Research in Developmental Disabilities 34 (2013) 2799–2809

Contents lists available at SciVerse ScienceDirect

Research in Developmental Disabilities

# Determinants of physical health parameters in individuals with intellectual disability who use long-term antipsychotics

Gerda de Kuijper [a,f,*], Hans Mulder [b,1], Heleen Evenhuis [c,2], Frans Scholte [a,b,c,d,e,3,4], Frank Visser [d,5,6], Pieter J. Hoekstra [e,7]

[a] Vanboeijen, Intellectual Disability Centre, Assen, The Netherlands
[b] Department of Clinical Pharmacy, Wilhelmina Hospital Assen, Assen, The Netherlands
[c] Erasmus University Medical Centre Rotterdam, Intellectual Disability Medicine, Rotterdam, The Netherlands
[d] 's Heeren Loo, Intellectual Disability Centre, Ermelo, The Netherlands
[e] Department of Psychiatry, University Medical Centre Groningen, University of Groningen, The Netherlands
[f] Centre for Intellectual Disability and Mental Health Care/GGZ Drenthe, Assen, The Netherlands

ARTICLE INFO

*Article history:*
Received 11 January 2013
Received in revised form 4 May 2013
Accepted 6 May 2013
Available online 20 June 2013

*Keywords:*
Antipsychotics
Long-term use
Extrapyramidal symptoms
Metabolic symptoms
Bone markers
Determinants
Genetic polymorphisms
Intellectual disability

ABSTRACT

Individuals with intellectual disability frequently use antipsychotics for many years. This may have detrimental health effects, including neurological symptoms and metabolic and hormonal dysregulation, the latter possibly affecting bone metabolism. There is large variability in the degree in which antipsychotic agents lead to these health problems. In the current study we investigated potential determinants of physical symptoms and biological parameters known to be associated with use of antipsychotics in a convenience sample of 99 individuals with intellectual disability who had used antipsychotics for more than one year for behavioural symptoms. We focused on extrapyramidal symptoms; on overweight and presence of components of the metabolic syndrome; and on elevated plasma prolactin and bone turnover parameters. As predictor variables, we used patient (sex, age, genetic polymorphisms, and severity of intellectual disability) and medication use (type and dosage) characteristics. We found extrapyramidal symptoms to be present in 53%, overweight or obesity in 46%, and the metabolic syndrome in 11% of participants. Hyperprolactineaemia and one or more elevated bone turnover markers were present in 17% and 25%, respectively. Higher age and more severe intellectual disability were associated with dyskinesia and a higher dosage of the antipsychotic drug was associated with parkinsonism. Less severe intellectual disability was related to higher Body Mass Index. Use of atypical antipsychotics was associated with higher diastolic blood pressure

* Corresponding author at: Vanboeijen, Intellectual Disability Centre, Assen, P.O. Box 30014, 9400 RA Assen, The Netherlands. Tel.: +31 592 305305; fax: +31 592 305599.
*E-mail addresses:* gerda.dekuijper@vanboeijen.nl, g.dekuijper@home.nl, gerda.de.kuijper@ggzdrenthe.nl (G. de Kuijper), hans.mulder@wza.nl (H. Mulder), h.evenhuis@erasmusmc.nl (H. Evenhuis), Frank.Visser@sheerenloo.nl (F. Visser), p.hoekstra@accare.nl (P.J. Hoekstra).
[1] Department of Clinical Pharmacy, Wilhelmina Hospital Assen, P.O. Box 30001, 9400 RA Assen, The Netherlands. Tel.: +31 592325450; fax: +31 592325601.
[2] Intellectual Disability Medicine, Erasmus University Medical Centre Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands. Tel.: +31 10 4088011; fax: +31 10 4632127.
[3] Deceased.
[4] The author was principal investigator at 's Heerenloo Apeldoorn.
[5] 's Heerenloo Ermelo, Intellectual Disability Centre, P.O. Box 550, 3850 AN Ermelo, The Netherlands. Tel.: +31 341 555400; fax: +31 341 555402.
[6] The author was principal investigator at 's Heerenloo Ermelo.
[7] University Medical Centre Groningen, University Centre Child and Adolescent Psychiatry, P.O. Box 660, 9700 AR Groningen, The Netherlands. Tel.: + 31 50 3610978; fax: + 31 50 3610979.

0891-4222/$ – see front matter 
http://dx.doi.org/10.1016/j.ridd.2013.05.016

and elevated fasting glucose. Clinicians who prescribe antipsychotics in individuals with intellectual disability should carefully balance the potential benefits of prolonged treatment against the risk of health hazards associated with the use of antipsychotics.


## 1. Introduction

Antipsychotics are frequently prescribed drugs in individuals with intellectual disability that are typically used for many years, and often outside their licensed indications (i.e., not for psychotic disorders, but often for alleviating behaviour problems de Kuijper et al., 2010; Stolker, Koedoot, Heerdink, Leufkens, & Nolen, 2002; Tobi et al., 2005; van Schrojenstein Lantman-de Valk et al., 1995). In a population of individuals ($N = 2373$) living in residential facilities, we found a prevalence of antipsychotic use of 32.2% ($n = 763$). Most of these 763 persons had used antipsychotics for decades. Duration of use of antipsychotics was in 2% less than 1 year, in 12% 1–5 years, in 8% 5–10 years, and in 78% more than ten years (de Kuijper et al., 2010).

