Off-label use of antipsychotic medication in people with intellectual disabilities
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CHAPTER 7

General discussion and conclusion
Aims of the thesis
The overall aim of this thesis was to add to the evidence-base for the prescription of antipsychotic drugs in people with intellectual disabilities. I intended to provide better insight into prescription practices of antipsychotic drugs to people with intellectual disabilities; therefore, I performed a medical record review to study the adherence to guideline recommendations with regard to the use of antipsychotic drugs in clinical practice. In addition, I studied the effectiveness of long-term use of risperidone, by means of a placebo-controlled, randomized, double-blind discontinuation trial. Last, I investigated the relationship between the use of antipsychotic drugs and health-related quality of life, and the effects of discontinuation of long-term used antipsychotic medication, by combining the risperidone trial with the results of an open-label discontinuation study of any antipsychotic drug.

Main findings
The risperidone trial showed that discontinuation of risperidone was possible for the majority of participants who attempted discontinuation, which resulted in immediate health benefits. These results correspond with previous open-label (Ahmed et al., 2000; de Kuijper, Evenhuis, Minderer, & Hoekstra, 2014; de Kuijper & Hoekstra, 2018) and double-blind discontinuation trials (McNamara et al., 2017). However, the results are in contrast with a double-blind discontinuation trial of risperidone after short-term use in children and adolescents with intellectual disability (Reyes, Buitelaar, Toren, Augustyns, & Eerdekens, 2006). Furthermore, interestingly, the rates of premature terminations of the double-blind discontinuation, due to a worsening in challenging behaviours, were similar in both the discontinuation group and the control group. This suggests that an increase in challenging behaviours could be a placebo effect of discontinuation and that the long-term use of risperidone may not be effective for reducing challenging behaviours.

Health-related quality of life and its association with long-term use of antipsychotic drugs was studied by a cross-sectional analysis of baseline data and by the analysis of the discontinuation data from two studies. Both confirmed that health-related quality of life may be affected by side-effects of antipsychotic drugs, such as parkinsonism and autonomic symptoms, and by challenging behaviours, such as irritability, lethargy and stereotypy. Similar associations with quality of life were previously found in relation to side-effects (Faulkner, Cohn, Remington, & Irving, 2007; Scheifes et al., 2016) and challenging behaviours in general (Koch et al., 2015). Furthermore, a lower score of mental/emotional well-being, according to the RAND-36, was found in people with intellectual disability who used antipsychotic medication, compared to the general population of the Netherlands (Ware et al., 1998). The results showed that complete discontinuation of antipsychotic drugs resulted in better physical well-being and that initial negative effects on mental well-being were only temporary. This result is in line with an improvement of side-effects found in previous discontinuation studies (de Kuijper et al., 2014; de Kuijper & Hoekstra, 2018).

However, there was also a considerable group, that could not discontinue antipsychotic drugs completely. In this group, the negative effects of attempted discontinuation were clearly visible in a decreased health-related quality of life, by a worsening in mental well-being, social functioning and role functioning related to physical well-being. Interestingly, these domains of quality of life recovered again after stopping the withdrawal or after restarting antipsychotic drugs, suggesting that the negative effects on quality of life were reversible.

Based on the studies in relation to quality of life, two conclusions can be drawn: (1) Discontinuation of antipsychotic drugs should be a priority. The beneficial effects of discontinuation on health outcomes and physical well-being are clear. Even though incomplete discontinuation may initially decrease quality of life, individuals do recover after discontinuation is stopped. (2) When complete discontinuation appears impossible, regular monitoring of side-effects and of health-related quality of life is warranted.

