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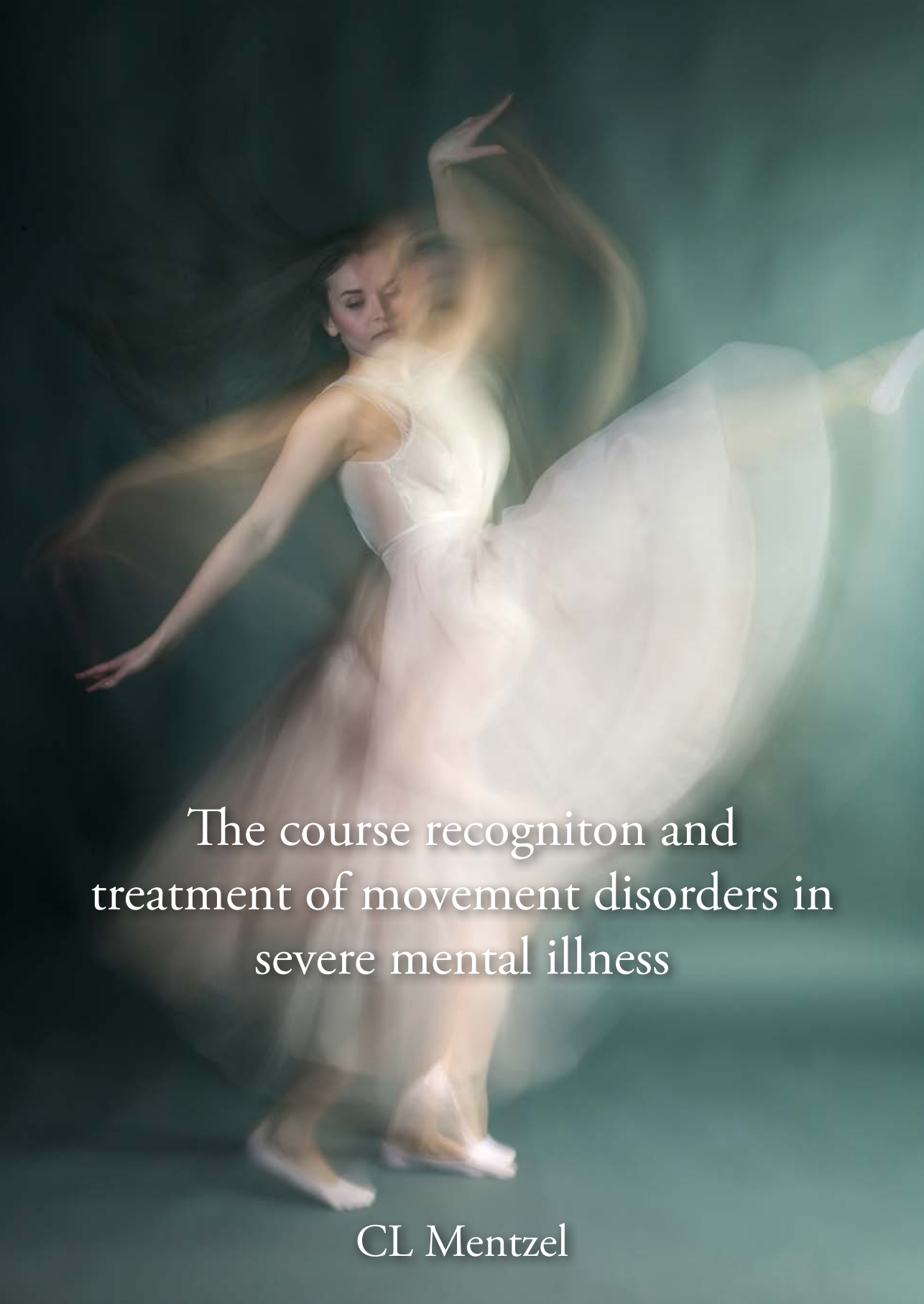

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ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
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volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
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door

Charlotte Liduine Mentzel

Promotores
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To Elijah, Freya and the ever patient Chris

(Ten people ten colours, Japanese proverb meaning everyone is different)

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Chapter 1

Introduction

Movement disorders (MD) occur frequently in psychiatric patients both as a part of the psychiatric illness and as a side effect of medication used to treat psychiatric disorders (1,2). Because of their visibility MD can be a source of shame for patients (3). They are also linked to poorer treatment adherence (4), poorer psychiatric prognosis, and increased mortality (5).

MD occur in patients with (all types of) psychiatric disorders with varying incidence and prevalence rates depending on MD type, underlying psychiatric disorder, and risk factors. In general, MD tend to occur more severely and more frequently in patients with more severe psychiatric disorders (6). Severe mental illness (SMI) in-patient populations have the highest frequency at 68% (7) to 74% (8). The prevalence of at least one movement disorder in an out-patient population with schizophrenia is lower at 37.9% (9) and 57.5% (10).

Types of movement disorders

MD are a group of disorders that affect the ability to produce and control movement. Most are involuntary, though patients can consciously exert a limited amount of influence over them (1,2). This thesis focuses on MD found in patients with psychiatric disorders, namely dyskinesia and dystonia, parkinsonism, resting and action tremor and akathisia. Other MD are beyond the scope of this thesis such as simulation, functional MD, tic disorders, myoclonus, intention tremor, and catatonia.

Parkinsonism

Parkinsonism is often seen in patients with psychiatric disorders (7,8). It is phenomenologically similar to Parkinson's disease (PD): both disorders have bradykinesia, tremor, and rigidity as core motor symptoms. In parkinsonism, the bradykinesia is often not as severe as in PD, although bradykinesia and tremor are usually the most prominent features (11). Both disorders are caused by a shortage of postsynaptic dopamine 2 (D2) receptor activation in the basal ganglia: in PD this shortage is caused by the degeneration of D2 producing cells in the substantia nigra (12) and in parkinsonism by blocking of postsynaptic D2 receptor by antipsychotics (11).

Tremor

The most frequently seen tremors in psychiatric patients are resting, postural action, and intention tremors (13,14). Resting tremor (RT) is usually seen as part of the parkinsonism phenomenology. Postural action tremor (AT) is a common side effect of

drugs used in psychiatry such as selective serotonin reuptake inhibitors (SSRIs), natrium valproate, and lithium (15). The third group, the drug-induced intention tremors, are most often seen as the result of an (accidental) intoxication with either drugs of misuse, such as alcohol, or prescribed medication such as lithium or clozapine (14). Intention tremors are not included in this thesis.

Akathisia

Akathisia, generally defined as drug-induced motor restlessness, is most often caused by antipsychotics (16–18), though it can also be caused by antidepressants, antiemetics, and some other types of medication (17,19). It is comprised of a subjective component of inner restlessness with the urge to move, and an objective component of observed fidgety or restless movements. Several prominent authors on the subject classify it as one of the least acknowledged MD (17–19) despite the fact it occurs in up to a quarter of patients treated with first generation antipsychotics (FGAs) (17).

Dyskinesia and dystonia

In the consensus report by Albanese et al (20) dystonia is defined as "a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both". Dyskinesia could be defined in a similar manner as intermittent muscle contractions causing abnormal, sometimes repetitive, fluid movements.

In both disorders all body parts can be affected but most prominent are usually the face, neck and hands (12). Because the line differentiating dyskinesia from dystonia is vague and both often occur in the same patient, MD specialists no longer consider them as distinct disorders, but simply classify dyskinesia as a more mobile form of dystonia (21). In this thesis we will do the same, hereafter both dystonic and dyskinetic movements will be referred to as dyskinesia.

Dyskinesia is a frequently occurring side effects of antipsychotic medication (19), and other types of medication, such as anti-emetics and dopamine agonists. It occurs: (i) soon after the start, i.e. acute dystonia; and (ii) after many years of antipsychotic use, and are called tardive dyskinesia.

Movement disorder diagnosis and recognition

The accepted method for diagnosing MD is through clinical rating scales (22). Often used scales are: (i) for dyskinesia and dystonia the Abnormal Involuntary Movement Scale (AIMS), the Dyskinesia Identification Scale, Condensed User Version (DISCUS), and the Burke Fahn Marsden Dystonia Rating Scale (BFMDRS); (ii) for parkinsonism the Unified Parkinsonism Rating Scale (UPDRS); (iii) for akathisia the Barnes Akathisia

Rating Scale (BARS); rating scales that combine multiple MD are the Extrapyramidal Symptom Rating Scale (ESRS) and the St Hans Scale.

On the one hand, rating scales can be relatively easy to use, requiring only the patient, a rater and the scale itself. On the other hand, these rating scales are rarely used in daily clinical practice. To achieve a reasonable inter- and intra-rater reliability, raters must be highly trained and specialized in the MD rating scales (22,23). In research, MD rating scales present difficulties, as they are time consuming, are difficult to analyze and interpret owing to their ordinal scale, and are not sensitive for subtle or subclinical movements (22,24–26).

An interesting alternative to rating scales could be the instrumental measurement of MD. Various methods have been proposed: a button measuring force velocity for tremor and dyskinesia (22,26), a spatula that measures lingual velocity for orofacial dyskinesia (26), wearable sensors that measure 3-D movement for bradykinesia (25), activity meters that measure overall movement for dyskinesia and akathisia (data not yet published), and handwriting assessments for parkinsonism (27). To date, instrumental measurement of MD has not gained widespread use in clinical practice, perhaps because complicated equipment is often needed at this moment.

Movement disorder pathophysiology

The relationship between MD and antipsychotic (AP) use is beyond doubt (1,19) and it seems likely that newer AP have a lower incidence of MD (10,19,28–30). However, there is an increasing amount of evidence linking MD to the underlying neuropathology of psychiatric disorders (1,2,6,31,31–37). This is evidenced by the fact that subtle MD are present in AP naïve patients with first episode schizophrenia and in ultra-high risk patients, who have also never received AP (31,32,34,35,37). Also, healthy family members of patients with schizophrenia with no clinical diagnoses have higher rates of subtle MD (31). Indeed, in these family members there is an association between schizotype and subtle MD (31). It is also important to remember that in the period before AP became available, MD were also prevalent, although comparison to current patient groups is difficult (1,2,19). Below the pathophysiology of the individual movement disorders is discussed.

- The pathophysiology of drug-induced parkinsonism is likely caused by the post synaptic D2 receptor blockade. This induces a shortage of D2 signalling in the basal ganglia leading to over activation of the indirect pathway and decreased activation of the direct pathway (12) and thus reduced movement.
- For tremor and akathisia the pathophysiology is much less clear. Articles and reviews note that these MD are caused by medication but do not elaborate on how Reference 13 (13,14,17,18). The pathophysiology of drug-induced AT and essential tremor are likely related, as both produce similar movements and drugs causing AT exacerbate essential tremor (14). The pathophysiology of akathisia unclear (16–19).

There are case reports on tumors or haemorrhage in the pons causing akathisia (17). D4 receptors seem to be implicated based on clozapine (with a greater D4 vs D2 affinity) rarely inducing parkinsonism but sometimes inducing akathisia(38)

- For acute dyskinesia/dystonia it is clear that dopamine receptors in the basal ganglia are involved, and that the abnormal movements are a result of a rapid fluctuation in neurotransmitter signalling. However, it is not clear whether an increase or a deficit in signalling or if D1, D2 or D3 receptor blockade is primarily involved (19,39).
- For tardive dyskinesia (TD) the situation is less clear cut. For a long time the dopamine supersensitivity was the dominant theory, positing that a long term dopamine blockade makes receptors supersensitive to dopamine. However, it has not been substantiated in experimental evidence and cannot explain a number of phenomena associated with TD, such as the late onset of symptoms after starting antipsychotics or the persistence of symptoms beyond a couple of months after stopping antipsychotics (1,19,40). Other theories are GABAergic neuronal dysfunction, cholinergic interneuron deficiency or burn-out, neurotoxicity/oxidative stress, synaptic plasticity, and defective neuroadaptive signalling (1,19,40).

Movement disorder prevalence and course

MD prevalence and persistence varies between populations. In a Dutch population first episode patients with psychosis MD prevalence is 32% for parkinsonism, 9.0% for tremor, 11% for akathisia and 3.7% for dyskinesia (41). While in a Dutch long-stay SMI population prevalence is much higher at 66% for parkinsonism 26% for RT, 10% for akathisia and 37% for dyskinesia (7). MD prevalence found in the Curacao SMI population was similar to the Dutch SMI population with a prevalence of 35% for parkinsonism(Chapter 2), 17% for RT, 5% for AT(Chapter 3), 7% for akathisia (data not published), and 54% for dyskinesia(Chapter 2)

MD and Mortality

A meta-analysis (5) showed that having TD increased the risk of death with an odds ratio of 1.4. However, there were methodological issues with some of the studies included, such as small sample sizes, short follow-up times and not controlling for known confounders. In a recent study by Dean et al. (42) the effect of TD on mortality disappeared after correcting for medication variables. As for the relationship between mortality and the other MD, to our knowledge only Modestin et al. (43) have published on this subject. In a multivariate analysis they found that none of the MD included in the model had a significant association with death. In the Curacao study we found that parkinsonism had a significant association with mortality whereas TD and akathisia did not (chapter 4).

Movement disorder treatment

Prevention of MD is preferable to treating them, yet the reality is that many patients still suffer from them (7,8,10). Indeed, one can suppose that if they are in part a consequence of the underlying psychiatric pathology (1,2,44,45) then they will be a part of clinical practice until we can better treat the underlying disorders.

It is important to remember that treatment efficacy for MD depends on patient characteristics and patients subpopulations, but guideline do not mention this yet (19). In general, as with psychiatric symptoms, MD are easier to treat in patients with less severe psychiatric symptoms, who have a shorter duration of illness and who function better in their daily lives. For example we found that treatments that were effective in parkinsonism and TD in outpatients (30,46) were far less, or even ineffective, in SMI patients (Chapter 3).

Parkinsonism

There are different treatment possibilities for drug-induced parkinsonism. (I) lowering the AP dose or switching to another type of AP and (II) adding anticholinergic medication (11,19). These interventions have a sound theoretical basis in parkinsonism pathology and have been proven effective in PD (12). However, research as to their effectiveness in drug-induced parkinsonism is scarcer. Dose reduction or switching AP type has been the focus of 6 articles with a variety of designs and results(46–52). Most likely the effect of these interventions depend both on the types of AP and dose reduction involved and on patient characteristics. In our study in SMI patients, for example, both AP dose reduction and AP type switching was only minimally and not significantly effective in reducing parkinsonism symptoms (Chapter 3).

Research on the use of anticholinergic medication in parkinsonism also shows varied results (11). This is somewhat surprising as this strategy is very widely used in clinical practice. Reviews by shin et al (11) and Owens (19) both note that there is no clear evidence for the effectiveness of anticholinergic medication. They note that there are a number of studies that failed to show an effectiveness of these agents over placebo, and that the studies that do show an effect report very different effect sizes, and have important flaws in the study designs.

Tremor

The treatment for RT is similar to that of parkinsonism. Although Sirisena et al note that anticholinergic medication in PD patients.

The treatment of drug-induced AT is relatively straightforward. When possible, action tremor inducing medications should be stopped. If this is not possible, a beta-blocker can be very effective in reducing symptoms (14).