The long-term use of antipsychotics may lead to neurological side effects, affecting the extrapyramidal system (Matson & Mahan, 2010; Stone, Alvarez, & Ellman, 1989). Extrapyramidal symptoms may include tardive akathisia, parkinsonism, and tardive dyskinesia and may lead to feelings of distress and secondary morbidity such as muscle aching and weakness. Other possible antipsychotic-induced long-term effects are metabolic symptoms such as weight gain, glucose dysregulation, dyslipidaemia, and increased risk for metabolic syndrome (comprising the presence of at least three of the five components: excess in abdominal fat, hypertriglicydaemia, hyperglycaemia, too low serum high-density-lipoproteins [HDL], and hypertension); (Bhuvaneswar, Baldessarini, Harsh, & Alpert, 2009; McKee, Bodfish, Mahorney, Heeth, & Ball, 2005; Newcomer, 2007). Furthermore, use of antipsychotics may lead to hormonal dysregulations, most notably an increase in the lactotrophic hormone prolactin and subsequently a decrease in sex hormone levels. The latter may result in disturbed bone metabolism, calcium bone loss, low bone density, and increased risk for osteoporosis (Bhuvaneswar et al., 2009; Misra, Papakostas, & Klibanski, 2004).

There is, however, large variability in the degree in which antipsychotic agents lead to detrimental health effects. First of all, the type of antipsychotic is an important factor. The extent to which different antipsychotics cause side effects varies considerably, depending on dopamine D2 and D3, serotonin 5-hydroxytryptamine 2C (5-HT2C), and histamine H1 receptor affinity. Use of atypical antipsychotics, which have more serotonin 5-hydroxytryptamine 2C (5-HT2C) and histamine H1 receptor affinity, is associated with less risk of tardive dyskinesia (Fodstad et al., 2010; Matson, Fodstad, Neal, Dempsey, & Rivet, 2010) but with higher risk of weight gain and metabolic dysregulation as compared with use of typical antipsychotics (Deng, Weston-Green, & Huang, 2010; McKee et al., 2005; Newcomer, 2007; Reynolds & Kirk, 2010). Furthermore, especially the atypical antipsychotics (amisulpiride, risperidone, and paliperidone) are most clearly associated with prolonged elevated levels of prolactin (Bushe, Shaw, & Peveler, 2008; Holt & Peveler, 2011).

Although less well studied, there is also some indication for interindividual differences in susceptibility to health hazards associated with antipsychotics. This may in part be genetically based (Lencz & Malhotra, 2009). For example, studies in patients with schizophrenia have shown that a single nucleotide polymorphism (SNP) of the *dopamine D2 receptor* gene rs1800497 (presence of the A allele); (Guzey, Scordo, Spina, Landsem, & Spigset, 2007; Liou et al., 2006) and of the *dopamine D3 receptor gene* SNP rs6280 (also presence of the A allele); (Al Hadithy et al., 2009; Rizos et al., 2009; Woo et al., 2002) were associated with increased risk of tardive dyskinesia. Also, carriers of the rs1800497 (Taq1A) A-allele of the *dopamine D2 receptor* gene, may be more at risk for antipsychotic induced prolactin elevation (Calarge et al., 2009; Lopez-Rodriguez et al., 2011), because of lower D2 receptor density in the striatum. Furthermore, a polymorphism of the X-linked 5-HT2C *serotonin receptor promoter* gene rs3813929 (i.e., the absence of the T allele) may increase the risk for weight gain through use of antipsychotics (Reynolds, Templeman, & Zhang, 2005; Risselada, Mulder, Heerdink, & Egberts, 2011; Ryu et al., 2007). Finally, a relationship has been found between presence of the intragenic 5-HT2C *serotonin receptor gene* SNP rs1414334C allele and presence of the metabolic syndrome in adult patients using antipsychotic medication (Mulder, Franke, van der-Beek, Arends, Wilmink, Egberts, et al., 2007; Mulder, Franke, van der-Beek, Arends, Wilmink, Scheffer, et al., 2007).

Individuals with intellectual disability may be especially vulnerable to the physically harmful side effects of antipsychotics (Matson & Mahan, 2010). However, in non-psychotic individuals with intellectual disability, who use antipsychotics on an off-label base, there is a scarcity of studies into patient and medication characteristics that may be related to health hazards associated with (long-term) use of these agents. In the current study we therefore systematically investigated determinants of physical symptoms and biochemical parameters, known to be associated with long-term use of antipsychotics, in a sample of individuals with intellectual disability who had used antipsychotics on an off-label base for more than one year. We focused on different types of extrapyramidal symptoms, on overweight and presence of components of the metabolic syndrome, and on elevated plasma prolactin and bone turnover parameters.