Off-label use of antipsychotic medication in people with intellectual disabilities

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CHAPTER 1

General introduction
In the last decades, the long-term use of antipsychotic drugs for challenging behaviours by people with intellectual disabilities has become more controversial. There are considerable doubts about the evidence-base for the effectiveness of antipsychotic drugs for challenging behaviours. While some studies found results supporting their effectiveness (Gagiano, Read, Thorpe, Ererkens, & Van Hove, 2005; Reyes, Buitelaar, Toren, Augustyns, & Ererkens, 2006; Troost et al., 2005; Zarcone et al., 2001), results of other studies could not confirm this (Brylewski & Duggan, 2004; Deb & Unwin, 2007; Tyrer et al., 2008). Moreover, several studies showed that discontinuation of long-term used antipsychotic drugs for challenging behaviours is possible in a sizeable number of people, without deterioration in challenging behaviours (de Kuijper, Evenhuis, Minderaa, & Hoekstra, 2014; de Kuijper & Hoekstra, 2018).

Another reason to consider discontinuation of long-term used antipsychotic drugs is the considerable risk of side-effects. However, in clinical practice discontinuation may be difficult and in some cases withdrawal does not seem possible. To prevent health damage due to drugs-related side-effects, it is important to frequently monitor the effects and side-effects of antipsychotic drugs. There are a number of guidelines available on the prescription and monitoring of psychotropic drugs, including antipsychotic drugs. Given the high frequency of long-term antipsychotic drug use for the management of challenging behaviour in the Dutch intellectual disabled population (de Kuijper et al., 2010; de Kuijper & Hoekstra, 2017; Stolker, Heerdink, Leufkens, Clerx, & Nolen, 2001), we were interested in the adherence of Dutch clinician to these guidelines and in knowing more about the long-term effectiveness of antipsychotic drugs.

The first part of the research presented in this thesis is a medical record study, aimed at evaluating the adherence of Dutch clinicians to guideline recommendations concerning antipsychotic drugs. Furthermore, during the data collection, we realized that only studying the adherence would not suffice, but that we also needed to investigate the barriers and facilitators in using the recommendations of guidelines.

The second part of the project originated from de Kuijper’s research on discontinuation of antipsychotics (de Kuijper et al., 2014). The aim was to repeat her discontinuation study and to investigate whether the previously found results could be confirmed. In my study, I focussed on only one agent, i.e., risperidone and I used a different study design. Risperidone was chosen, because it is one of the only antipsychotic drugs with a licenced indication for short-term use for challenging behaviours, as studies have found effects for short-term use (Gagiano et al., 2005; Reyes et al., 2006; Zarcone et al., 2001). The aim was to study the long-term effectiveness of risperidone in reducing challenging behaviours, by studying the effects of placebo-controlled discontinuation on behaviour and health parameters. We also included outcome measures on health-related quality of life for all antipsychotic agents.

This thesis starts with an explanation of the main concepts and the aims addressed in this thesis, followed by the outline.

**Intellectual disability**

It is estimated that between 1% and 3% of the world population has an intellectual disability, defined by the World Health Organization as “a condition of arrested or incomplete development of the mind, which is especially characterized by impairment of skills manifested during the developmental period, which contribute to the overall level of intelligence, i.e., cognitive, language, motor, and social abilities”. A meta-analysis established a prevalence of 10.37/1000, with a slightly higher prevalence in men, in both adults and children/adolescents (Maulik, Mascarenhas, Mathers, Dua, & Saxena, 2011). A Dutch study suggests a prevalence ranging from 0.64% to 0.70% (Wullink, Van Schrojenstein Lantman-de Valk, Dinant, & Metsemakers, 2007). Known causes of intellectual disability may include antenatal (such as genetic causes), perinatal, and postnatal factors. The precise cause of intellectual disability is often unknown, but due to recent advances in genetic analyses up to 50% of the cases of intellectual disability can be explained. For example, 15% can be attributed to chromosomal abnormalities. Mild intellectual disabilities may be part of normal variation (Vissers, Gilissen, & Veltman, 2016).

In 2015 a new classification for intellectual disability was published in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM 5). DSM 5 defines intellectual disability as limitations in intellectual and adaptive functioning, in the conceptual domain, social domain and practical domain. Due to this new classification, intellectual disability is not merely diagnosed by IQ testing, but also by clinical judgement on deficiencies in functioning.