Akathisia

As with other drug-induced movement disorders, the first step in treating akathisia is to lower the dose of the medication thought to be inducing it, often AP. If this is not effective or not possible, switching to a different medication with a lower risk of akathisia is a good second step. When acute management is needed, temporarily adding a benzodiazepine may be effective. This will reduce feelings of anxiety produced by both the subjective feeling of restlessness as well as the increased movements (17,18).

If dose reduction or switching is not possible or not effective, a number of other medications have been shown effective in small, often open label, trials. The most important are beta-blockers, mirtazapine and trazodone (17,19). There is no evidence to support one drug over the other so the choice should depend on patient characteristics (19).

Dyskinesia

The treatment possibilities of both acute and tardive dyskinesia have been by far the most researched. For acute dyskinesia, anticholinergic medication is highly effective (1). It can be given orally, as an intramuscular injection, and intravenously, depending on both the time in which an effect is required as well as the clinical setting.

The research on the treatment of TD shows diverse results. While some studies report that switching the AP type hasa moderate (0.5) effect size (30,53), others find minimal effect (54). The prognosis for mild forms of TD with a relatively short duration in patients with less severe psychiatric illness is probably better. Indeed, a study by van Harten et al. (55) showed that in nearly 80% of cases tardive dystonia remitted or showed a relapsing remitting course over the course of 9 years. However, the severe forms of tardive dystonia did persist the entire follow-up period in most patients.

While switching AP is often a clinical consideration, this is not always effective for TD in all patients. Other treatment options such as botulinum toxine injections and D2 depletors such as tetrabenazine have been shown effective in small trials (56). Deep Brain Stimulation (DBS) is highly effective, with an average improvement of symptoms of nearly 80% (Chapter 7). At the time of the review, in November 2012 50 patients had been described in the literature. This number has increased to nearly 70 at the moment of writing this introduction. A few studies did also systematically screen on psychiatric symptoms with validated rating scales (57,58). These studies show no side effects of DBS on psychiatric symptoms other than a mild improvement of the mood on depression rating scales.

A larger systematic study is needed to confirm the results of the smaller studies. This was originally part of this thesis, but at this time there are too few patients included in the trail to report relevant results.

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Chapter 2

The effect of antipsychotic type and dose changes on tardive dyskinesia and parkinsonism severity in patients with a Serious Mental Illness (SMI)

The Curacao extrapyramidal syndromes study XII

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Abstract

Objective: To test the efficacy of current treatment recommendations for parkinsonism and tardive dyskinesia(TD) severity in patients with severe mental illness (SMI) as defined by the National Institute of Mental Health.

Methods: We present an 18-year prospective study including all 223 SMI patients receiving care from the only psychiatric hospital of the former Netherlands Antilles. Eight clinical assessments (1992-2009) focused on movement disorders and medication use. TD was measured on the Abrnormal Involntary Movement Scale and parkinsonism on the Unified Parkinson's Disease Rating Scale. Antipsychotics were classified into both first generation (FGA) versus SGA, as well as high versus low D2 affinity categories. The effect of switching within each category on subsequent movement scores was calculated separately by using time-lagged multilevel logistic regression models.

Results: There was a significant association between reduction in TD severity and starting/switching to an FGA (B= -3.54, $p<0.001$) and starting/switching to a high D2 affinity antipsychotic (B=-2.48, $p<0.01$). Adding an SGA to existing FGA treatment was associated with reduction in TD severity (B=-2.43, $p<0.01$). For parkinsonism, stopping antipsychotics (B=-7.76, $p<0.01$ in FGA/SGA-switch model; B=-7.74, $p<0.01$ in D2 affinity switch model) predicted symptom reduction. While starting a high D2- affinity antipsychotic (3.29, $p<0.05$ in D2 affinity switch model) predicted an increase in symptoms.

Conclusion: The results show that switching from an FGA to an SGA does not necessarily result in a reduction of TD or parkinsonism. Only stopping all antipsychotics reduces (the severity of) parkinsonism, and starting an FGA or a high D2 affinity antipsychotic may reduce (the severity of) TD.

Despite the introduction of Second Generation Antipsychotics (SGAs), medication-induced movement disorders still occur frequently in psychiatric patients (1). Although movement disorders may have a lower incidence rate with SGAs compared with First Generation Antipsychotics (FGAs) they are still highly prevalent side effects of antipsychotics(2–4). Movement disorders are especially prevalent among patients with serious mental illness (SMI), owing to frequent polypharmacy and because more severe symptoms are associated with increased risk of movement disorders (5–8).

The two most prevalent movement disorders in this sample are parkinsonism and tardive dyskinesia (TD) (1,9,10). Current treatment guidelines vary for the management of tardive dyskinesia(11–13). For parkinsonism, lowering antipsychotic dose is the recommended first step followed by switching to a lower D2 affinity antipsychotic or an SGA(12,13). Randomised controlled trials on starting or switching antipsychotic medication mostly focus on the risk of developing movement disorders but not on treatment of movement disorders. Even in large real-world trials, patients with treatment resistance, cognitive disorders (CATIE)(8) or substance misuse (CUTLASS) (14), all of which represent known moderators of movement disorders (15), were excluded, reducing generalizability.

Given the fact that lowering antipsychotic dose or switching the antipsychotic are acknowledged therapeutic strategies for movement disorders, it is important to examine the effect of changing antipsychotic dose or type on the presence and severity of TD and parkinsonism. In a long term naturalistic follow-up study with few exclusion criteria, findings can most easily be generalized to other settings. We, therefore, examined these issues over an 18-year period in a representative sample, consisting of all clinical psychiatric patients in a naturalistic well-defined catchment area, namely the islands of the former Netherlands Antilles. Our aims were to verify the efficacy of switching antipsychotic type or lowering antipsychotic dose on lowering parkinsonism TD severity.

Method

Subjects

Data originated from a cohort of all 223 patients hospitalized or receiving structured outpatient care from the Dutch Antilles only psychiatric hospital, the Dr. D.R. Capriles Clinic. The institutional review board approved the study and informed consent was obtained from all patients included in the study. Over the course of 18 years, a total of 8 assessments focusing on movement disorders were carried out. More information about the design of the study can be found in a previous publication (16).

Inclusion criteria were minimum age of 18 years and cumulative exposure to antipsychotics of at least 3 months; current antipsychotic use was not required. All patients met the of the 1987 National Institute of Mental Health definition of SMI, which was based on DSM-III-R criteria (17). Exclusion criterion was a history of neurological disorders affecting motor function. Of the 223 patients that met the original inclusion criteria, a further 22 were later excluded as they had undergone a lobotomy prior to the study and, therefore, were not considered representative for current patients. Also, patients with dementia (N=7) or mental retardation (N=3) as primary diagnosis were excluded, although these disorders were not excluded when they were not the primary diagnosis. This resulted in a dataset of 191 patients (162 inpatients could be included at T0 in 1992; due to practical considerations, the 29 day-treatment patients on the island where included at T1 in 1993). The advantage of an island is that it is relatively easy to minimize the dropout rate as patients rarely moved off the island and thus were easy to locate at the next time point; the main reason for attrition was death.

Movement disorder severity was assessed in a standardized manner, using the Abnormal Involuntary Movement Scale (AIMS)(18) for TD and the Unified Parkinson's Disease Rating Scale (UPDRS)(19) for parkinsonism, administered by the same two raters (PvH and GM) at all 8 time points. TD was defined according to the Schoolar and Kane criteria(20), parkinsonism was defined as a score of at least 2 on a rigidity or tremor item or a score of at least 3 on a bradykinesia item(19). The first assessment was in 1992, the 7 subsequent measurements were in 1993, 1994, 1996, 1997, 1998, 2001 and 2009, respectively.

In addition, information on medication was collected by a trained physician. Information on age, DSM-III-R diagnosis, sex and cocaine use were extracted from the patient's file at the time of inclusion. Cocaine use was also assessed at the first 4 time points.

Definition and coding of variables

The defined daily dose (DDD) (21)was calculated for both antipsychotics and benzodiazepines and information on antipsychotic type and administration route was extracted(21). The total anticholinergic load of the combined medication was calculated for each patient by summing the anticholinergic load of each medication according to the Anticholinergic Drug Scale (ADS) (22). The ADS assigns a score to each medication (ranging from 0 to 3) in accordance with the level of anticholinergic action of the compound.

Change scores were defined as the difference between the current and the previous assessment for: (i) the AIMS or UPDRS, and (ii) antipsychotic DDD for antipsychotic dose change. For both TD and parkinsonism, an FGA/SGA switch defined as starting and stopping an antipsychotic medication, switching from FGA to SGA, and adding an SGA to an FGA were coded for all eight time points. FGAs used in the study population were benperidol, droperidol, fluphenazine, flupentixol, haloperidol, pro-

methazine, penfluridol, pericyazine, perphenazine, pimozide, pipamperon, thioridazine, trifluoperazine, and zuclopentixol and SGAs were clozapine, olanzapine, quetiapine, risperidone, and sulpiride. A separate analysis was done for both movement disorders based on D2-affinity. FGAs were coded as high-dopamine-2 (D2)-affinity antipsychotics, except for promethazine which was coded as a low-D2 affinity antipsychotic. SGAs were coded as the low-D2 affinity antipsychotics, except for risperidone which was coded as a high-D2 affinity antipsychotic. Hereafter, models focusing on switching from an FGA to an SGA will be referred to as a FGA/SGA models, and models focusing on switching from a high-D2 affinity antipsychotic to a lower D2 affinity antipsychotic will be referred to as D2 affinity models.

Statistical analyses

The Stata(23) XTMIXED command was used, given the multilevel structure with repeated assessments clustered within subjects. Per movement disorder, three analyses were carried out, two for the antipsychotic switch, and one for the effect of antipsychotic dose change on TD and parkinsonism, respectively. In all analyses, the main independent variables were time-lagged; all other, independent variables were either time-independent or pertaining to the current time point.

For TD and parkinsonism, the dependent variable was the difference over two consecutive time points in the AIMS and UPDRS scores, respectively. For both TD and parkinsonism switch analyses, the main independent variable was antipsychotic switch (either FGA/SGA switch or D2-receptor-affinity switch in 2 different models). For the change in antipsychotic dose analyses, the main independent variable was the change in antipsychotic DDD over two consecutive time points.

All analyses were corrected for (i) age, sex, diagnosis, and cocaine use as time-independent variables; (ii) and benzodiazepine DDD, anticholinergic load, administration route of the antipsychotic, and antipsychotic DDD as time-dependent variables. For the antipsychotic dose change analysis, the main independent variable antipsychotic type was included instead of antipsychotic DDD as time dependent variable. All regression models where checked for a normal distribution of the residuals and the absence of heteroscedasticity.

Results

At baseline, patients had a mean age of 50 (SD 16) years; men (n=139) had a mean age of 47 (SD 14) years and women (n=52) a mean age of 58 years (SD 19)years. Nearly all patients (95.4%) were of African-Caribbean origin. The primary diagnoses according to DSM-III-R criteria were schizophrenia (80.2%), affective disorder (5.1%) and other (14.7%). Cocaine use was stable within patients over the time points with 17% patients using the drug.

Prevalence and persistence of TD and parkinsonism

The mean prevalence for both movement disorders was high with an average of 54% for TD and 35% for parkinsonism (Table 1), 18% of patients had both movement disorders. Both disorders showed a relapsing-remitting course with an average persistence to the next time point of 70% (range 67%-72% per time point) and 59% (range 56%-72% per time point) for TD and parkinsonism, respectively. The results for the FGA/SGA models were very similar to those of the D2 affinity models.

Table 1: Patient characteristics over time

Movement disorders								
Time point[a]	T0	T1	T2	T3	T4	T5	T6	T7
N	162	149	129	98	94	87	114	87
Parkinsonism %	38	41	35	36	31	30	37	31
Severity on the UPDRS(SD)	20 (11)	18 (12)	18 (11)	22 (10)	22 (11)	23 (13)	20 (12)	15 (11)
Dyskinesia %	35	52	63	61	55	52	60	52
Severity on the AIMS (SD)	8 (3)	8 (4)	10 (4)	10 (4)	9 (4)	9 (4)	10 (4)	9 (3)
Medication variables								
No AP %	10	10	8	6	5	7	7	7
Only FGA %	85	83	86	84	80	76	65	36
Only SGA %	4	7	6	10	15	16	17	27
Both FGA and SGA %	1	0	0	0	0	1	11	30
AP DDD mean (SD)	1.8 (1.5)	1.9 (1.4)	2.0 (1.4)	2.0 (1.7)	2.1(1.5)	2.1 (1.8)	2.1 (1.6)	2.3 (1.4)
Depot AP %	60	62	69	59	59	56	55	61
Benzodiazepine use%	20	21	28	33	35	41	49	53
Benzodiazepine DDD mean (SD)	1.2 (0.9)	1.3 (1.0)	1.0 (0.7)	1.0 (0.8)	1.2 (1.1)	1.3 (1.2)	1.2 (1.0)	1.4 (1.0)
Anticholinergic load mean (SD)	2.7 (2.6)	3.1 (3.0)	3.6 (3.0)	3.7 (2.6)	3.9 (2.7)	4.4 (3.1)	4.5 (3.0)	4.9 (2.9)

T0=1992, T1=1993, T2=1994, T3=1996, T4=1997, T5=1998, T6=2001 and T7=2009
Abbreviations: Abnormal Involuntary Movement Scale (AIMS), antipsychotic (AP), defined daily dose (DDD), first generation antipsychotic (FGA), standard deviation (SD), second generation antipsychotic (SGA), Unified Parkinson's Disease Rating Scale (UPDRS)

TD

Patients with TD had an average AIMS score of 9.1 (SD 3.9). Both the FGA/SGA and the D2 affinity-switch time-lagged multilevel logistic regression model yielded significant coefficients for switching to/starting an FGA or an antipsychotic with high-D2 receptor affinity (B= -3.54, $p<0.001$ and B=-2.49, $p<0.01$ for the respective FGA/SGA and D2-receptor affinity-switch model)(Table 2). In the FGA/SGA switch analysis, adding an SGA to existing FGA treatment also reduced TD severity (B=-2.43, $p<0.010$).
Average antipsychotic DDD was 2.09 (1.81 -2.32), with the average DDD getting higher with each subsequent time point (Table 1). Increasing the antipsychotic dose by

1 DDD resulted in a reduction of TD severity of 0.42 points on the AIMS ($p<0.05$). TD severity was also related to benzodiazepine DDD (B =-0.71 $p<0.01$).

