Movement disorders in psychiatry as symptom, as side effect, and as risk factor

Impact

Patients suffering from psychiatric illnesses often display movement abnormalities[1-4]. These movement abnormalities can take many forms. This thesis focuses on three specific movement disorders (MDs): parkinsonism, akathisia, and (tardive) dyskinesia (definitions can be found in the General Introduction). MDs can develop spontaneously, as symptom of the underlying psychiatric disorder[3-10]. Also, antipsychotic medication can cause MDs or may enhance or alleviate existing MDs[3, 11]. Additionally, the presence of MDs may be a risk factor for an earlier death[12-15]. This thesis examines MDs from these three perspectives: as symptom, as adverse effects of antipsychotic medication, and as risk factor that may contribute to a reduced lifespan.

The study described in chapter 2[16] aimed to uncover if individuals with auditory verbal hallucinations (AVH, or hearing voices without a physical source), but without a psychiatric disorder, would display dyskinesia. A second objective was to determine if the severity of dyskinesia is related to the severity of schizoptypy. Schizotypy refers to personality traits including unusual perceptual experiences, magical beliefs, suspiciousness, disorganized thoughts and speech, eccentric behavior, social anxiety, and feeling emotionally flat[17, 18]. Dyskinesia was measured with a sensitive instrument, allowing the detection of even subtle forms of MDs[19-22].

We found a higher proportion of subjects with dyskinesia in the AVH than in the control group and a positive association between schizotypy and dyskinesia in the combined group of participants with and without AVH. These results have scientific relevance in the debate if psychiatric disorders in general, and psychotic disorders in particular, can best be viewed as distinct categories, clearly different from a state of mental health, or, alternatively, that there may be a continuum ranging from mental health through the presence of mild symptoms to severe symptoms associated with suffering and dysfunction[23-26]. The current results show that the correlation between psychotic symptoms and MDs, which has long been known to exist in psychotic disorders, is also present in people who have just one psychotic symptom but do not have a psychiatric diagnosis[23, 25]. Therefore, our results support the continuum view of psychosis.

In chapter 3 we examined the presence of MDs in children and adolescents/young adults with autism spectrum disorders (ASD)[27]. We assessed parkinsonism and dyskinesia using both a mechanical instrument and observational rating scales. Based on the rating scales both the children and adolescent/young adult

groups with ASD showed more bradykinesia (slowness of movement) compared to their control groups. The adolescent/young adult group with ASD also had greater rigidity. Surprisingly, we did not find any differences between ASD and control groups on the mechanical measurements. In psychosis spectrum conditions, measurements of MDs with the same instrument used in the current study, have been generally more sensitive than rating scales, meaning that more cases could be detected using the instrumental approach[19-22]. We hypothesized that the opposite pattern displayed in ASD might be explained by different underlying pathophysiology than in psychotic disorders. Furthermore, in the ASD groups, interference from social information processing may have influenced the outcomes on the rating scales[28]. During these assessments, the participant must pay attention to the test-taker, imitate motor tasks, and be watched while performing, which may be very demanding for those with ASD. These findings are important for future studies on movement abnormalities in ASD. Indeed, future studies can help determine the impact of social information processing on movement performance and identify which networks contribute to these abnormalities.

The conflicting results from the instrumental measurements and the rating scales also called for further investigation of the sensitivity and validity of the instrumental measurements. Therefore a mini review was conducted which is presented in the General Discussion. The results indicated that the instrumental approach was generally more sensitive in detecting cases with MD in patients with psychotic disorders, compared to rating scales. The degree to which the instrumental measurements seemed to measure the same construct as the rating scales varied over studies. An important difference between the two ways of measurement which explains part of the conflicting results is that the instrument only measures MDs in the arms/hands/fingers, whereas with the rating scales, the whole body is taken into account. This is relevant for the development of future instruments or digital techniques, which should aim to cover movement in the whole body as well, thus providing more complete information.

Chapter 4 sought to determine the risk of acute antipsychotic-induced MDs in borderline personality disorder (BPD)[29]. Therefore, we conducted meta-analyses on MD measurements obtained from randomized controlled trials (RCTs) that were placebo-controlled. We were able to include data from four studies: three on olanzapine[30-32] and one on ziprasidone[33]. There was no evidence of a higher risk of MDs in the groups receiving an antipsychotic drug versus placebo. However, the two largest studies included in the meta-analyses had stringent exclusion criteria. Patients with comorbid psychiatric disorders, substance abuse, or those

using most other types of psychoactive medication, could not participate[31, 32]. Caution is therefore advised in applying the present results to all patients, as they may not be applicable to everyone. However, the findings are consistent with the observation that low to moderate doses of olanzapine have a low likelihood of inducing MDs in other populations[34, 35].