**Mental health conditions and challenging behaviour**

People with intellectual disability often have comorbid health and/or mental health conditions (White, Chant, Edwards, Townsend, & Waghorn, 2005). They have twice as many mental health problems, compared to people without intellectual disabilities. Between 30-50% have a dual diagnosis, combining intellectual disability with a diagnosis of a mental disorder, including Autism Spectrum Disorder (ASD) and challenging behaviours (Cooper, Smiley, Morrison, Williamson, & Allan, 2007; Einfeld, Ellis, & Emerson, 2011; White et al., 2005). About 50-70% of people with ASD also has an intellectual disability (Bertelli et al., 2015; Fombonne, 2003; Ghaziuddin, 2005; Matson & Shoemaker, 2009), while between 5-40% of people with intellectual disability have a...
diagnosis of ASD (Matson & Shoemaker, 2009). Due to the overlap between ASD and intellectual disability, it is hard to differentiate between the diagnoses, especially in people with severe or profound intellectual disability. Furthermore, a diagnosis of schizophrenia or a psychotic disorder was present in 4.5-5.2% of an Australian intellectually disabled population (White et al., 2005). Mental disorders may present with challenging behaviours in people with intellectual disabilities, making it difficult to differentiate between the several factors underlying the origin of challenging behaviours. Challenging behaviour may be defined as behaviour of such an intensity, duration, or frequency that the behaviour is a danger to the physical safety of the person or others. Furthermore, these behaviours could lead to exclusion from the community (Lennox et al., 2005). Challenging behaviours may manifest as irritability (including aggression), lethargy, stereotypical behaviour and hyperactivity (Aman, Singh, Stewart, & Field, 1985). The prevalence of challenging behaviours in people with intellectual disability varies from 15% in community settings (Lloyd & Kennedy, 2014) to 80% in inpatient care facilities (Poppes, van der Putten, & Vlaskamp, 2010). The prevalence of challenging behaviours among children with intellectual disability is three to four times higher compared to children without intellectual disability (Aman et al., 2014). Often there is an underlying cause that results in these behaviours, such as physical pain, mental health disorders, environmental factors, or medication side-effects (Grey & Hastings, 2005). Furthermore, several studies found that the severity of challenging behaviour is influenced by the attitude and cognitions of caregivers towards challenging behaviours. For that reason, there should always be a comprehensive assessment of the challenging behaviours (Hastings, 1997; Lambrechts, Kuppens, & Maes, 2009).

Historically, challenging behaviours have been approached by analysing the functionality of the behaviour. Similar behaviour can have different underlying reasons and different behaviours can have similar reasons. The more severe the level of intellectual disability, the more difficult it is to interpret challenging behaviour or to diagnose an underlying mental health condition (Wachtel & Hagopian, 2006). Challenging behaviours are often managed with antipsychotic drugs when they are not understood.

Antipsychotic drugs

The first antipsychotic drug, chlorpromazine, was originally an antimalarial drug, that was found to have a sedative effect, due to its working mechanism in the central nervous system. Soon after the introduction of chlorpromazine in the treatment of schizophrenia, the drug was also introduced for managing challenging behaviours in people with intellectual disabilities (Shen, 1999).
effectively reduces challenging behaviours, such as aggression (Gagiano et al., 2005; Zarcone et al., 2001). However, in 2008 Tyrer et al. (2008) found that both haloperidol and risperidone were no more effective than placebo in reducing aggression (Tyrer et al., 2008). As studies were limited to the short-term effectiveness of risperidone (use up to one year), little is known about its long-term effects in managing or reducing challenging behaviours.

**Discontinuation**

There have been several open-label studies that investigated the effects of discontinuation of antipsychotic drugs, including risperidone, prescribed for challenging behaviours in people with intellectual disabilities. However, Sheehan & Hassiotis (2016) concluded, after a literature review, that the knowledge on the feasibility of withdrawal of antipsychotic medication was still insufficient (Sheehan & Hassiotis, 2016). Two open-label studies showed that the discontinuation of antipsychotic drugs after long-term use was possible in 40% of patients (Ahmed et al., 2000; de Kuijper et al., 2014). This was recently confirmed in a new discontinuation study by de Kuijper and Hoekstra (2018). In these studies, challenging behaviours (total ABC score) did not worsen, but on average improved in the participants who achieved complete discontinuation. However, in the more recent study of de Kuijper & Hoekstra (2018) a clinically relevant worsening in total ABC scores was found in 21% of people who were able to completely discontinue antipsychotic drugs, compared to 49% in people who were unable to completely discontinue. Other open-label discontinuation studies did not involve risperidone (Sheehan & Hassiotis, 2016). For these other types of antipsychotic drugs, mixed results were found when the drugs were discontinued. Between 40-96% had a deterioration in challenging behaviours associated with the withdrawal (Sheehan & Hassiotis, 2016).