Table 2: Effect of Changing Antipsychotic Type on Dyskinesia Severity (a time-lagged regression model)

	FGA/SGA switch			D2 Affinity switch		
	Coefficient	95% confidence interval		Coefficient	95% confidence interval	
Demographic variables[1]						
Age	-0.02	-0.05	0.02	-0.02	-0.05	0.02
Sex	0.08	-0.89	1.05	0.07	-0.91	1.04
Cocaine use	-1.23*	-2.39	-0.07	-1.23*	-2.38	-0.08
Diagnosis	-0.29	-1.37	0.78	-0.28	-1.37	0.80
Medication variables[2]						
Benzodiazepine DDD	-0.60*	-1.09	-0.11	-0.64**	-1.13	-0.16
Antipsychotic DDD	-0.26	-0.55	0.03	-0.27	-0.56	0.03
Depot Antipsychotic	0.05	-0.83	0.94	0.26	-0.64	1.17
Anticholinergic load	0.03	-0.12	0.17	0.03	-0.12	0.17
Antipsychotic switch variable[3]						
Switch to SGA/low affinity	0.68	-1.05	2.40	1.06	-0.74	2.87
Adding other antipsychotic type	-2.43**	-4.27	-0.60	-1.19	-2.66	0.27
Start FGA/high affinity	-3.54***	-5.51	-1.57	-2.49**	-4.14	-0.84
Stop FGA/high affinity	0.10	-2.57	2.78	0.23	-2.46	2.91

* $p<0.05$ ** $p<0.01$ *** $p<0.001$

[1] Demographic variables are time invariant. Regression coefficients reflect general association and cannot be interpreted temporally in relation to time-lagged outcome variables.

[2]Medication variables are time-dependent but not time-lagged. Regression coefficients express the association between the variable and change in dyskinesia severity. Regression coefficients do not inform on possible causality.

[3] As the switch variable and the dyskinesia severity outcome variable are both time-lagged variables that express a change in state within a patient, it is likely that a switch in antipsychotic type has a causal relationship with a change in dyskinesia severity. Regression coefficients should be interpreted as the average change in points on the Abnormal Involuntary Movement Scale (AIMS) as a result of the antipsychotic switch."

Abbreviations: defined daily dose (DDD), first generation antipsychotic (FGA), second generation antipsychotic (SGA),

Parkinsonism

Patients with parkinsonism had an average UPDRS score of 19.6 (SD 11.6). Both the FGA/SGA and the D2 affinity-switch time-lagged multilevel logistic regression model yielded significant coefficients for stopping antipsychotics, with a severity reduction of over 7 points (B= -7.76, $p<0.01$ for the FGA/SGA model and B= -7.74, $p<0.01$ for the D2 affinity model)(Table 3). In the D2 affinity model, starting antipsychotics in unmedicated patients was followed by an increase in parkinsonism severity (B= 3.29, $p<0.05$).

No significant association was found between changing antipsychotic dose and parkinsonism (B= -0.05; Table 4). There was, however, a significant association between higher parkinsonism severity and FGA use (B= 3.68, p<0.05)

Table 3: The effect of switching antipsychotic type on parkinsonism severity (a time-lagged regression model)

	FGA/SGA switch			D2 affinity switch		
	Coefficient	95% confidence interval		Coefficient	95% confidence interval	
Demographic variables[1]						
Age	0.05	-0.01	0.10	0.04	-0.02	0.09
Sex	-0.82	-2.61	0.98	-0.71	-2.49	1.08
Cocaine use	0.81	-1.33	2.95	0.39	-1.72	2.50
Diagnosis	0.94	-1.05	2.93	0.77	-1.21	2.76
Medication[2]						
Benzodiazepine DDD	0.61	-0.30	1.52	0.48	-0.42	1.37
Antipsychotic DDD	-0.15	-0.69	0.39	-0.23	-0.77	0.31
Depot Antipsychotic	0.35	-1.29	1.99	0.11	-1.55	1.76
Anticholinergic load	0.05	-0.21	0.31	-0.00	-0.27	0.26
Antipsychotic switch variable[3]						
Switch to SGA/low affinity	-2.73	-5.92	0.45	-2.90	-6.22	0.42
Adding other antipsychotic type	-0.59	-3.99	2.82	2.42	-0.28	5.11
Start FGA/high affinity	3.42	-0.23	7.07	3.29*	0.25	6.33
Stop FGA/high affinity	-7.76**	-12.70	-2.81	-7.74**	-12.68	-2.81

* p<0.05 ** p<0.01

[1] Demographic variables are time invariant. Regression coefficients reflect general association and cannot be interpreted temporally in relation to time-lagged outcome variables.

[2]Medication variables are time-dependent but not time-lagged. Regression coefficients express the association between the variable and change in parkinsonism severity. Regression coefficients do not inform on possible causality.

[3] As the switch variable and the parkinsonism severity outcome variable are both time-lagged variables that express a change in state within a patient, it is likely that a switch in antipsychotic type has a causal relationship with a change in parkinsonism severity. Regression coefficients should be interpreted as the average change in points on the Unified Parkinson's Disease Rating Scale (UPDRS) as a result of the antipsychotic switch.

Abbreviations: defined daily dose (DDD), first generation antipsychotic (FGA), second generation antipsychotic (SGA)

Table 4: Time-lagged regression model on the effect of antipsychotic dose change on movement disorder severity

	Dyskinesia			Parkinsonism		
	Coefficient	95% confidence interval		Coefficient	95% confidence interval	
Demographic variables[1]						
Age	0.01	-0.03	0.01	0.05	-0.02	0.12
Sex	0.40	-0.64	0.40	-0.29	-2.26	1.68
Cocaine use	-0.28	-1.50	-0.28	1.00	-1.29	3.30
Diagnosis	-0.25	-1.45	-0.25	0.17	-2.09	2.42
Medication[2]						
Benzodiazepine DDD	-0.71**	-1.24	-0.18	0.62	-0.38	1.63
Depot Antipsychotic	0.36	-0.71	1.43	0.65	-1.37	2.66
Anticholinergic load	0.02	-0.14	0.17	0.03	-0.26	0.32
Antipsychotic type						
FGA	-1.63	-3.52	0.27	3.68*	0.10	7.25
SGA	-0.43	-2.61	1.76	3.02	-1.11	7.16
Both	-2.57	-5.82	0.68	4.51	-1.63	10.65
Time lagged variable						
Antipsychotic DDD change	-0.42*	-0.78	-0.05	-0.05	-0.74	0.63

* $p<0.05$ ** $p<0.01$

[1] Demographic variables are time invariant. Regression coefficients reflect general association and cannot be interpreted temporally in relation to time-lagged outcome variables.

[2]Medication variables are time-dependent but not time-lagged. Regression coefficients express the association between the variable and change in movement disorder severity. Regression coefficients do not inform on possible causality.

[3] As the dose change variable and the movement disorder severity outcome variable are both time-lagged variables that express a change in state within a patient, it is likely that a switch in antipsychotic type has a causal relationship with a change in movement disorder severity. Regression coefficients should be interpreted as the average change in points on the Abnormal Involuntary Movement Scale (AIMS) or the Unified Parkinson's Disease Rating Scale (UPDRS) as a result of the antipsychotic switch.

Abbreviations: defined daily dose (DDD), first generation antipsychotic (FGA), second generation antipsychotic (SGA),

Discussion

The results show that switching from an FGA to an SGA, in SMI patients, does not necessarily lead to a reduction of dyskinetic or parkinsonism symptoms. In both the parkinsonism and TD analyses, switching from an FGA to an SGA, or from a high-D2 affinity antipsychotic to one with a lower affinity, had no significant impact on the movement disorder. Instead, in the case of parkinsonism, only complete cessation of AP medication resulted in significantly lower UPDRS scores. In the TD analysis, adding an SGA to current FGA treatment or starting an FGA resulted in significantly lower scores. Surprisingly, lowering AP dose had no effect on parkinsonism severity. One explanation is that movement disorders in SMI patients behave differently than movement disorders in patients with less severe mental disorders. Therefore, more research on the treatment of movement disorders in SMI patients is warranted.

TD

According to English and American treatment guidelines, there is insufficient evidence for switching (11,12)from an FGA to an SGA as treatment of TD. In contrast, the Dutch treatment guideline classifies switching as level-3 evidence (13). This is based on two studies (24,25) with the strongest evidence coming from the industry-sponsored trial(25). Our analysis, however, showed the opposite pattern, with a 3-point reduction on the AIMS for starting or switching to an FGA and a 2 to 3 point reduction for adding an SGA to FGA treatment. While a lower incidence of TD with SGA medication has been extensively documented (4), the treatment of established tTDis difficult. Jeste and colleagues (26) found remission of TD after cessation of all antipsychotic medication in 37% of cases. However, this study is over 30 years old. More recent studies show only a limited effect of antipsychotic dose reduction. Complete cessation of all antipsychotics leads to complete remission in only 2% of cases (27)and to a reduction of severity in 20% cases. While it is possible that switching to an FGA reduces the probability of spontaneous remission of the TD, however, spontaneous remission is most unlikely given the 2% probability of remission with cessation of all antipsychotic medication (27).

In our study, increasing antipsychotic dose led to a small but significant reduction of TD symptoms. This is in line with previous observations that an increase of the antipsychotic dose can mask TD (20). Adding an SGA to existing FGA treatment was also significantly associated with a TD severity reduction. This could be the same masking effect but it is also possible that adding an SGA to an FGA truly reduces TD severity. The current study cannot distinguish between the two scenarios.. However, antipsychotic polypharmacy has many disadvantages, amongst which a sharp increase in the rate of side effects. These include parkinsonism, cognitive impairment, weight gain and diabetes (28), and therefore adding an SGA to an FGA cannot be recommended.

In all models, known moderators of movement disorders were added to improve efficiency of the statistical models. The time dependent medication variables can be interpreted as having an association with a change in movement disorder outcome, but interpretations of causality cannot be made. In the TD analyses, benzodiazepine DDD was significantly associated with an increase in AIMS severity in both models.. Time-independent variables such as cocaine use were added to improve the efficiency of the model, however it is not possible to interpret any association between those variables and TD severity.

Parkinsonism

Current treatment guidelines suggest lowering the antipsychotic dose if parkinsonism occurs, with switching to an SGA as the second step(12,13). However, the current long-term follow-up study in SMI patients does not support these interventions. While

the few RCTs on treating parkinsonism in non-SMI patients had small to moderate effect sizes (29,30), the association between antipsychotic type and dose and parkinsonism symptoms in SMI patients has also been inconsistent (7,10). Possible reasons for this are that SMI patients generally receive such a high dose of AP medication (1,31), around 2 DDD in our study, that a small dose reduction will have little effect. It is also possible that bradykinesia and parkinsonism symptoms in SMI patients are not side effects of AP medication but neurological soft signs that are part of the endofenotype of the underlying mental disorder (32). Whatever the reason, these results point to a difference between SMI and non-SMI patients, possibly warranting different treatment algorithms.

Strengths

Naturalistic studies, such as the Curacao extrapyramidal syndromes study, are important to test the results of pharmacological interventions in a real world setting. The Curacao extrapyramidal symptoms study is one of the few longitudinal studies in SMI patients with a long follow-up and many repeated measures. This makes it ideal for studying movement disorders, as these often show a relapsing and remitting course, in unique recurrent patterns, over the years. Because all SMI patients in a well-defined catchment area were included, loss to follow-up was mainly due to death, and given the naturalistic design of the study, results can be considered representative for comparable real world SMI populations. The lagged design also allows the study to examine the effect of switching antipsychotics on movement disorders at a later time point.

Another strong point is that over the years, all ratings were carried out by the same raters, reducing problems of interrater reliability.

Limitations

Some limitations need to be taken into account when interpreting the results. First, in this naturalistic study, the reason for switching antipsychotics is unknown and could not be included as a possible confounder in the analyses. Switching may occur for a variety of reasons, i.e. development of movement disorder, lack of effect of the medication, or a request from patients or their family. This could have influenced the results as high risk patients for developing movement disorders might receive a different pharmacological regime compared to patients with a low risk. However, the time lagged design, in which patients function as their own controls, limits this possible bias. If there is such a bias it would be expected that regression coefficients would be more extreme but in the same direction. Second, the study population consisted mostly of participants who were of African-Caribbean origin, therefore generalizing the results to other ethnic groups requires caution. However, Owens(15) rightly states that differences in movement disorder risk in different ethnic groups is likely due to confounding between ethnicity and medication use. Third, the study could be underpowered owing

to the limited number of antipsychotic switches (to SGA N=40, high-D2 affinity N=36) and the variables showed truncated distributions. Lack of statistical significance can therefore not be interpreted as lack of clinical effect. Instead, the size of regression coefficients should be considered when judging whether a change is clinically relevant. For example, in the antipsychotic switch and parkinsonism analyses, switching to an SGA/low-D2 affinity antipsychotic has a large regression coefficient even though the confidence interval does contain the 0. Also, while there were no indications for heteroscedasticity, the residuals were symmetrical but not normally distributed. However, when assumptions were relaxed in bootstrapped analyses, very similar results were obtained. Therefore, we chose to present the original results instead of the bootstrap analyses.

Finally, in an ideal situation we would have considered all antipsychotics on their individual merits instead of classifying them in two groups. As Leucht et al.(4) have shown the characteristics of antipsychotics vary widely within the FGA and SGA groups. They therefore propose considering each individual antipsychotic on its own merits. However, considering all antipsychotics separately would leave our study underpowered. In order to assess the validity of the classic FGA/SGA classification, while not sacrificing too much power, we replicated the analyses with antipsychotics classified according to their D2-receptor affinity(33). Also, patients in this study did not receive some of the newer antipsychotics such as aripiprazol, thus no conclusions can be drawn about these antipsychotics.

In conclusion, this study suggests that movement disorders in SMI patients may respond differently to switching antipsychotics than treatment guidelines would lead us to expect. Results indicate that for parkinsonism, with the exception of stopping all antipsychotic medication, effects of switching antipsychotic medication on both movement disorders are modest. However, there are additional considerations when it comes to clinical recommendations. Stopping medication increases risk of psychotic relapse, so stopping cannot be recommended for more than a brief interval to relieve parkinsonism. Moreover some patients may have both parkinsonism and TD leading to conflicting treatment advice. For parkinsonism, if antipsychotic cessation is not possible, dose reduction may be attempted, as this has little clinical consequences. Switching antipsychotics to SGAs or low-D2 affinity antipsychotics solely to reduce parkinsonism is not recommended, given the small effect and the fact that these antipsychotics have their own limitations such as sedation, weight gain and other metabolic and anticholinergic side effects. For TD, switching to an FGA may be a strategy to provide relief from TD in some cases. However, as it may increase parkinsonism or akathisia this may not be wise especially in elderly patients. An antipsychotic dose increase can also be considered, as it may mask the TD symptoms for at least a number of years, but it increases the risk of dose dependent side effects. Adding an SGA to current FGA treatment cannot be recommended, as antipsychotic polypharmacy carries a much higher risk for psychiatric and somatic side effects.

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Chapter 3

Risk factors for tremor in a population of patients with severe mental illness: an 18-year prospective study in a geographically representative sample

The Curacao Extrapyramidal Syndromes study XI

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Abstract

Objective: To assess incidence, prevalence and risk factors of medication-induced tremor in African-Caribbean patients with severe mental illness (SMI);

Method: A prospective study of SMI patients receiving care from the only mental health service of the previous Dutch Antilles. Eight clinical assessments, over 18 years, focused on movement disorders, medication use, and resting tremor (RT) and (postural) action tremor (AT).. Risk factors were modeled with logistic regression for both current (having) tremor and for tremor at the next time point (developing). The latter used a time lagged design to assess medication changes prior to a change in tremor state.

