X^2 (1) = 6.591, p = 0.010\). Off-label prescribing was as high as 83.0% in the autism ID group and 76.2% in the non-autism ID group. This difference was not significant \(X^2 (1) = 0.105, p = 0.746\). (See table 1 below.)

**Comparison of the participant characteristics within the autism-ID group**
Amongst the participants with autism a comparison was made between AP users (n=47) and non-users (n=39). Findings are summarised in table 2. (See table 2 below.)

Although the percentage of males in the AP user group (89.4%) was higher than in the non-user group (71.8%), this difference was not significant \((t(84) = -1.273, p = 0.207)\) and the level of ID \((X^2 (3) = 5.149, p = 0.161)\).

An ABC score was not available for six patients in the autism group (three in the AP user group and three in the non-user group). The mean scores on the ABC subscales irritability and stereotype behaviour in the remaining AP user group (n= 44) were compared with the correspon-

### Table 1. Descriptives of the participant characteristics of the total study group and the subgroup with and without autism.
Values are numbers (percentages) unless stated otherwise.

<table>
<thead>
<tr>
<th></th>
<th>Total study group (n=305)</th>
<th>Autism ID group (n=86)</th>
<th>Non-autism ID group (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>191 (62.6%)</td>
<td>70 (81.4%)</td>
<td>38 (58.5%)</td>
</tr>
<tr>
<td>Mean age in years</td>
<td>51.1 (SD 17.1)</td>
<td>45.0 (SD 15.6)</td>
<td>54.2 (SD 16.0)</td>
</tr>
<tr>
<td>Borderline Intellect (IQ = 70-84)</td>
<td>1 (0.3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mild ID (IQ = 50-69)</td>
<td>53 (17.4%)</td>
<td>17 (19.8%)</td>
<td>9 (13.8%)</td>
</tr>
<tr>
<td>Moderate ID (IQ = 35-49)</td>
<td>87 (28.5%)</td>
<td>19 (22.1%)</td>
<td>17 (26.2%)</td>
</tr>
<tr>
<td>Severe ID (IQ = 20-34)</td>
<td>107 (35.1%)</td>
<td>39 (45.3%)</td>
<td>31 (47.7%)</td>
</tr>
<tr>
<td>Profound ID (IQ &lt; 20)</td>
<td>55 (18%)</td>
<td>11 (12.8%)</td>
<td>8 (12.3%)</td>
</tr>
<tr>
<td>ID unknown</td>
<td>2 (0.7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Use of AP drugs</td>
<td>107 (35.1%)</td>
<td>47 (54.7%)</td>
<td>21 (32.3%)</td>
</tr>
<tr>
<td>Off label AP use</td>
<td>85/107 (79.4%)</td>
<td>39/47 (83.0%)</td>
<td>16/21 (76.2%)</td>
</tr>
</tbody>
</table>

### Table 2. Descriptives of the participant characteristics of the total autism group and the subgroup AP users and AP non users.
Values are numbers (percentages) unless stated otherwise.

<table>
<thead>
<tr>
<th></th>
<th>Autism ID group n = 86</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=86)</td>
<td>AP users (n=47)</td>
<td>AP non users (n=39)</td>
</tr>
<tr>
<td>Male sex</td>
<td>70 (81.4%)</td>
<td>42 (89.4%)</td>
</tr>
<tr>
<td>Mean age in years</td>
<td>45.0 (SD 15.6)</td>
<td>46.9 (SD 15.1)</td>
</tr>
<tr>
<td>Mild ID (IQ = 50-69)</td>
<td>17 (19.8%)</td>
<td>12 (25.5%)</td>
</tr>
<tr>
<td>Moderate ID (IQ = 35-49)</td>
<td>19 (22.1%)</td>
<td>10 (21.3%)</td>
</tr>
<tr>
<td>Severe ID (IQ = 20-34)</td>
<td>39 (45.3%)</td>
<td>17 (36.2%)</td>
</tr>
<tr>
<td>Profound ID (IQ &lt; 20)</td>
<td>11 (12.8%)</td>
<td>8 (17.0%)</td>
</tr>
<tr>
<td>Mean score ABC irritability scale</td>
<td>8.1 (SD 7.4)</td>
<td>8.6 (SD 7.6)</td>
</tr>
<tr>
<td>Mean score ABC stereotype behaviour scale</td>
<td>2.7 (SD 2.8)</td>
<td>2.6 (SD 2.4)</td>
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d respirations, 