Discontinuation results of risperidone after short-term use differ from the results found after discontinuation of longer-term use. There have been several studies that evaluated discontinuation of risperidone after short-term use in children and adolescents in a placebo-controlled manner, as part of larger trials on the effectiveness of risperidone when first prescribed (Research Units on Pediatric Psychopharmacology Autism Network (RUPP), 2005; Reyes et al., 2006; Troost et al., 2005). The studies included participants that had shown improvements on the behavioural outcomes after prescription of risperidone. In the discontinuation phase the studies showed a higher reoccurrence of challenging behaviours in the group that discontinued risperidone, compared to the group that was maintained on risperidone (RUPP, 2005; Reyes et al., 2006; Troost et al., 2005). Furthermore, the placebo-controlled discontinuation phase of The Research Units on Pediatric Psychopharmacology Autism Network (RUPP) study was terminated prematurely after considerable more relapses in the discontinuation group, compared to the continued use group (RUPP, 2005).

McNamara et al. (2017) were the first to discontinue risperidone placebo-controlled after the participants had used the drug for a longer period of time, mostly longer than one year. In their study, 55% of the participants could successfully discontinue risperidone. In comparison, in the control group, which was maintained on the baseline dosage of risperidone, also 55% could continue through the study without premature deblinding. A small number of the participants who discontinued did have an increase in aggression (measured with the Modified Overt Aggression Scale), irritability and stereotypy (measured with the Aberrant Behavior Checklist). The study also demonstrated that discontinuation of risperidone in current clinical practice is difficult. Furthermore, the study showed that complex study designs, such as placebo-controlled studies, are difficult to implement in clinical practise, making it challenging to find participants to include in the trials. They highlighted that there are currently no guidelines supporting the discontinuation process of risperidone and other antipsychotic drugs, complicating the process in practice (McNamara et al., 2017).

**Prescription practice guidelines**

There are many guidelines for prescribing antipsychotic drugs in general and for prescribing antipsychotic drugs to people with intellectual disabilities specifically. Dutch guidelines include the guideline on psychotropic drugs from the “Nederlandse Vereniging voor Arten Vestandelijk Gehandicapten” (NVAVG, 2007; NVAVG, 2016), a psychotropic drug guideline for children- and adolescent psychiatry (“psychofarmaca in de Kinder- en Jeugdpsychiatrie” (Dieleman, Dierckx, & Hofstra, 2011)); and a general guideline on schizophrenia (van Alphen et al., 2012). In addition, guidelines were created for monitoring side-effects (Cahn et al., 2008). International guidelines include the guidelines from the National Institute for Health and Care Excellence (NICE) on mental health in people with intellectual disabilities, challenging behaviours and on schizophrenia (NICE, 2014; NICE, 2015; NICE, 2016; NICE, 2017). Furthermore, international scientific publications, such as Deb et al. (2009) and de Leon et al. (2013) provided recommendations for antipsychotic drugs prescriptions for challenging behaviour (Deb et al., 2009; de Leon, Greenlee, Barber, Sabaawi, & Singh, 2009).

Most guidelines include recommendations for the steps taken before prescription (reason for prescription, alternative treatments, and cause of challenging behaviour), the type and duration of use of antipsychotic drugs, the evaluation of the effects of the drug, the monitoring
of side-effects and discontinuation. In chapter 2 and 3 of this thesis, adherence to these recommendations has been investigated and discussed.

**Side-effects**

All antipsychotic drugs, including risperidone, have broadly similar side-effects, with slight differences, based on the working mechanisms of the specific drug. Side-effects of antipsychotic drugs can be differentiated in metabolic, endocrine, and neurological side-effects and a miscellaneous category. Examples are weight gain, increased risk for diabetes, sexual side-effects, sedation and emotional flattening, autonomic symptoms such as constipation and drooling and movement disorders such as extrapyramidal symptoms (Matson & Mahan, 2010).

Metabolic symptoms are often most prominent in the second-generation antipsychotic drugs, such as risperidone. An endocrine side-effect of especially risperidone is the elevation of prolactin levels. Elevated prolactin levels may result in lower testosterone and oestrogen levels and subsequent sexual function disorders (Halbreich, Kinon, Gilmore, & Kahn, 2003). Furthermore, elevated prolactin may result in disturbed bone metabolism, calcium bone loss, low bone density and an increased risk of osteoporosis. A 47% rate of hyperprolactinemia has been found in adolescent males without intellectual disabilities who used risperidone (Roke, Buitelaar, Boot, Tenback, & van Harten, 2012). Furthermore, 17% of antipsychotic drugs users with intellectual disability had hyperprolactinemia and 25% had clinically relevant elevated bone metabolism markers (de Kuijper, Mulder, Evenhuis, Visser, & Hoekstra, 2014).

Extrapyramidal symptoms, often linked to first generation antipsychotic drugs, but also present in the second-generation antipsychotic drugs include (tardive-) dyskinesia, akathisia and parkinsonism. A 17% rate of extrapyramidal symptoms among risperidone users has been reported, with tremors being the most frequent symptom (Friedlander, Lazar, & Klancnik, 2001). De Kuijper et al. (2013) found that 53% had one or more extrapyramidal symptoms after the long-term use of antipsychotic drugs (de Kuijper et al., 2013).