Results: Yearly tremor incidence rate was 2.9% and mean tremor point-prevalence was 18.4%. Over a third of patients displayed tremor during the study. Of the patients 5.2% had AT with 25% of cases persisting to the next time point, while 17.1% of patients had RT of which 65.3% persisted. When tremor data was examined in individual patients they often had periods of tremor interspersed with periods of no tremor.

Having RT was associated with age (OR=1.07 per year; 95% Confidence Interval 1.03-1.11), sex (OR=0.17 for males; 0.05-0.78), cocaine use (OR=10.53; 2.22-49.94), dyskinesia (OR=0.90; 0.83-0.97), and bradykinesia (OR=1.16; 1.09-1.22). Developing RT was strongly associated with previous measurement RT (OR=9.86; 3.80-25.63), with previous RT severity (OR=1.22; 1.05-1.41) and higher anticholinergic load (OR= 1.24; 1.08-1.43)

Having AT was associated with tremor-inducing medication (OR= 4.54; 1.90-10.86), cocaine use (OR=14.04; 2.38-82.96) and bradykinesia (OR=1.07; 1.01-1.15). Developing AT was associated with, previous AT severity (OR=2.62 per unit; 1.64-4.18) and tremor reducing medication (OR=0.08; 0.01-0.55).

Conclusions: Long-stay SMI patients are prone to developing tremors, which show a relapsing-remitting course. Differentiation between RT and AT is important as risk factors differ and they require different prevention and treatment strategies.

Tremors are rhythmic, involuntary, oscillatory movements of body parts (1). In clinical psychiatric practice tremor is one of the most frequently occurring movement disorders (2) most often as a side effect of medication(3). Tremor negatively influence quality of life, contributes to stigmatization (2) and is an important reason for medication non-compliance (2,3).

Tremors can be divided into resting tremor (RT) and action tremor (AT). AT can be further subdivided into postural, simple kinetic, and intention tremor (4). In the literature, lithium, mood stabilizers, and antidepressants are described in relation to postural action tremors, which occur during voluntary muscle contraction or suspension against gravity (2,5) with a frequency of 4-12Hz(4). In contrast, antipsychotics appear to be associated more with parkinsonism with RT as part of its triad (1,6) . RT has a frequency of between 3 and 6 HZ and occurs when the affected limb, usually the hand, is fully supported against gravity (4).

In general, patients with severe mental illness (SMI) are at high risk for developing movement disorders, given the fact that they are often exposed both to high doses and to polypharmacy (7)(8)(9). Movement disorders include akathisia (4.5%(7)-9.3%(10),(11) prevalence) tardive dyskinesia (28.4%(7)- 39.7%(10) prevalence), dystonia (5.7%(7)-13.4%(10) prevalence) and parkinsonism (36.1%(10)-56.2%(7) prevalence). To our knowledge, no articles have been published focusing on tremor in SMI patients. Figures on tremor incidence and prevalence in SMI populations are difficult to find. While the literature suggests that about 40-50% of patients with medication-induced parkinsonism develop some form of tremor (12), the incidence has never been studied. In addition, very little is known about risk factors for development and cessation of tremor in SMI populations.

The Curacao Extrapyramidal Syndromes study represents an 18-year follow-up of the SMI patients in a geographically circumscribed area(10)(13)(14). The database represents a valuable opportunity to prospectively study tremor subtypes in a complete sample of SMI patients, in order to obtain population-based estimates of incidence, prevalence and association.

Methods

Subjects

The protocol was approved by the Curaçao Institutional Review Board, and written informed consent was obtained by a psychiatrist from each patient. All patients were considered capable of making the decision to take part in the trial themselves, as the study had no risks for patients, required only a small time investment, and had possible benefits. Details on the Curacao Extrapyramidal Syndromes study, a longitudinal co-

hort study spanning 8 measurements over 18 years, have been published in previous reports (10)(13)(14). At baseline, data was gathered pertaining to all SMI patients (223) receiving care from the Capriles Hospital, the only psychiatric hospital in the Dutch Antilles and providing services to all patients with psychotic disorders on the islands. A baseline measurement was carried out in 1992 (N=162) followed by 7 follow-up visits in 1993 (N=149), 1994 (N=129), 1996 (N=98), 1997 (N=94), 1998 (N=87), 2001 (n=114) and 2009 (N=87). Loss to follow-up was rare as was patients rarely moved out of the catchment area and mainly due to death. Inclusion criteria were: (1) a history of antipsychotic medication use for at least 3 months; and (2) no obvious organic disorders that could cause movement disorders, such as Parkinson's disease. Essential tremor was not an exclusion criteria.

Assesments

Movement disorders were rated on the (i) the Unified Parkinsons Disease Rating Scale (UPDRS)(15) for tremor, bradykinesia and rigidity; (ii) the Abnormal Involuntary Movement Scale (AIMS) (16) for tardive dyskinesia; and (iii) the Barnes Akathisia Rating Scale (BARS) (17) for akathisia. Rating was achieved by consensus and the inter-rater reliability kappa for tremor was 0.70; a detailed description of the test situation can be found in previous publications (10) . The UPDRS version 3.0 only includes the postural subtype of AT, hence all AT in this article are postural. All movement disorders where assessed in person by the same two raters (PvH and GM), both psychiatrist specialized in movement disorders in psychiatry; medication data and diagnosis was extracted from patient records by trained clinicians and all patients gave informed consent. Patients with mental retardation (N=3)and dementia (N=7) where excluded as they were not considered SMI disorders. Patients who had undergone a lobotomy (N=22) were also excluded. This resulted in a dataset of 191 patients; 162 patients were included at T0 and a further 29 (SMI day treatment patients) where included at T1.

Demographic variables such as age, sex, DSM-III-R diagnosis, and cocaine use were collected from records at time of inclusion. Medication data was collected at all time points and was converted in defined daily doses (DDD) (18). Information on the type of antipsychotic, i.e. first-generation antipsychotic (FGA) or second-generation antipsychotic (SGA), and the route of administration, oral or depot, was collected. The total anticholinergic load of the combined medication was calculated for each patient by summing the anticholinergic load pertaining to each medication according to the Anticholinergic Drug Scale (ADS) (19). The ADS assigns a score to each medication (ranging from 0 to 3) in accordance with the level of anticholinergic action of the compound.

Tremor-protective medication was defined as beta-blockers (propranolol and sotalol) and dopamine agonists (levodopa and carbidopa). Lithium, antidepressants and other medication were considered tremor-inducing if they were listed by Arbaizar et

al. (2), Morgan et al. (3), Puschmann et al. (5), and Zeng et al. (20) or had at least 1% risk of tremor according to the Dutch pharmaceutical reference manual (21). Antipsychotics were not included in this category as they were already represented separately in the total antipsychotic DDD.

RT was dichotomously defined as a severity score of at least mild (a score of 2, range 0-4) on the RT subscale (item 3) and AT as a severity score of at least mild on the AT subscale (item 4) of the UPDRS (15). Movement disorder variables where continuous and defined as; (i) the sum of items 1-7 of the AIMS for tardive dyskinesia; (ii) item 4 of the BARS for akathisia; (iii) the sum of the sub items of item 5 of the UPDRS for rigidity; and (iv) the sum of items 1,2, 6-12 and 14 of the UPDRS for bradykinesia.

Descriptive statistics

At each time point prevalence was calculated. In addition, the 18-year average prevalence was calculated over all time points. Incidence rates were calculated by dividing the number of new cases by the number of person-years of follow-up.

Regression models

All analyses were performed using STATA (22). As all assessments of each subject were included in the analyses, data had a multilevel structure with multiple assessments clustered within subjects. The Stata xtlogit command is ideally suited to analyse this type of data. The obtained odds ratios can be interpreted as odds ratio results obtained from unilevel logistic regression. The dependent variable was the dichotomised tremor variable. Effect sizes of the risk factors were expressed as odds ratios and their 95% confidence interval (CI). To assess which factors where related to the development or cessation of a tremor type over time, a time-lagged analysis was performed, using the xtlogit random effects procedure. In this analysis, the dichotomous tremor type was the outcome, while the same dichotomous tremor type and clinician-influenced variables at the previous time point were entered as independent variables.

Results

Demographic characteristics

Of the 191 patients included, 162 were included at baseline and 29 were included at the first follow-up measurement, resulting in a total of 876 observations. Most (95.4) were of African-Caribbean origin. At baseline, mean age was 50 (SD 16)years; men were 47 (SD 14) years and women 58 (SD 19) years. The primary diagnoses according to DSM-

III-R were schizophrenia (80.2%), affective disorder (5.1%) and other (14.7%). Information about medication use at baseline is displayed in Table 1.

Table 1: Demographic characteristics, movement disorder prevalence and medication use at baseline

	No tremor		Resting tremor		Action tremor		All patients	
	N	%	N	%	N	%	N	%
Demographic variables								
Subjects	137	85	22	14	6	4%	162	100%
Age (mean; SD)	50.12	16.77	50.17	13.48	58.28	19.45	50.43	16.45
Male sex	94	69%	20	91%	5	83%	116	72%
Cocaine use	23	17%	5	23%	1	17%	28	17%
Diagnosis schizophrenia	112	82%	17	77%	3	50%	130	80%
Movement disorders								
Dyskinesia	19	14%	3	14%	1	17%	22	14%
AIMS (mean; SD)	6	4.11	6	4.58	2	.	6	4.06
Akathisia	5	11%	1	5%	0	0%	16	10%
BARS (mean; SD)	2.53	0.74	4	.	.	.	2.63	0.81
Bradykinesia	32	23%	9	41%	4	67%	42	26%
UPDRS ** (mean; SD)	14.81	6.71	15.22	8.89	19	7.53	14.93	7.03
Rigidity	22	16%	7	32%	2	33%	29	18%
UPDRS *** (mean; SD)	8.64	3	6.71	3.77	9.5	3.54	8.17	3.24
Medication variables								
Antipsychotic type								
No AP	16	12%	0	0%	1	17%	17	10%
FGA only	115	84%	20	91%	4	67%	137	85%
SGA only	5	4%	2	9%	1	17%	7	4%
Both AP types	1	1%	0	0%	0	0%	1	1%
AP DDD (mean; SD)	1.58	1.48	2.05	1.88	1.12	0.78	1.62	1.53
Depot use	81	59%	15	68%	3	50%	97	60%
Tremor inducing medication use	37	27%	4	18%	2	33%	43	27%
Tremor reducing medication use	3	3.5	1.97	2.72	2.55	0%	3	2%
Anticholinergic load (mean; SD)	2.58	2.55	3.41	2.54	3.5	1.97	2.72	2.55
Benzodiazepine DDD (mean; SD)	0.23	0.64	0.34	0.7	0.08	0.2	0.24	0.64

Abbreviations: AP Antipsychotic, DDD: Defined Daily Dose , FGA: First Generation Antipsychotic, SGA: Second Generation Antipsychotic
* Patients can have both action and resting tremor
** list items bradykinesia
*** list items rigidity

Tremor prevalence and incidence

Over a third of patients had tremor at least once during the study. Overall, the average prevalence of the combined RT and AT outcome (hereafter: combined tremor) was 18%, with a time-specific distribution of 15%, 23%, 25%, 18%, 16%, 13%, 21%, and 15% over the consecutive time points. RT occurred at an average prevalence of 17%,

with a time-specific distribution of 14%, 21%, 22%, 18%, 15%, 13%, 20%, and 14% over the consecutive time points. AT had a lower rate at an average prevalence of 5% and a time-specific distribution of 4%, 3%, 7%, 2%, 6%, 2%, 11%, and 7% over the consecutive time.

Longitudinally, tremors displayed a relapsing-remitting course; in two thirds of cases the combined tremor at one time point was also present at the next time point. AT persisted less frequently compared to RT (25% and 67% persistence to next time point, respectively). Incidence rates were 29 per 1000 person-years (2.9%) for all tremors; 26 per 1000 person-years, or 2.6% (95% CI 1.9%-3.6%), for RT and 12 per 1000 person-years, or 1.2% (95% CI 0.8%-1.9%), for AT. The number of patients displaying a first time tremor is balanced by the number of patients permanently remitting for tremor resulting in a flat tremor prevalence over time despite the incidence of new tremor cases.

Risk factor analysis

The results of the risk factor analyses are described in Table 2. Three separate analyses where done: one on combined tremor, one on RT and AT types.

The combined tremor analysis

The multilevel logistic regression yielded significant odds ratios (OR) between combined tremor and age (OR 1.06 per year), sex (reference male; OR 0.18) and cocaine use (OR 8.32) Of the other movement disorders, bradykinesia (OR 1.14 per unit UPDRS increase), but not rigidity (OR=1.09), was positively associated with tremor while dyskinesia (OR 0.92 per unit AIMS increase) displayed a negative association. Of the medication variables, only the number of tremor-inducing medications (OR 2.23 per added medication) was significantly associated with tremor.

Tremor subtype analysis

Cocaine use (OR 10.53 for RT and 14.04 for AT) and bradykinesia (OR 1.16 for RT and 1.07 for AT) were associated with both tremor types. Age (OR 1.07), sex (OR 0.19) and dyskinesia (OR 0.90) were associated only with RT. Although for age and sex the odds ratio is similar in both tremor types, the number of AT cases, however, is smaller number of RT cases (48 AT cases versus 161 RT cases). The number of tremor-inducing medications other than antipsychotics (OR 4.54) was significantly associated only with AT.

Table 2: Relationship between covariates and tremor subtypes in psychiatric patients with Severe Mental illness, 18 year follow-up data

	Any Tremor			Resting Tremor			Action Tremor		
	OR	95% CI		OR	95% CI		OR	95% CI	
Demographic variables									
Age	1.06**	1.02	1.10	1.07**	1.03	1.11	1.05	1.00	1.11
Sex	0.18*	0.05	0.69	0.19*	0.05	0.78	0.18	0.032	1.07
Cocaine use	8.32**	2.01	34.4	10.53**	2.22	49.94	14.04**	2.38	82.96
Diagnosis	2.42	0.66	8.87	2.17	0.53	8.90	2.26	0.49	10.35
Other movement disorders									
Dyskinesia	0.92*	0.86	0.99	0.90**	0.83	0.97	1.04	0.95	1.15
Akathisia	1.32	0.88	1.98	1.30	0.84	2.01	1.34	0.74	2.44
Bradykinesia	1.14***	1.08	1.21	1.16***	1.09	1.22	1.07*	1.01	1.15
Rigidity	1.09	0.99	1.21	1.09	0.98	1.22	1.10	0.96	1.27
Medication variables									
Benzodiazepine DDD	1.18	0.77	1.81	1.14	0.70	1.84	1.37	0.78	2.38
No antipsychotic use (base = only FGA)	0.57	0.13	2.51	0.54	0.11	2.57	1.75	0.27	11.51
Only SGA use (base = only FGA)	0.42	0.11	1.56	0.51	0.13	2.01	1.00	0.17	5.76
Both FGA and SGA (base = only FGA)	0.48	0.11	2.08	0.47	0.10	2.42	0.69	0.09	5.23
Antipsychotic DDD	1.12	0.84	1.48	1.13	0.84	1.53	0.97	0.66	1.45
Depot use (base= no)	2.15	0.90	5.17	2.14	0.85	5.40	1.65	0.47	5.81
Number of tremor inducing medications	2.23*	1.10	4.52	1.83	0.86	3.92	4.54***	1.90	10.86
Number of tremor reducing medications	0.71	0.09	5.76	0.45	0.05	4.21	5.94	0.63	55.94
Anticholinergic load	0.99	0.85	1.16	0.97	0.82	1.15	1.15	0.93	1.42

Abbreviations: CI: 95% confidence interval, DDD: Defined Daily Dose, OR: odds ratio, FGA: First Generation Antipsychotic, SGA Second Generation Antipsychotic
* $p<0.05$ ** $p<0.01$ *** $p<0.001$

Time-lagged regression analysis

The results of the time-lagged analyses are described in Table 3. For the combined tremor analysis, previous combined tremor (OR 7.87) and previous tremor severity (OR 1.20 per point on the UPDRS) were significantly associated with current tremor. Of the medication variables, previous higher anticholinergic load was associated with more tremor (OR 1.19), whereas previous depot medication (OR 0.29) was associated with less tremor.