The results of the discontinuation studies underline the necessity of proper evaluation of the effects of antipsychotic drugs and of monitoring side-effects, but also the importance of providing psychosocial interventions. Conversely, the main finding from the medical record review showed that especially these recommendations are often insufficiently adhered to by clinicians. This was in line with previous studies, which showed that the annual monitoring of side-effects is often insufficient (Griffiths, Halder, & Chaudhry, 2012; Teeluckdharry et al., 2013; Thalitaya, Udu, Nicholls, Clark, & Prasher, 2011). Other studies showed better results with regard to annual antipsychotic drugs evaluations: according to Paton (2011), almost all treatments with antipsychotic drugs were regularly evaluated, while a study from the United Kingdom by Marshall (2004) showed results more similar to my study (Marshall, 2004; Paton et al., 2011).

Suggestions towards a solution to the above described issues may be derived from the findings of the qualitative interviews. A multidisciplinary approach to prescribing antipsychotic drugs is suggested. All relevant clinicians (ID physicians, behavioural scientists and psychiatrists) and support staff should be involved in translating guideline recommendations into organisation specific treatment policies. This approach was also endorsed by Grol et al (2003), who additionally also recommends the involvement of the whole network of the client (Grol & Grimshaw, 2003). Involving all relevant stakeholders may not only improve the awareness, and the use of guidelines
recommendations on antipsychotic drugs, it may also enhance the implementation of new care initiatives. Nevertheless, there remains a lot of un-clarity on the causes of challenging behaviours and the effectiveness of alternative interventions to antipsychotic drugs.

**Strengths and limitations**

A strength of the discontinuation study was the double-blind, placebo-controlled design. After several open-label discontinuation studies, this design allowed to further address the uncertainty regarding the effectiveness of risperidone, used to reduce challenging behaviours. Furthermore, the medical record study was, to our knowledge, the first to comprehensively study adherence to guideline recommendations with regard to prescribing antipsychotic drugs in people with intellectual disabilities. Previous studies always focused on a small part of the process, such as reasons for prescription or the monitoring of side-effects.

Generalizability was the main limitation of all three projects within my thesis. There are several concerns that need to be considered in light of this. First, for the discontinuation study, we planned a much larger sample size, but faced inclusion difficulties. The small sample size should be considered when interpreting the results. Furthermore, clients who used risperidone were only approached for participation in the discontinuation trial, if their physician thought they were able to withdraw from the medication, which may have resulted in a selection bias.

A small sample size was also a limitation of the interview study. However, the small number of respondents was intended, because of the exploratory nature of the study. A second limitation of the interview study, related to generalizability, was selection bias, caused by the non-random selection of respondents. Last, the Dutch settings from which the clinicians were included was also a limitation. Some of the issues that were raised in the interviews are universal, such as the frequent prescription of antipsychotic drugs and the need for inclusion of the whole network of the client in drafting and implementing guidelines. However, the ID physician is a medical specialism specific for the Netherlands, delivering both general and specialist health care to people with intellectual disabilities. Previous studies always focused on a small part of the process, such as reasons for prescription or the monitoring of side-effects.

A limitation of the medical record study was the incompleteness of the records. Therefore, it was not possible to differentiate between non-adherence to guideline recommendations, or incompleteness of the medical records.

Clinical implications

The discontinuation studies imply that discontinuation of antipsychotic drugs, including risperidone, should be attempted for clients who use long-term antipsychotic drugs for the management of challenging behaviours. Many clients, their legal representatives or support staff do not want to withdraw from antipsychotic drugs, because they are afraid for the reoccurrence of challenging behaviours that were present before starting antipsychotics. Although both previous studies and this study showed that discontinuation is not always possible, the present study did not find evidence for the reoccurrence of these previous behaviours, except for stereotypical behaviours. Furthermore, when discontinuation is incomplete, the negative effects of discontinuation on health-related quality of life are reversed when withdrawal is suspended or antipsychotic drugs are started again.

A second clinical implication applies to the organizational/management level of (mental health) organizations for people with intellectual disabilities. More facilitation is needed to promote proper monitoring of treatment effects and side-effects of antipsychotic drugs. Facilitation may be provided by nursing teams, functional monitoring options in the electronic patient records and by involving all clinicians in developing organisation specific treatment policies. Involving all clinicians in developing treatment policies, may improve a multidisciplinary approach to antipsychotic drug prescriptions. A multidisciplinary approach may also be supported by more and better collaboration between service providers for intellectual disability care and mental health care organisation, assuring more access to psychosocial treatments in service providers.