Discussion

In this study, the prevalence of AP use in ID clients was 35.1% in the total study group. The prevalence of AP drug use in the autism ID group was significantly higher (54.7%) than in the non-autism ID group (32.3%). Prevalence of off-label AP prescribing in the autism ID group (83%) and the non-autism ID-group (76.2%) was not significantly different. Within the autism ID group no significant differences were found between AP users and non-users in sex, age, level of ID and ABC scores on the subscales irritability or stereotype behaviour.

AP have been reported to be the most common type of psychotropic medication prescribed to people with ID. 

The prevalence of AP drug use in our total study group (35.1%) was even higher than that reported in earlier Dutch studies by de Kuijper et al. in 2010 and 2017 (respectively 32.2% and 29.6%).

Within the ID population AP drugs are often prescribed off-label to manage challenging behaviour. This was also the case in our study: off-label prescribing was as high as 83.0% in the autism ID group and 76.2% in the non-autism ID group.

High levels of off-label prescribing has also been found by others such as Sheehan et al. (2015), Spreat and Conroy (1998), de Kuijper et al (2017) and Matson and Neal (2009).

Various ID studies, not necessarily with a focus on autism, found higher rates of AP prescribing for males compared to females. However, in this study, we did not find a difference in AP use between sexes within the autism group. The expected association of increased AP use with a more severe ID or increasing age (Sheehan 2015) was again not replicated in the autism group of this study.

Reported prevalence rates from solely specialised ID care settings (like our study group) may tend to enrol participants with more challenging behavioural or mental health problems and thus lead to an overestimation of the use of psychotropic drugs in people with ID. Community based cohort studies as discussed by Sheehan et al. (2015) and Bowring et al. (2017), reported significant lower prevalences of AP use (respectively 21.0% and 21.9%).

In the last mentioned study of Bowring et al., prevalence of AP drug use was found to be 29.5% in paid /congregate care versus 21.4% in independent living and 11% for those living with their family.

As part of the ChallBe-ID study, this cross sectional study benefitted from a randomised selected large cohort of the Dutch ID population derived from 11 specialised ID care providers with representation across all levels of ID.

To the knowledge of the authors, this is the first Dutch study that has quantified the high prevalence AP use in ID clients with comorbid autism (54.7%).

With the aim to gain further insight into possible contributing factors about why reduction seems so problematic in this group, AP-users and non-users within the autism group were compared on sex, age, level of intellectual disability and challenging behaviour (ABC scores). No significance was found between these variables. These results, therefore, have not clarified why AP use is so high.

Limitations of this study are the relatively small numbers in the various subgroups and the lack of availability of the ABC scores prior to AP treatment. Both might have contributed to the lack of significant outcomes between the user and non-user group within the autism ID group. As irritability or serious stereotypical behaviour are both indications for using AP in autism, we expected that the ABC scores would have shown differences between the two groups. This, however, does not exclude the possibility that people in the autism AP group might have shown more problems (and different ABC scores) prior to using AP, as AP may have muted behaviour.

Multiple professional caregivers and other health professionals were involved in collecting data through questionnaires with its inherent risk of more subjective interpretation of e.g. challenging behaviours.

As discussed in previous research a lot of attempts fail to reduce longstanding off-label AP use for challenging behaviour in the ID population. Our findings highlight the need to understand underlying reasons for disproportionate AP use, especially for the ID group diagnosed with comorbid autism - with the aim to optimising individually tailored drug treatment and finding alternative approaches for managing challenging behaviour.

Conclusion

In our study, the prevalence of AP use in people with ID was high (35.1%). In those diagnosed with ID and comorbid autism the prevalence was even higher (54.7%), and significantly higher than AP use for people with ID but without autism (32.3%). Prevalence of off-label AP prescribing in the autism ID group (83%) and the non-autism ID-group (76.2%) was not significantly different. No significant differences in sex, age, level of ID and ABC scores on the subscales irritability or stereotype behaviour were found between AP users and non-users within the autism group.
References