In the tremor RT and AT subtype analysis only previous tremor severity was significantly associated with both subtypes. RT was strongly associated with previous RT (OR 9.86), but previous AT was not significantly associated with previous AT (OR 0.24). Medication variables also had different effects on resting and action tremors compared to the combined tremor. Previous number of tremor-reducing medications (OR 0.08 per medication) was negatively associated with AT at the next time point. Previous depot medication did not predict either type of tremor subtype however the effect size for RT (0.33) was similar to the effect size for the combined tremor outcome (0.29).

Table 3: Time-lagged relationship between covariates and tremor subtypes in psychiatric patients with Severe Mental illness, 18 year follow-up data

	All Tremor			Rest Tremor			Action Tremor		
	OR	95% CI		OR	95% CI		OR	95% CI	
Having tremor at the previous time point	7.87***	3.45	17.94	9.86***	3.80	25.63	0.24	0.03	1.96
Severity of tremor	1.20***	1.08	1.34	1.22**	1.05	1.41	2.62***	1.64	4.18
Medication variables									
Change in benzodiazepine dose	0.90	0.68	1.28	0.72	0.48	1.08	1.59	0.91	2.79
Change in antipsychotic dose	0.88	0.67	1.14	0.91	0.69	1.20	0.98	0.68	1.43
Switching antipsychotics	0.84	0.38	1.89	0.70	0.29	1.68	0.79	0.21	2.98
Getting depot medication	0.29*	0.09	0.94	0.33	0.10	1.09	0.89	0.14	5.52
Stopping depot medication	1.97	0.60	6.50	2.04	0.60	6.94	1.90	0.29	12.32
Number of tremor inducing medications	0.56	0.30	1.06	0.67	0.34	1.34	0.45	0.17	1.18
Number of tremor reducing medications	0.27	0.04	1.71	0.63	0.11	3.72	0.08*	0.01	0.55
Anticholinergic load	1.19*	1.04	1.37	1.24**	1.08	1.43	1.10	0.88	1.38

Abbreviations: CI: 95% confidence interval, DDD: Defined Daily Dose, OR: odds ratio, FGA: First Generation Antipsychotic, SGA Second Generation Antipsychotic
* $p<0.05$ ** $p<0.01$ *** $p<0.001$

Discussion

To our knowledge this is the first long-term follow-up study on medication-induced tremor in SMI patients, which demonstrates that tremor is a frequently occurring relapsing-remitting disorder with over a third of patients having tremor at least once during the eighteen years of the follow-up. In two thirds of the SMI patients tremors were present at the next assessment with the more severe tremor forms being more likely to be present at the next time point. The importance of the distinction in RT and AT should be noted, as each tremor type is associated with different medication and demographic variables. Tremor is highly noticeable and is often associated with shame, stigma, and physical handicap, active assessment, treatment and prevention of tremor is therefore of great clinical importance (2,3).

Since most previous studies used a cross-sectional model and did not focus on the vulnerable subgroup of SMI patients, it is difficult to compare prevalence rates. Bakker et al. (7) found an average of 20% for combined tremor prevalence and a prevalence of 14% and 16% for RT and AT respectively. The higher AT prevalence could be attributed to a different composition of the population. In the study by Bakker et al. 13.5% of patients had an affective disorder as primary diagnosis, in contrast to only 5.1% of patients in the current study. While Bakker et al. did not collect data on antidepressant and lithium use, both medications known to induce AT, it is to be expected that they would be prescribed more frequently than in the current study.

The relapsing-remitting course of both tremor subtypes indicates that environmental factors, such as medication or cocaine use, play an important role in the development and cessation of tremor. The relationship between age and RT is in line with

previous research (3). The association between cocaine use and both tremor types has been described before (2),(3), whereas the association between sex and parkinsonism is found inconsistently (12).

The risk factor analysis in the current study further underline the difference between RT and AT by their difference in association with other movement disorders. As RT is part of the parkinsonism triad (RT, bradykinesia, and rigidity) (6), it is associated with bradykinesia as expected. However, RT was not associated with rigidity, even though the relationship between drug-induced parkinsonism and rigidity has been extensively described (12),(23). This could be in line with the subdivision of Parkinson's disease in a tremor-dominant and rigidity-gait disturbance subtypes, which have different underlying neuropathological mechanisms (24).

There was also a significant association between AT and bradykinesia. Medication-induced parkinsonism can sometimes present with postural action rather than RT (12) and with more severe tremors it is sometimes difficult to differentiate between the tremor types (4). Dyskinesia on the other hand was solely and inversely associated with RT as described in other studies (25) and is sometimes suggested that parkinsonism and dyskinesia are at the other ends of the spectrum of basal ganglia disorders (6)

AT was associated with medication, other than antipsychotics, known to induce tremor, as has been extensively described in the literature(2),(3). However, no relationship was found between RT and antipsychotic type or dose, even though antipsychotic medication is considered a primary cause for drug-induced parkinsonism (12),(23). The most likely explanation is that the effect of antipsychotic dose on tremor is obscured due to the high doses of antipsychotics most patients receive. .

The time-lagged analysis was added to ascertain if there was the temporal relationship between adapting medication and a subsequent change in tremor status. This temporal relationship is one of the Bradford Hill guidelines (26) and is an argument for causality. The fact that there seems to be a strong relationship (OR 0.08) between adding a beta-blocker and the cessation AT makes it highly likely that there is a causal relationship highly likely. The time-lagged models also showed a strong association between previous tremor severity and previous tremor. There was also a relationship between any type of tremor and receiving depot medication. Because this relationship could not be replicated in the tremor subtypes it is possible that this relationship is spurious. It is also possible that the small number of depot changes has left this variable underpowered.

Surprisingly, a higher anticholinergic load led to a higher risk of tremor in the following assessment, for which different explanations could be given. Firstly, clinicians might treat the parkinsonism spectrum of bradykinesia and RT (12) with an anticholinergic high enough to reduce bradykinesia but not to reduce RT, owing to anticholinergic side effects, such as a dry mouth, constipation, cognitive problems. Secondly, anticholinergics may not be entirely effective in treating RT in SMI patients. Mena et al.(23), Caroff et al (27)and Dayalu et al.(28) noted the paucity of evidence supporting

anticholinergic treatment of drug-induced parkinsonism. Mena et al. even stated that there is little rational for it.

Strengths

The inclusion of all inpatients (and outpatient clinic treatment patients) of a restricted area reduces selection bias. Second, the long follow-up period of eighteen years with eight assessments over time increases the validity of the findings. Third, loss to follow-up, which mainly was by death, was limited, further reducing selection bias. Last, all measurements were done by the same two raters, both psychiatrists specialising in movement disorders (PvH and GM), increasing the reliability.

Limitations

The study population was already ill and taking antipsychotics for, on average, 20 years before inclusion. For an incidence study it would be more appropriate to include a population with no history of psychopharmacology. Prevalence and risk factors for persistence, as described in this article, may be more suitable to describe a relapsing remitting disorder such as tremor in a SMI population. Secondly, the UPDRS does not really provide an in-depth examination of tremor, as it focuses on parkinsonism symptoms as a whole. For this study a rating scale focussing solely on tremor would have been better suited. However, the UPDRS is a valid and reliable rating scale that measure each of the three core symptoms of parkinsonism, bradykinesia, rigidity and tremor. Thirdly, it may be argued that a slight (score 1, range 0-5) rest tremor is already abnormal and the cut off for RT should therefore be lowered from mild (score 2) to slight. We examined the results of lowering the cut off in a post-hoc analysis and found that this resulted in more extreme odds ratio's and lower p-values for the variables in the risk analysis. In the time –lagged analysis the same occurred for previous tremor status and previous tremor severity. However the relationship between anticholinergic load and rest tremor now has a p-value of 0.51 making it non significant. Also essential tremor was not an exclusion criteria for the study as in the time-lagged analysis design patients are their own controls and a pre-existing tremor should not influence results. When the analyses are redone excluding the 4 patients who had a pre-existing ATresults are nearly identical. Finally it would have been preferable to ascertain cocaine use not only via medical records but also via urine toxicology and to also register patient alcohol use.

In conclusion medication-induced tremor is a frequently occurring relapsing-remitting disorder with serious adverse effects for patients. For clinicians it is important to differentiate between postural action and RTs as both are caused by different types of medication and require different treatment.

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Chapter 4

Movement disorders and mortality in severely mentally ill patients

The Curacao Extrapyramidal Syndromes Study XIV

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Abstract

There is a substantial gap in life expectancy between patients with severe mental illness (SMI) and the general population and it is important to understand which factors contribute to this. Research suggests an association between tardive dyskinesia (TD) and mortality but results are inconclusive, while few studies have investigated parkinsonism and akathisia and survival. We studied a cohort of 158 patients with predominantly schizophrenia on the Island of Curacao. TD, parkinsonism, and akathisia were assessed with rating scales on eight occasions over a period of 18 years. 24 years after baseline, survival status was assessed. Associations between movement disorders (MD) and survival were calculated using Cox regression. Sex, age, diagnosis, use of cocaine at baseline and use of antipsychotics, antidepressants and benzodiazepines per measurement were used as covariates. Parkinsonism was a significant risk factor with an HR of 1.02 per point on the motor part of the Unified Parkinson's Disease Rating Scale. TD and akathisia were not significantly associated with mortality. In conclusion, parkinsonism may be an important risk factor for mortality in SMI patients and our findings warrants further study into this association.

Patients with severe mental illness (SMI) are at an increased risk of early death in comparison with the general population(1,2). SMI patients are those with the most severe psychiatric disorders as the most common definition requires them to require consecutive treatment of at least two years and to have a Global Assessment of Functioning (GAF) of 50 or lower(3). In schizophrenia and bipolar disorder, diagnoses frequently found in SMI populations, standardized mortality rates of 2 – 3 have been found(4,5), leading to a reduced life expectancy of 12 – 25 and 8.5 – 14 years(4,6-8), respectively.

Besides major life style related problems such as smoking, little physical activity and unhealthy diet(9), and problems with access to and quality of physical healthcare(10), movement disorders (MD) may also play a role in shortening the lifespan of SMI patients(11,12).

In non-affective psychoses reported MD prevalence ranges from 3% to 70% for tardive dyskinesia (TD), from 17% to 72% for parkinsonism and from 9.3% to 31.3% for akathisia(13). MD are induced by antipsychotics, but also reflect a fundamental aspect of neurodevelopmental pathophysiology involving the sensitization of dopaminergic nigrostriatal circuits(14).

Several studies suggest that MD are a risk factor for mortality. Some authors found higher mortality rates in SMI patients with TD than in patients without TD(11,12,15-17) but others reported negative findings(18-21). While TD has often been studied in relation to mortality(11,12,15-23), there is a paucity of research on parkinsonism and akathisia and studies rarely investigate more than one MD(21). Because of the high prevalence of MD and the importance of understanding which factors contribute to the shortened lifespan of patients with SMI, we used data of the Curacao Extrapyramidal Syndromes Study in which we assessed the association of MD with mortality. The Curacao Extrapyramidal Syndromes Study comprises a 24-year follow-up study in which all patients with SMI on the island of Curacao were repeatedly assessed for the presence and severity of MD since 1992(24-28). In the present study we investigate if TD, parkinsonism and akathisia are associated with mortality in a sample of 158 mainly African Caribbean patients.

Method

Setting and patients

The present study is part of the Curacao Extrapyramidal Syndromes Study. Patients of the only psychiatric hospital of the island of Curacao, the dr. D. R. Capriles clinic, were assessed 8 times over the course of an 18 years period for both MD and medication use. The study protocol was approved by the Curacao institutional review board.

Inclusion criteria for the present study were: 1) age of 18 years or older; 2) cumulative history of antipsychotic use of at least three months. Current use of antipsychotics was not required; 3) absence of organic disorders that could cause MD; 4) no diagnosis of dementia 5) no history of lobotomy 6) informed consent.

Patients were mainly of Afro-Caribbean descent and the majority were inpatients. Characteristics of the study design and the cohort are described in more detail in an earlier publication[24].

Measurements

Patients were assessed in 1992, 1993, 1994, 1996, 1997, 1998, 2001, and 2009 for TD, parkinsonism, akathisia and dystonia. All eight assessments were carried out by the same two skilled raters (PvH and GM) simultaneously. TD was assessed with the Abnormal Involuntary Movement Scale (AIMS)(29) and case definition was based on Schooler and Kane criteria for probable TD(30). The motor examination part of the Unified Parkinson's Disease Rating Scale (UPDRS)(31) was used to assess parkinsonism. Since rest-tremor and rigidity are core symptoms of parkinsonism, cases were assigned to the parkinsonism group when they scored 'mild' on one of those two items. If neither tremor nor rigidity was present, the cut-off point was at least one 'moderate' or two 'mild' scores on the other items(24). Akathisia was rated with the Barnes Akathisia Rating Scale (BARS)(32) and a patient was considered a case when a score of 2 or higher on item 4 was given.

At baseline and at each follow-up assessment, a trained physician collected current medication use. Guided by previous research, at baseline variables possibly affecting risk were extracted from patients' files including age, sex, DSM II-R diagnosis (schizophrenia or other, where schizophrenia included codes 295.1, 295.2, 295.3, 295.4, 295.6, 296.7 and 295.9), and cocaine use (yes/no).

On the first of April 2016, all cause mortality was investigated using the patient's charts and the mortality register of Curacao.

Data analysis

The relationship between MD and mortality was analyzed using a multilevel Cox regression with the measurement occasion (baseline and 7 follow-ups) as level 1, and subjects as level 2, with the STCOX robust procedure of the STATA 13 statistical program (StataCorp. 2009). Mortality data of each deceased subject were appended to the dataset. Associations were expressed as hazard ratios and proportional-hazard assumptions were tested using the Stata stcox PH assumption tests module.