Future research

Trials on antipsychotic drugs

An uncertainty remains regarding the effectiveness of risperidone and other antipsychotic drugs; therefore, new trials are necessary. However, when designing a new trial studying the effectiveness of antipsychotic drugs, we should consider the difficulties and lessons learned from the double-blind, placebo-controlled trial discussed in this thesis. Inclusion from only the North of the Netherlands has proven to be insufficient in achieving an adequate sample size. Moreover, the frequent use of risperidone and antipsychotic drugs for challenging behaviours is a universal issue. Hence, to establish a sample size large enough for sufficient statistical power, an international multicentre study should be considered.

To prevent difficulties related to placebo-controlled, double-blind studies, such as inclusion problems, alternative designs may be considered. The complex nature of the design made it difficult to explain to participants, their legal representatives, but also support staff, which
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may have led to some hesitation to enter the study. Study designs, such as open-label trials or prospective studies in daily practice, may be more attuned to clinical practice. These designs may be easier to explain and therefore may be more successful in finding an adequate number of participants. When a design with a control group is preferred, a cross-over design could be considered, assuring that all participants will receive the intervention.

The current studies mainly focussed on challenging behaviours and the negative effects of discontinuation on these behaviours. From conversations with participants and their direct support staff, we were also informed of the appearance of positive behaviours during discontinuation, such as becoming more active, more assertive, better concentration and better ability to stay awake. Only a few of these positive effects of discontinuing risperidone were systematically measured. For future research inclusion of outcome measures on these positive behaviours might be useful.

Other suggestions for future research

The discontinuation studies presented in this thesis and previous discontinuation studies showed that some participants can completely discontinue antipsychotic drugs and others cannot. Often the reason for incomplete discontinuation is the reoccurrence of challenging behaviours. To enable full discontinuation, an alternative treatment is necessary to replace and improve on the treatment with antipsychotic drugs. Future research is needed to study alternative pharmacological or behavioural interventions. Furthermore, more research is necessary to better understand why complete discontinuation is not always possible.

From this thesis, we have learned that not only is it difficult to conduct scientific research within the clinical practice of people with intellectual disability, but it is also difficult to implement new or already existing guideline recommendations. Both need commitment and time investments from support staff, clinicians and management. We tried to make a start in unravelling the barriers and facilitators in using guidelines, but more research is needed to better understand the factors that hamper scientific research, and the implementation of evidence-based recommendations in clinical practice.

Overall in future studies, the participation of people with intellectual disabilities, their legal representatives and support staff should play a bigger role. The relevance of complex clinical studies will increase when it is aimed at answering questions important to people with intellectual disabilities themselves. By improving the participation in future research, inclusion issues might be less.

Conclusions

To conclude, the research in this thesis showed that the discontinuation of antipsychotic drugs should be a priority, even though complete discontinuation could not always be achieved. We found that complete withdrawal from risperidone is possible for a considerable number of clients, although an increase in stereotypical behaviours may occur. Discontinuation of risperidone has a direct positive effect on health, due to a decrease in weight, body mass index, waist circumference, lowered prolactin levels and an increase in testosterone levels. Withdrawal from antipsychotic drugs may also have positive effects on health-related quality of life, while incomplete discontinuation may result in a temporal negative effect on health-related quality of life. However, after stopping the withdrawal or restarting the prescription of antipsychotic drugs, health-related quality of life recovered.

Since the prescription of antipsychotic drugs to manage challenging behaviours may be unavoidable for some clients, better monitoring of effects and side-effects is necessary. This may be achieved by a better integration of guideline recommendation into organizational policy and better facilitation of monitoring effects and side-effects.
References