**Quality of life**

Quality of life considers the impact of both physical health and mental health factors on the life of patients. Some propose that quality of life is only measurable in individuals with sufficient cognitive skills, who can apply personal meaning to quality of life, and that it therefore cannot be assessed in people with intellectual disabilities. However, studies have provided no evidence that people with intellectual disabilities have no ability to process information and emotions (Bertelli & Brown, 2006). Furthermore, some suggest that quality of life cannot only be assessed through self-expression, but also through proxies. Recently, the belief that also people with intellectual disabilities can improve their quality of life has become more widely accepted (Bertelli & Brown, 2006).

Schalock (2008) described a general framework of quality of life in people with intellectual disability, distinguishing three factors: independence, social participation, and well-being. Independence includes personal development and self-determinations. Social participation concerns interpersonal relations, social inclusion and rights. Last, well-being relates to emotional well-being, physical well-being and material well-being (Schalock, Bonham, & Verdugo, 2008).

In previous research, Schalock (2004) suggested that among others, health status, challenging behaviours and perceived social support are factors associated with quality of life (Schalock, 2004). Both in the general population and in people with intellectual disabilities, mental health problems and psychological distress were found to explain a significant amount of variance in overall well-being and health status (Koch et al., 2015; Rand & Malley, 2016; Schalock, 2004).

For the purpose of measuring disease- and treatment outcomes, the concept of health-related quality of life was developed. This concept overlaps with the general concept of quality of life on the domains of physical and emotional well-being, interpersonal relations and social inclusion. The purpose of health-related quality of life is to comprehensively describe a person’s health status (Wilson & Cleary, 1995). The model of health-related quality of life includes objective factors, such as a diagnosis of a health condition, but also subjective factors such as the experience of symptoms and the effects on participation and functioning. These factors can be translated in different domains of health-related quality of life, including physical well-being, role limitations caused by physical and emotional problems, mental well-being, vitality, pain, social participation, general health and the belief that changes in health are possible (Wilson & Cleary, 1995).

Before the introduction of the concept of health-related quality of life, medical interventions, such as medication, were focussed mainly on biological outcomes. Health-related quality of life can supplement the traditional endpoints of treatments. Quality of life assessment should be used to improve the individual care and provide insights for quality improvement in services and policy. Furthermore, quality of life can be used as a multidimensional view on the (mental) health of a person with intellectual disabilities, in order to identify needs and to plan interventions, especially in challenging behaviours (Bertelli & Brown, 2006).

**Aims of this thesis**

The overall aim of this thesis was to add to the evidence-based use of antipsychotic drugs in people with intellectual disabilities and improve on the quality of mental health care provided,
by studying the current antipsychotic drug prescription practices, the effectiveness of risperidone in reducing challenging behaviours and its effects on the quality of life of users. More specifically, the aims of this thesis were:

1. Adherence to guideline recommendations
   a. To evaluate the adherence to guideline recommendations of prescribing antipsychotic drugs to people with intellectual disabilities, by comparing the medical records of antipsychotic drug users to guideline recommendations
   b. To study the barriers and facilitators in implementing and adhering to guideline recommendation on prescribing antipsychotic drugs to people with intellectual disabilities, experienced by Dutch Intellectual Disability (ID) physicians, psychiatrists and behavioural scientists.

2. Long-term effectiveness of risperidone
   a. To study the long-term effectiveness of risperidone in reducing challenging behaviours, by placebo-controlled discontinuation of risperidone.
   b. To study the effects of discontinuation of risperidone on physical parameters, after long-term use.

3. Health-related quality of life associated with long-term antipsychotic drug use
   a. To study the association of health-related quality of life with challenging behaviours and side-effects of antipsychotic drugs, after long-term use and its relevance for the management of challenging behaviours.
   b. To study the effects of long-term antipsychotic drug use on health-related quality of life, by discontinuing the antipsychotic drugs.

Outline
This thesis starts with a medical record study, examining the current prescription practice of antipsychotic drugs (chapter 2). Chapter 3 describes a qualitative study of barriers and facilitators in adhering to guidelines recommendations for prescribing antipsychotic drugs. The following three chapters describe the effects of antipsychotic drugs on challenging behaviour and quality of life in people with intellectual disabilities, who have used antipsychotic drugs long-term. In chapter 4 the associations between health-related quality of life and symptoms of challenging behaviour and physical symptoms associated with antipsychotic drug use are discussed. In chapter 5 the effects of discontinuation on health-related quality of life are described. Chapter 6 of this thesis focuses on risperidone and its effectiveness in reducing challenging behaviours. The final chapter, Chapter 7, provides a general discussion and the overall conclusion.


General introduction

Off-label use of antipsychotic medication in people with intellectual disabilities