The total score of the AIMS, the motor part of the UPDRS and the score of item 4 of the BARS per assessment were included as continuous time-varying variables, as were type of antipsychotic (only first generation antipsychotic (FGA)/only second generation antipsychotic (SGA)/both FGA and SGA, dose in defined daily dose

(DDD)(33) of antipsychotic, benzodiazepine, and antidepressant were used as covariates. Age, sex, diagnosis (schizophrenia or other), cocaine use (yes/no, based on the first measurement), were included as time-independent variables. Extra-linearity was assessed by including quadratic effects for all continuous independent variables . In case of non-linearity ($p<0.05$ of the quadratic term), the quadratic term remained in the final model. (Cleves, 2008).

Results

Description of the sample

The original dataset of the Curacao Extrapyramidal Syndromes Study consisted of 222 patients. For the current study, patients who had undergone a lobotomy (N=23), who had a diagnosis of dementia (N=13) or a primary diagnosis of mental retardation (N=3) where excluded as not being representative of current SMI populations, leading to a dataset of 183 patients. 25 patients could not be analyzed due missing data. Therefore data of 158 patients were used for analyses with Cox proportional hazards regression.

Table 1 shows the demographic and clinical characteristics of the sample at baseline.

In table 2, medication use, and prevalence and severity of MD per assessment are presented. Of the 158 included in the Cox regression 86 patients (57%) died during follow-up. Mean age of death was 68.2 years (sd 15.0, range 34 – 94).

Table 1: Sample characteristics at baseline

Characteristics	n = 144* mean (SD)
Age at baseline	50.5 (15.4)
Age at first admission	26.2 (10.1)
	N (%)
Male	103 (71.5)
Ethnicity	
African-Caribbean	104 (72.2)
Mixed	32 (22.2)
Caucasian	6 (4.2)
Other	2 (1.4)
Primary diagnosis schizophrenia	120 (83.3)
Cocaine abuse	24 (16.7)

*Patients with missing values for ethnicity and age at first admission (not included in analysis) excluded from the table.

Table 2: Time varying sample characteristics

Measurement number Year	Baseline 1992 (n = 144)	T1 1993 (n = 115)	T2 1994 (n = 107)	T3 1996 (n = 95)	T4 1997 (n = 92)	T5 1998 (n = 86)	T6 2001 (n = 95)	T7 2009 (n = 71)
Mean age (SD)	50.5 (15.4)	52.8 (15.1)	52.1 (13.7)	54.0 (13.5)	53.1 (12.9)	54.2 (12.8)	56.3 (12.7)	62.3 (10.7)
Medication								
Antipsychotics								
FGA only, n (%)	131 (91.0)	95 (82.6)	93 (86.9)	81 (85.3)	76 (82.6)	69 (80.2)	65 (68.4)	33 (46.5)
SGA only, n (%)	0	9 (7.8)	7 (6.5)	9 (9.5)	12 (13.0)	10 (11.6)	13 (13.7)	13 (18.3)
Combination FGA and SGA n (%)	0	0	0	0	0	1 (1.2)	11 (11.6)	19 (26.8)
No antipsychotic, n (%)	13 (9.0)	11(9.6)	7 (6.5)	5 (5.3)	4 (4.3)	6 (7.0)	6 (6.3)	6 (8.5)
DDD antipsychotics*, mean (SD)	1.8 (1.5)	1.8 (1.4)	2.0 (1.3)	2.0 (1.6)	2.1 (1.5)	2.3 (1.7)	2.1 (1.6)	2.4 (1.4)
Antidepressants, n (%)	9 (6.3)	9 (7.8)	9 (8.4)	10 (10.5)	7 (7.6)	3 (3.5)	9 (9.5)	4 (5.6)
DDD antidepressants*, mean (SD)	0.9 (0.4)	0.8 (0.4)	0.9 (0.3)	0.9 (0.4)	0.8 (0.3)	0.9 (0.3)	1.1 (0.3)	1.3 (0.5)
Benzodiazepines, n (%)	28 (19.4)	26 (22.6)	31 (29.0)	32 (33.7)	33 (35.9)	36 (41.9)	47 (49.5)	36 (50.7)
DDD benzodiazepines*, mean (SD)	1.4 (1.0)	1.3 (1.0)	1.0 (0.7)	1.0 (0.8)	1.2 (1.1)	1.3 (1.2)	1.2 (1.0)	1.3 (1.0)
Movement disorders								
Tardive dyskinesia, cases (%)	52 (36.1)	60 (52.2)	67 (62.6)	57 (60.0)	50 (54.3)	44 (51.2)	54 (56.8)	37 (52.1)
AIMS Mean (SD) cases	7.4 (3.1)	7.8 (2.7)	9.6 (4.3)	9.6 (4.0)	9.2 (3.8)	9.1 (3.9)	9.9 (4.2)	8.7 (3.0)
Parkinsonism, cases (%)	55 (38.2)	47 (40.9)	35 (32.7)	34 (35.8)	27 (29.3)	25 (29.1)	35 (36.8)	23 (32.4)
UPDRS Mean (SD) cases	19.3 (9.8)	18.1 (11.9)	19.0 (10.8)	21.5 (9.5)	22.0 (10.3)	21.6 (12.1)	20.2 (12.1)	15.8 (12.2)
Akathisia, cases (%)	16 (11.1)	9 (7.8)	12 (11.2)	7 (7.4)	1 (1.2)	5 (5.8)	4 (4.2)	1 (1.4)
BARS Mean (SD) cases	2.6 (0.8)	2.7 (0.7)	2.8 (0.6)	2.6 (0.8)	3.0	2.6 (0.5)	2.8 (1.0)	3.0

T: time point; FGA: first generations antipsychotic; SGA: second generation antipsychotic; AIMS: Abnormal Involuntary Movement Scale; UPDRS: Unified Parkinson Disease Rating Scale; BARS: Barnes Akathisia Rating Scale

*Means and SDs for DDD for users of the respective medications are given.

Cox regression

Hazard ratios (HR) and significance for the variables in the final model are presented in Table 3. Sex, diagnosis and cocaine use at baseline did not show a significant relation with mortality.
Parkinsonism was positively associated with mortality (HR =1.02, 95% CI 1.005 - 1.038, p = 0.011). Effects for TD and akathisia were not significant.
Type of antipsychotic did not show a significant association with mortality and neither did total dose of benzodiazepine nor total dose of antidepressant. Total dose of antipsychotic was significant both as a linear and as quadratic predictor (more details are available upon request).

Table 3: Final Cox proportional hazards model

Variable	Hazard Ratio	SE	z	P>|z|	95% Confidence interval
Sex	1.39	0.37	1.23	0.219	0.82 - 2.33
Diagnosis	1.14	0.31	0.47	0.640	0.66 - 1.95
Age	0.99	0.02	-0.71	0.475	0.96 - 1.02
Age squared	1.001	0.001	1.65	0.099	1.000 - 1.003
Cocaine use	0.53	0.21	-1.59	0.112	0.24 - 1.16
Dyskinesia	0.96	0.03	-1.47	0.141	0.91 - 1.01
Parkinsonism	1.02	0.01	2.56	0.011*	1.005 - 1.038
Akathisia	1.24	0.27	0.98	0.328	0.81 - 1.89
DDD antipsychotics	0.67	0.10	-2.75	0.006**	0.50 - 0.89
DDD antipsychotics squared	1.20	0.08	2.83	0.005**	1.06 - 1.36
FGA only	1.38	0.51	0.87	0.386	0.67 - 2.86
SGA only	0.73	0.37	-0.61	0.539	0.27 - 2.00
Both FGA and SGA	0.92	0.63	-0.12	0.901	0.24 - 3.56
DDD benzodiazepines	0.73	0.15	-1.57	0.116	0.50 - 1.08
DDD antidepressants	0.81	0.26	-0.66	0.512	0.43 - 1.52

Discussion

Our findings indicated that parkinsonism was a significant risk factor for mortality whereas TD and akathisia were not.

For parkinsonism, one point increase on the motor examination part of the UPDRS was associated with a 2% increase in the risk of death. The motor part of the UPDRS consist of 14 items which can be scored 0-4 leading to a range of possible scores of 0 – 56. For a patient with score of 50, the HR will be twice as for a patient with a score of 0. Therefore, a 2% increase in risk of death per point can be considered substantial. Previous studies on the relation MD and mortality in SMI focused on TD(2-10) while only two studies also included parkinsonism (19,29). Modestin and colleagues(19) found in 200 psychiatric patients treated with antipsychotic medication

after 9 years follow-up a higher mortality rate in patients with parkinsonism than without. However, after adjustment only age remained as a significant risk factor. There were, however some limitations compared with the current study, given the fact that this study (I) assessed MD only at baseline (ii) had half of the follow-up time. Assessing MD only at one time point is a major flaw given the fluctuating nature of MD[34]. Measuring MD multiple at multiple time points, as we did in the current study, is therefore a more valid designs to address this research question. A retrospective study by Schoepf and colleagues (2014) examined deaths in schizophrenia patients in general hospitals in relation to physical comorbidity. The authors found that the presence of parkinsonism was associated with an odds ratio of 5.0 for hospital mortality which can be considered a very strong effect. However, regarding parkinsonism, the study had serious design flaws, the most important of which was that no formal rating scales were used. The resulting lack of validity of the diagnoses of parkinsonism makes the findings difficult to interpret.

Outside the field of psychiatry, two studies reported an association between parkinsonism and mortality in people aged 65 and over(30,31). (i) in a community sample the presence of parkinsonism was associated with a two fold increase in the risk of death(30) and gait disturbance in particular heightened the risk (ii) in a mixed sample of patients with Alzheimer's disease and subjects without dementia, parkinsonism was a risk factor for mortality in the total sample, the subgroup of patients with Alzheimer's Disease, and in the subjects without dementia. Interestingly, the latter study focused on spontaneous parkinsonism as subjects receiving parkinsonism-inducing medication were excluded which suggest that, next to drug-induced, also spontaneous parkinsonism may be a risk factor. Taken together with the current study, it can be hypothesized that parkinsonism is an independent predictor of all cause mortality.

It is not directly clear how parkinsonism itself increases mortality risk, but parkinsonism is related to several other factors associated with mortality such as a higher rate of fall incidents. Also it could be hypothesized that the relationship is more indirect and based on the well known relationship between both spontaneous(35-36) and drug-induced parkinsonism(37) and cognitive impairments. Indeed, cognitive deficits are related to unhealthy life style or less awareness of physical problems and/or access to physical healthcare.

Given the high prevalence of parkinsonism in SMI and several studies suggesting that parkinsonism may lead to shorter survival, it is important for this relation to be further explored, e.g. would reducing parkinsonism also increase survival?

TD was not significantly associated with risk of death. Previous studies have reported inconsistent results. Four of eleven studies reported an association between TD and mortality(12,15-17), two reported a trend(22,23), and five no association(18-21,23). In 2000, a meta-analysis by Ballesteros and colleagues consisting of seven studies demonstrated a significant overall OR of 1.4(11). However, some of the studies included suffered from methodological flaws, such as small sample sizes(18,19), fewer than five years follow-up(3,4,6,8) and not controlling for known confounders such as

antipsychotic dose(15-17,19,22). In 2009, three additional studies on the association of TD and mortality were published using the more sophisticated Cox and logistic regression analyses, which are better suited to this type of data(12,20,21).: (i) Dean and Thuras (20) used multiple measurements of TD - although they only identified patients with TD at baseline or TD at any time instead of entering TD as a time varying covariate - and found a significant association between TD and mortality, which disappeared after adjusting for age and antipsychotic drug use; (ii) Modestin and colleagues (19) did not find an association; and (iii) Chong et al (12) found an age- and antipsychotic dose-adjusted association with a HR of 1.38 for mild and 1.90 for definite TD which - considering the dose response effect, represents relatively strong evidence in favor of a real effect of TD on mortality. However they did not include other MDs and had a relatively short study duration.

Evidence shows that severity of TD is positively correlated with symptom severity in schizophrenia(38) which may therefore be a confounding factor in the correlation between TD and survival. However, none of the studies up to now controlled for symptom severity.

Akathisia did not show a significant association with mortality which is consistent with a previous study(21).

In light of all the findings so far, we think the evidence with regard to both TD and parkinsonism is still inconclusive and large well controlled studies with multiple measurements over time with regard to both MD, use of psychotropic medication, symptom severity and cognitive functioning are needed to gain insight into this subject.

A major strength of our study was the use of multiple measurements of MD as time varying covariates, allowing for more precise modelling than earlier studies. This is especially important given the fluctuating nature of MD in SMI patients(34). Moreover our follow-up period of 24 years is the longest up to now.

Limitations of the study were that, like previous studies, we had no measures of cognitive functioning and symptom severity which may have a association with MD.

Conclusion

In conclusion, parkinsonism was a significant risk factor for mortality in a cohort of patients with SMI. TD and akathisia were not related to mortality. Given the contradictory findings with regard to the association of TD and mortality and the present findings that parkinsonism may be a risk factor we argue that large well controlled studies on the association of MD and mortality are needed.

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Chapter 5

Blink rate is associated with drug-induced parkinsonism in patients with severe mental illness, but does not meet requirements to serve as a clinical test

The Curacao extrapyramidal syndromes study XIII

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Abstract

Background: Drug-induced parkinsonism (DIP) has a high prevalence and is associated with poorer quality of life. To find a practical clinical tool to assess DIP in patients with severe mental illness (SMI), the association between blink rate and drug-induced parkinsonism (DIP) was assessed.

Methods: In a cohort of 204 SMI patients receiving care from the only mental health service of the previous Dutch Antilles, blink rate per minute during conversation was assessed by an additional trained movement disorder specialist. DIP was rated on the Unified Parkinson's Disease Rating Scale (UPDRS) in 878 assessments over a period of 18 years. Diagnostic values of blink rate were calculated.

Results: DIP prevalence was 36%, average blink rate was 14 (standard deviation (SD) 11) for patients with DIP, and 19 (SD 14) for patients without. There was a significant association between blink rate and DIP ($p<0.001$). With a blink rate cut-off of 20 blinks per minute, sensitivity was 77% and specificity was 38%. A 10% percentile cut-off model resulted in an area under the ROC curve of 0.61. A logistic prediction model between dichotomous DIP and continuous blink rate per minute an area under the ROC curve of 0.70.

Conclusions: There is a significant association between blink rate and DIP as diagnosed on the UPDRS. However, blink rate sensitivity and specificity with regard to DIP are too low to replace clinical rating scales in routine psychiatric practice.

Drug-induced parkinsonism (DIP) prevalence in patients with severe mental illness (SMI) varies between 36% (1) and 56%(2), and is associated with a poorer quality of life(3), falls (4) and antipsychotic non-compliance (5). However, DIP is poorly recognized and both DIP and Parkinson's disease (PD) rating scales requiring lengthy training sessions are difficult to implement, hence rating scales are not suitable for clinical practice (6). Therefore, simple and easy to use diagnostic methods for DIP are warranted. Diagnostic methods based on blink rate as a clinical test for diagnosing DIP would be a good measure because: (i) the assessment of blink rate during conversation is easy and quick, (ii) requires no specialized equipment, (iii) has a high interrater reliability (7), and (iv) research in PD has shown that reduced blink rate during conversation discriminates well between PD and healthy controls when compared to the Unified Parkinson's Disease Rating Scale (UPDRS) (8). Blink rate may be easily measured with the use of mobile apps, thus enabling clinicians to diagnose DIP.