The results are valuable for patients with BPD and their treating psychiatrist when considering the use of olanzapine and weighing possible benefits in terms of symptom reduction versus possible adverse effects. Olanzapine has a low risk of causing MDs as a side effect when it is the only psychoactive drug used. Nonetheless, olanzapine is known to be associated with other side-effects, most notably weight gain, which should be discussed with the patient before starting the drug.

In chapter 5, we presented the first results from a study about the effect of switching from a combination of two different classes of antipsychotics to one antipsychotic[36]. The two classes of antipsychotic medication were first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). FGAs and SGAs have different effects on the brain due to their influence on neurotransmitter receptors, particularly dopamine and serotonin[37, 38]. However, it is important to note that there are also significant differences between antipsychotics within the same class[38, 39].

Participants were inpatients from long-stay wards with psychotic disorders. One of the most important findings was that switching to one antipsychotic did not lead to a higher risk of relapse. For patients who were prescribed a combination of the SGA clozapine and an FGA, switching to clozapine monotherapy even diminished the risk of relapse. The clinical value of switching to one antipsychotic was supported by the finding of a greater reduction in psychotic symptoms compared to the patients who had continued combination therapy.

These findings are relevant for patients using antipsychotic polypharmacy consisting of a combination of FGA(s) and SGA(s), their family members and treating psychiatrists, suggesting that it may be worthwhile to try and switch to one antipsychotic. Such a switch may be beneficial for the patient in terms of relapse prevention if clozapine is continued as monotherapy, and switching may lead to a reduction in psychotic symptoms. Preliminary results also show a small improvement of MDs after switching to monotherapy (article in preparation).

Furthermore, currently, in the case of a partial non-response to clozapine monotherapy, there is uncertainty about adding a second antipsychotic in treatment-resistant schizophrenia. Treatment guidelines for schizophrenia (including the Dutch guideline), advise prescribing clozapine monotherapy as the preferred option for treatment-resistant schizophrenia. However, in case of a partial non-response to clozapine monotherapy, the Dutch guideline recommends combining clozapine with 'an antipsychotic with a different pharmacological profile'[40]. Which antipsychotic that should be is not further specified. The results of the present study may be used to fill in this gap. Although more research is needed, our results suggest that clinicians should avoid FGAs when considering adding a second antipsychotic to clozapine. Indeed, the new findings can be used in systematic reviews on antipsychotic monotherapy in comparison with specific combinations of antipsychotic polypharmacy, which in turn can help improve treatment guidelines in this respect.

The objective of the study described in chapter 6 was to examine whether MDs are related to a shortened lifespan in patients with severe mental illness (SMI)[41]. Patients with SMI have a 9-25 year shorter life expectancy than people from the general population[42-45], which is a major concern for patients, their relatives, and caregivers. Several factors contributing to this huge difference have been known from earlier research, including smoking, lack of physical activity, an unhealthy diet, and reduced access to and quality of physical healthcare[46, 47]. Additionally, some studies have suggested that MDs may also play a role[12, 13].

We conducted the most comprehensive investigation to date on the relationship between MDs and mortality, by tracking the same group of people over a period of 18 years, during which MDs were measured eight times. Twenty four years after the first measurement, information about which patients had deceased was obtained. The results showed that parkinsonism was a risk factor for a shorter lifespan whereas tardive dyskinesia and akathisia were not. Since this study is only the second one to demonstrate a relationship between parkinsonism and mortality, the results should be replicated in future research to confirm the findings. If more studies confirm the link between parkinsonism and mortality, researchers should investigate how this connection works. This could lead to new interventions for the treatment of parkinsonism. If for example, research will show that patients with parkinsonism are at a higher risk of falling, one could think of providing similar gait and balance training programs which have been developed for individuals with Parkinson's Disease[48-50]. Also, research suggest that parkinsonism in patients with SMI is currently under-recognized, under-treated or that attempts at treatment are not effective[51]. Taken together, efforts

at clarifying these issues and adjusting existing practices are highly needed. Improvement in prevention and treatment of parkinsonism in individuals with SMI can enhance the well-being of these patients and potentially decrease their elevated risk of mortality.

In conclusion; MDs are strongly associated with psychiatric disorders. They can occur as a symptom, as a side effect of antipsychotic medication, and they can be a risk factor for an earlier death. This underscores the importance of careful diagnosis of MDs. In practice, they are often missed and/or remain untreated. Regular screening for MDs and state of the art treatment can prevent much patient suffering.

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