D2-receptor involvement has been linked consistently to spontaneous blink rate, both in human and animal experiments (9). In their 1990 seminal paper, Karson et al. (7) conclude that blinks are most likely generated in the pontine reticular formation and signals are then transmitted to the lateral geniculate bodies. Since this publication, to our knowledge, only three articles examining blink rate in schizophrenia have been published. These studies linked blink rate to various neurological soft signs (NSS) in patients (10–12) however no association between blink rate and central dopaminergic activity was found in healthy controls(9). While several studies indicate that blink rate is a good clinical test for the diagnosis of PD, as far as we know, no such study has been published on the use of blink rate as a clinical test for DIP in patients with severe mental illness (SMI) .

The present paper aims to assess (i) the association between DIP and blink rate, and (ii) the possibilities of using blink rate as a clinical test to diagnose DIP with the UPDRS (1,13) as gold standard. As the goal of the paper is to develop a clinical test to differentiate between SMI patients with DIP and SMI patients without DIP, patients were compared to other patients and no healthy control group was used.

Methods

Subjects

All 204 patients hospitalized or receiving structured outpatient care from the Dr. D.R. Capriles Clinic, the only psychiatric hospital in the Dutch Antilles, in 1991 were asked to take part in the Curacao extra pyramidal syndromes study, an 18 year (1993, 1994, 1996, 1997, 1998, 2001 and 2009) prospective naturalistic follow-up study. Informed consent was obtained from all patients and the protocol was approved by the Curaçao

Institutional Review Board. A total of 8 assessments focusing on movement disorders and medication use were performed over the 18 years follow-up. A detailed description of the patients and assessments has been published previously (1).

Inclusion criteria were a minimum age of 18 years, and cumulative exposure to antipsychotics of at least 3 months; current antipsychotic use was not required. Exclusion criteria were a history of neurological disorders affecting motor function, including PD, and having undergone a lobotomy. Patients with dementia (N=7) or mental retardation (N=3) as primary diagnosis were excluded. The total number of patients was 191 and the dataset is available from the corresponding author upon request.

Assessments

The UPDRS version 3.0 was used to define DIP (13). Blink rate per minute was assessed for one minute during conversation at each measurement (N=878) by one author with a stopwatch while the other author conducted the interview (PvH and GM), a more detailed description of the test has been published previously (1). Both raters are psychiatrists specialized in movement disorders. They were blind to the UPDRS score while blink rate was being assessed and vice versa. An exact description of the test circumstances can be found in a previous publication (1). DIP was defined as (i) a score of at least 'moderate' (score 3, range 0-4) on one of the bradykinesia items (1, (2), 6-14) or two or more scores of 'mild' (score 2) on these items; (ii) a rigidity (item 3) or tremor (item 4-5) score of at least 'mild'. The more stringent criteria used for bradykinesia were chosen as motor slowness can also be caused by mental symptoms or medication. Time points on which the patient scored 'mild' or higher on the blepharospasm item on the Burke Fahn Marsden Dystonia Rating Scale (BFMDRS) were excluded (N=54), as blepharospasm can cause involuntary contractions in the eyelid and hence can be misclassified as blink-related DIP. The BFMDRS was also scored at all of the time points by the same raters (PvH and GM). DSM-III-R diagnosis and demographic variables (age, sex, diagnosis, and antipsychotic type and dose), were extracted from the case file by a trained physician.

Statistical analyses

Analyses were carried out with Stata, version 12 (14). Blink rate per minute was (i) used as a continuous variable, (ii) dichotomized using a cut-off point of 20 blinks per minute, as suggested by Fitzpatrick et al (8), and (iii) as 10% percentile cut-offs (hereafter: continuous and dichotomous blink rate, and 10% percentile blink rates, respectively). Using both dichotomous blink rate and 10% percentile blink rates we calculated: (i) sensitivity and specificity using the roctab (nonparametric ROC analysis) command; (ii) positive predictive value (PPV) and negative predictive value (NPV) using the diagt (summary statistics for diagnostic tests compared to true disease status) command. The association between blink rate and DIP as a continuous variable was calculated using

the regress (linear regression) command. Areas under the ROC curves were calculated: (i) for the 10% percentile blink rate using the roctab command, and (ii) for the continuous blink rate per minute using the lroc (computes area under ROC curve and graph the curve)command based on the logistic prediction model using the logit (logistic regression, reporting coefficients) command, with DIP as a dichotomous dependent variable and continuous blink rate, age, sex, diagnosis (schizophrenia or other) and antipsychotic defined daily dose (DDD)(15) and type as independent variables.

Results

A total of 878 assessments in 191 patients were available for analysis. All patients provided written informed consent. Of the sample, 72% was male, 95% was of African-Caribbean origin and 84% had a DSM-III-R diagnosis of schizophrenia. The mean age was 53 years with a standard deviation (SD) of 15 years, DIP prevalence according to the gold standard was 36% (317 instances in 890 measurements, mean severity 20 points on the UPDRS, SD 12), DIP persisted to the next time point in 65% of cases. Mean blink rate was 14 (SD 11) for patients with DIP, and 19 (SD 14) for patients without DIP.

For the dichotomous blink rate, sensitivity (the test's ability to correctly designate a subject with the disease as positive) was 77%, specificity (the test's ability to correctly designate a subject without the disease as negative) 38%, PPV 41% (meaning there is a 41% probability that if a patient's blink rate is below 20 blinks per minute that patient does indeed have DIP), and NPV 74.5 % (meaning there is a 74.5% probability that if a patients blink rate is higher than 20 blinks per minute, the patient does not have DIP)(Table 1). For the 10% percentile blink rates sensitivity, specificity, PPV and NPV are reported in Table 1. The area under the ROC curve was 0.61 (Figure 1).

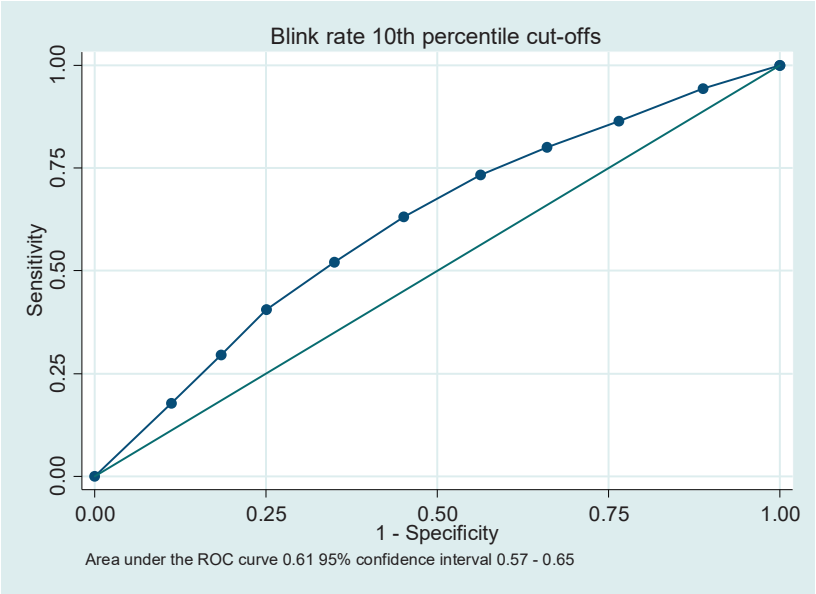

Figure 1: Receiver operated curves (ROC) for blink rate as a diagnostic tool for drug-induced parkinsonism using 10th percentile cut offs

Table 1: Sensitivity, specificity and positive and negative predictive value using a 10TH percentile cut off

Percentile	N	Blink rate per minute	Sensitivity	Specificity	Correctly Classified	PPV	NPV
10th	101	37-87	100.00%	0.00%	36.98%	22%	63%
9th	94	28-36	92.47%	10.98%	41-.11%	25%	62%
8th	97	23-27	85.71%	21.34%	45.15%	25%	60%
7th	120	18-22	76.88%	30.95%	47.93%	26%	58%
6th	108	15-17	68.05%	44.05%	52.93%	27%	57%
5th	65	13-14	58.70%	55.03%	56.39%	29%	56%
4th	105	10-12	52.21%	61.13%	57.83%	31%	54%
3rd	131	7-9	43.12%	71.80%	61.19%	33%	55%
2nd	88	5-6	27.27%	82.47%	62.06%	34%	56%
1st	132	0-4	16.10%	89.33%	62.25%	35%	83%
base		0	0.00%	100.00%	63.02%		

Linear regression yielded significant coefficients between DIP and blink rate (B -0.14, $p < 0.000$) with an R-squared of explained variance of 0.025 or 2.5%. In the logistic regression prediction model adjusted for age, sex, diagnosis, and antipsychotic type and dose, R-squared explained variance was marginally higher at 0.095 or 9.5% (Figure 2 and Table 2). The ROC derived from the prediction model yielded an area under the curve of 0.70, slightly higher than the ROC of the 10th percentile cut-off.

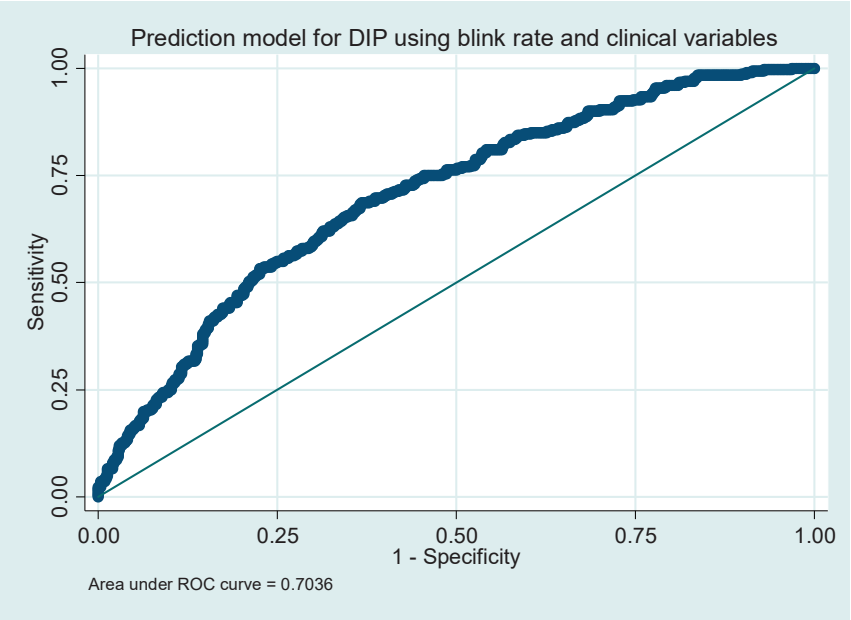

Figure 2: Receiver operated curves (ROC) constructed from the prediction model for drug-induced parkinsonism using blink rate and covariates

Table 2: Prediction model for drug-induced parkinsonism using covariates and continuous blink rate

	Odds Ratio	p-value	95% Confidence interval	
Blink rate per minute	0.97	<0.0000	0.96	0.98
Age	1.04	<0.000	1.03	1.05
Female sex	0.64	0.03	0.44	0.95
Diagnosis other than schizophrenia	1.73	0.01	1.12	2.65
Antipsychotic DDD	1.00	0.96	0.51	0.87
Antipsychotic type				
only FGA	1.83	0.07	0.96	3.50
only SGA	0.62	0.28	0.26	1.47
both FGA and SGA	1.58	0.36	0.60	4.20

Discussion

The association between blink rate and DIP and UPDRS score in patients with SMI is highly significant ($p<0.000$). However, the explained variance of 9.5% of the logistic regression model is too small, and sensitivity and specificity of blink rate are too low for use as a clinical tool in SMI patients. With the most efficient cut-off, only 62% of patients was correctly classified by the blink rate test. Other clinical parameters (that are easily accessible to clinicians) that are known to affect DIP, such as age, diagnosis, and sex, were added to a logistic regression model. The variables displayed significant

associations with DIP, however the explained variance was still too low for the model to be useful in a clinical setting.

The present findings are in contrast with results found in PD. Using the same cut off point of 20 blinks per minute, a meta-analysis (8) reported a sensitivity and specificity of 65% and 83%, respectively, whereas the present study found a sensitivity and specificity of 77% and 38%, respectively. A possible cause for the discrepancy is the greater difference in mean blink rate between patients with PD and healthy controls (18 versus 34 blinks) compared to the difference between SMI patients with and without DIP (14 versus 19 blinks) in the present study. An explanation is that patients with PD and healthy controls are distinct groups, without much overlap, whereas the SMI patients in the present study originate from the same population and have DIP on a continuous scale.

In the present study, SMI patients without DIP showed a lower average blink rate per minute compared to healthy controls from other studies with similar methodology. This is surprising as studies have consistently shown that patients with schizophrenia have a higher average blink rate compared to healthy controls (7,11,12), with a blink rate of 27 for patients with a psychotic disorder and 22-18 for other mental disorders (7). Although this difference is most striking in drug-naive patients with a diagnosis of schizophrenia (7,11,12,16), it is also present in patients treated for schizophrenia (10,12). Furthermore, blink rate is associated with subsets of symptoms such as hallucinations and anxiety (10–12) in patients with a diagnosis of schizophrenia. Associations with neurological soft signs (10,11,16) and antipsychotic dose(16) have been inconsistent. It is likely that blink rate in patients with schizophrenia is influenced by more factors than just DIP. What these factors are and how they relate to the current study population remains unknown. Further investigation into the pathophysiology of abnormal blink rates in patients with a diagnosis of schizophrenia is warranted as it could shed light on underlying disease mechanisms.

Limitations

Due to the naturalistic setting, the well-defined catchment area and the broad inclusion criteria, results from this study are likely to be a good representation of movement disorders in a real world SMI population; Bakker et al(17) found very similar results for medication use and movement disorders in a Dutch population However, there are a number of limitations to the study. First, blink rate varies with context and, therefore, also varies between tests. Although no data on inter-rater reliability was available in this study, both Karson et al. (7) and Fitzpartrick et al. (8) reported good inter-rater reliability and test-retest reliability of blink rate assessment during conversation. However, comparisons with blink rate in other studies that use different tests are difficult. Second, the more stringent criteria for bradykinesia used in the current study to diagnose DIP (2) is not in line with the UK brain bank cut-off for PD (18). However, post-hoc analysis using the UK brain bank cut-off showed highly similar results. Third, the UP-

DRS is the most common tool to diagnose PD and is much more comprehensive than other scales used to measure DIP(19). However, a number of experimental instrumental measurements of both PD (20) and drug-induced bradykinesia (21) are likely more accurate than the UPDRS, hence might result in a more accurate diagnosis of DIP and possibly a higher sensitivity and specificity for blink rate. Fourth, repeated measures over time could result in bias if there were differential attrition. However, post-hoc analyses with only one measurement per patient showed very similar results. Finally, Annamalai et al.(22) found an association between smoking and nicotine in their impact on the dopaminergic system. Unfortunately, in the current study, no data on smoking was available. However, it is very unlikely that adding a smoking variable to the logistic regression model would have a substantial impact on the sensitivity en specificity of the test.

Conclusions

There is a significant association between blink rate and DIP as diagnosed on the UPDRS. Unfortunately, blink rate sensitivity and specificity with regard to these outcomes are too low to replace clinician rating scales in routine practice. However, there is still a need for an easier and more accessible way to diagnose movement disorders in mental health services, as DIP is highly prevalent in SMI patients (1,2,19) and negatively impacts quality of life. DIP is currently under-diagnosed (19–21), as clinical rating scales present a number of problems for use in daily clinical practice (20,21).Therefore, future research and clinical practice into diagnosing DIP may be served by combining blink rate with instrument measurements, e.g. a finger tapping test, a tremor test and/or a reaction speed test. All these measures could be programmed as an app on a mobile device for ease of use. More research needs to be done into the validity of these combinations.

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Chapter 6

Instrumental Assessment of Bradykinesia: a Comparison Between Motor Tasks

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Abstract

Bradykinesia, a common symptom in psychiatry, is characterized by reduced movement speed and amplitude. Monitoring for bradykinesia is important, as it has been associated with reductions in quality of life and medication compliance. Subtle forms of bradykinesia have been associated with treatment response in antipsychotic-naïve first episode patients. Therefore, accurate and reliable assessment is of clinical importance. Several mechanical and electronic instruments have been developed for this purpose. However, their content validity is limited. This study investigated which tasks, or combinations thereof, are most suitable for assessing bradykinesia instrumentally. Eleven motor tasks were assessed using inertial sensors. Their capability of distinguishing bradykinetic patients with schizophrenia (n=6) from healthy controls (n=5) was investigated. Seven tasks significantly discriminated patients from controls. The combination of tasks considered most feasible for the instrumental assessment of bradykinesia was the gait, pronation/supination, leg agility and flexion/extension of elbow tasks (effect size=2.9).

Antipsychotic-induced bradykinesia is associated with physical disability, social stigmatization, lower quality of life and reduced medication compliance (1-4). Bradykinesia expresses itself as a reduction in speed and amplitude of voluntary movement (5). Bradykinesia occurs as a symptom of Parkinson's Disease, drug-induced parkinsonism, depression, negative symptoms of schizophrenia and others. The pathophysiological basis of bradykinesia lies in a dysregulation of the basal ganglia, specifically the pathways involved with the scaling of the amplitude and velocity of movement (5). Dysregulation of these pathways can be a result of psychotic disorders and/or antipsychotic treatment (6).

In first-episode antipsychotic naïve patients with schizophrenia, bradykinesia is a predictor of reduced treatment response (7). Bradykinesia can also debut as a prodrome for psychosis in antipsychotic-naïve Ultra-High Risk (UHR) groups (8). Therefore, accurate assessment of bradykinesia is of clinical and scientific importance. Bradykinesia is typically assessed using observer rated scales, for example the Unified Parkinson's Disease Rating Scale (UPDRS) and the St. Hans Rating Scale For Extrapyramidal Side-Effects (SHRS). However, the assessment of movement disorders using observer rated scales is subjective, has a moderate reliability, and shows a low sensitivity to subtle forms of movement disorders (9-10). Consequently, rating scales are less suitable for both the monitoring of bradykinesia and the detection of subtle prodromal bradykinesia. A logical alternative would be instrumental assessment.

Several objective and reliable instrumental methods of assessing bradykinesia have been developed (8, 11-18). However, they are rarely applied in research and clinical practice, likely due to their cost and ease of use in comparison to rating scales. Nowadays, more affordable and user-friendly motion capture technologies are available (13, 15-17). To assess the severity of bradykinesia instrumental assessments mechanically or electronically capture performances on motor tasks (8, 11-18). These instruments focus on measuring a specific motor task, for example handwriting or spiral drawing. As a result, the scope of these instruments does not cover the entire construct of bradykinesia.

Content validity of instrumental assessments can be improved by assessing a broader selection of motor tasks. As a proof of principle discriminability between patients with bradykinesia and healthy controls was investigated for a wide range of motor tasks. We hypothesized that a suitable selection of tasks should be able to discriminate between these two groups.

Method

Subjects

Power calculations indicated that in order to significantly discriminate between groups, n = 5, an effect size of at least 2.0 is required to ensure a p-value of 0.05 with a power of 0.8. Therefore, we opted to investigate two very distinct populations in order to be able to achieve meaningful results with a small subject population. We recruited six DSM-IV schizophrenic inpatients with antipsychotic-induced bradykinesia from Zon & Schild, a psychiatric hospital in the Netherlands. Criteria for bradykinesia were at least one moderate or two mild scores on the UPDRS bradykinesia items (19). Five healthy controls were recruited from the staff and local community. Criteria for inclusion were age between forty and sixty and male gender, as age and gender affect bradykinesia (20). Considering the scale of this study we opted to investigate a homogeneous population to reduce the risk of a type II error. Exclusion criteria were use of other medication that can induce movement disorders, severe cognitive impairment or mental retardation and injuries or neurological diseases affecting movement.

All subjects provided informed written consent, and the study was approved by the local ethics committee.

Instruments

Subjects' movements were registered using six inertial sensors (MTx, XSENS, Enschede, the Netherlands). In contrast to inertial sensors used in previous studies (12-14), these sensors use a proprietary Kalman filter that combines data from the accelerometer, gyroscope and magnetometer to reduce sensor drift and improve the accuracy of movement registration (21). Sensors were attached to the subjects' dominant upper and lower arm and leg, ring and middle finger and to their sternum using Velcro straps. The sensor secured to the ring and middle finger was only attached during the hand movements task. Exact placement of the sensors is illustrated in Fig. 1. Each sensor connected to an XBUS receiver (XSENS, Enschede), worn around the waist, that registered data and sent it via Bluetooth to a computer running MT software 1.8.1 (XSENS, Enschede, the Netherlands).

Tasks

Repetitive movements are one of the primary clinical measures of bradykinesia. Velocity and amplitude are impaired when performing repetitive motor tasks at high movement rates with large amplitudes (22). Therefore, the selection of tasks primarily existed of repetitive motor tasks. Tasks were derived from existing observer rated scales and instrumental assessments. The following tasks were selected: (1) hand movements, (2) pronation/supination movements of hand, (3) leg agility, (4) arising from chair and

(5) gait tasks from the UPDRS following previous studies (13, 14-15). Tasks selected from other instruments were the (6) Flexion/extension of elbow (19) and small and large (7) tapping and (8) tracing tasks (17). On the tapping and tracing tasks subjects were instructed to repeatedly tap on two lines, 30 and 55 cm apart, and trace circles, 17 and 32 cm in diameter. Patel et al. proposed that the instrumental assessment of bradykinesia could be extended to motor tasks derived from activities of daily living (12). Therefore, the following three tasks were also included: (9) pouring water from a plastic jug into four plastic glasses, (10) repeatedly flipping over a plastic glass and setting it down on the table, and (11) twisting a peppermill (similar to the pronation/supination movements of hand task of the UPDRS). Subjects were instructed to perform tasks with a large amplitude as fast as possible for thirty seconds. Except for the gait, arising from chair and pouring tasks. In these tasks subjects were instructed to walk in their own pace for twenty meters between two markers on the floor spaced five meters apart, arise from their chair and sit back down twice, and pour a marked volume of water into four glasses. Subjects were given thirty seconds to practice each task and two minutes rest between tasks.

Task Outcomes

For each task mean cycle duration, amplitude and velocity were determined. An exception was made for the arising from chair and pouring glass tasks, because they were only performed a couple of times. A linked segment model was built using the sensor output, the sensors absolute orientation as a rotation matrix, in Matlab 2012a (Mathworks), Fig. 1. Segment lengths were corrected for body height (23).

Analysis of hand movements, flexion/extension of elbow, pronation/supination movements of hand, leg agility, flipping glass and peppermill tasks was based on joint angles. These angles were defined as the angle between the sensors proximal and distal to the joint, determined using Euler decomposition and filtered using a low pass bidirectional Butterworth filter. The cut-off frequency was determined by adding 2 Hertz to the frequency with the highest power in the joint angle signal, calculated using Direct Fourier Transformation. Each tasks' average cycle duration, amplitude and velocity were calculated from the joint angle using a peak detection algorithm, where peaks in joint angle were defined as subsequent minima an maxima that are at least one standard deviation apart, see Fig. 1.

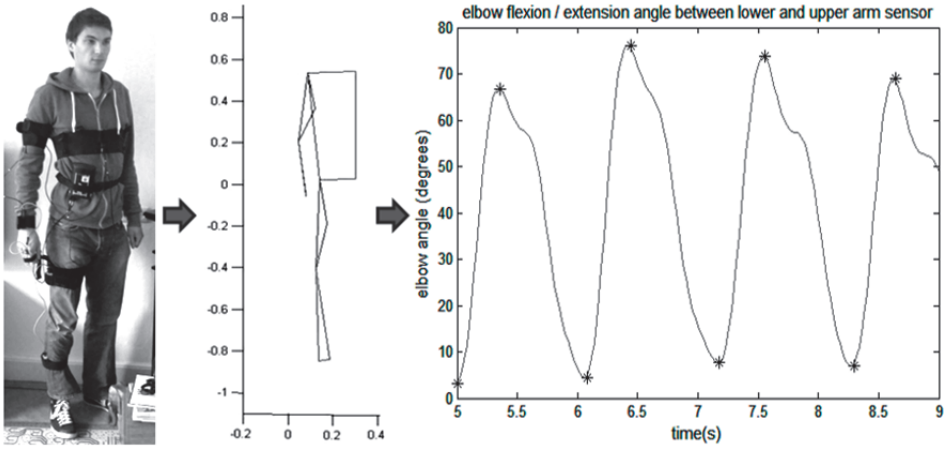

Figure 1: Overview of the instrumental setup and data analysis. Left: Placement of the inertial sensors attached to the index and middle fingers, upper and lower arm and leg, and sternum. Sensors connected to a Bluetooth receiver worn around the waist. Middle: 3D-Model constructed from sensor data. Right: Elbow angle (degrees) plotted against time (seconds) during the flexion/extension task. Asterisks indicate when the elbow is fully extended and flexed, and were used to determine the mean duration, amplitude and velocity of a flexion/extension cycle.

To analyze gait, arising from chair and the small and large tapping and tracing tasks, the positions of either the ankle, torso or wrist were investigated respectively. The linked segment model was used to determine the position of the ankle/wrist relative to the hip/shoulder joint in the transversal plane, the plane parallel to the ground. To analyze arising from the chair the sternum's position was used relative to the ankle in the longitudinal plane, perpendicular to the transversal plane. The gait task also required regular walking to be differentiated from turning, which was defined as a rotation over 160 degrees of the sensor attached to the sternum. Mean cycle/stride durations, amplitudes and velocities on these tasks were obtained by analyzing the positions of the ankle, wrist and sternum filtered and analyzed using the same method and algorithm as mentioned above. For the arising from chair task the average durations of standing up and sitting down were determined as well as their average velocities.

Differences in the execution of the pouring glass task resulted in data not suitable for automated analysis. Therefore, the average pouring time per glass was determined by visually inspecting the data.

Statistical Analysis

Statistical analysis was performed using SPSS 17.0 for Windows (IBM). Group means of task outcomes were determined for patients and controls. To investigate the discriminability of the combined task outcomes (durations, amplitudes and velocities) of selections of tasks, the outcomes were normalized and summed. Differences between groups were investigated with two tailed t-tests assuming unequal variances. To

achieve sufficient statistical power to significantly differentiate patients from controls an effect size above 2.0 was required. Therefore, effect sizes, Cohen's D, were determined using the pooled standard deviations of the groups.

Results

Subjects

Age and height of patients and controls were 52.2 ± 6.8 and 52.0 ± 3.9 years, and 1.87 ± 0.10 and 1.80 ± 0.07 meters. One patient used a walking aid, therefore, his scores on gait, leg agility and arising from chair tasks were excluded from the analysis.

Tasks

Gait, leg agility, elbow flexion/extension, arising from chair, small and large tracing, small and large tapping, and flipping glass tasks significantly discriminated patients from controls, Table 1. Differences between patients and controls were largest on the flipping glass task. This was also the only task to significantly discriminate on its duration, amplitude and velocity, with respective effect sizes of 2.3, 2.8 and 2.8. Thereafter the flexion/extension of the elbow task was most discriminative, effect sizes for duration and velocity were 2.1 and 2.7, as seen in figure 2. An interesting finding is that in contrast to standing up, patients sat down significantly slower than controls.

Task Combinations

Combining tasks increased effect sizes by as much as 50%, illustrated in Fig. 2. Table 1 lists the differentiability of the combinations of tasks derived from the Unified Parkinson's Disease Rating Scale (hand movements, pronation-supination movement of hands, leg agility and gait tasks), tracing/tapping tasks (small and large tapping and tracing tasks), the combination of all tasks, except for the arising from chair and pouring glass tasks. These tasks could not be combined with the other task due to their outcomes being different.

Also included in Table 1 is the recommended selection of tasks (flexion/extension of elbow, gait, leg agility and pronation/supination movements of hand tasks). Criteria for the selection of these tasks are described in the discussion. The highest effect size, 4.2, was reported for the combined durations of all tasks.

Table 1: Task outcomes and combinations thereof significantly discriminating patients from controls

Task	Duration (s)			Amplitude (deg)■			Velocity (deg/s)■		
	Patient Mean (SD)	Control Mean (SD)	p-value (effect size)	Patient Mean (SD)	Control Mean (SD)	p-value (effect size)	Patient Mean (SD)	Control Mean (SD)	p-value (effect size)
Arising from chair▲	0.7 (0.1)*	0.6 (0.1)	0.23 (0.8)	< 0.1 (< 0.1)*	<0.1 (< 0.1)	0.32 (0.7)	0.4 (0.1)*	0.6 (0.1)	0.01 (2.2)
Gait	1.3 (0.1)*	1.2 (< 0.1)	0.05 (1.7)	1.3 (0.1)*	1.5 (< 0.1)	0.03 (1.9)	1.0 (0.2)*	1.3 (<0.1)	0.03 (2.1)
Flexion / Extension of elbow	1.2 (0.4)	0.6 (0.1)	<0.01 (2.1)	76.8 (22.9)	81.4 (23.9)	0.75 (0.2)	138.9 (43.0)	290.0 (68.2)	<0.01 (2.7)
Tapping small	1.1 (0.2)	0.6 (0.2)	0.01 (1.9)	0.1 (< 0.1)	0.2 (< 0.1)	0.38 (0.5)	0.3 (0.1)	0.6 (0.2)	0.02 (2.1)
Tapping large	2.0 (0.7)	0.8 (0.3)	<0.01 (2.3)	0.3 (0.1)	0.3 (0.1)	0.28 (0.7)	0.3 (0.1)	0.9 (0.4)	0.02 (2.3)
Tracing large	3.9 (1.2)	1.2 (0.6)	<0.01 (2.7)	0.2 (< 0.1)	0.3 (< 0.1)	0.05 (1.4)	0.2 (0.1)	0.9 (0.4)	0.02 (2.5)
Flipping	2.8 (0.9)	1.2 (0.4)	<0.01 (2.3)	32.8 (14.4)	88.1 (24.8)	<0.01 (2.8)	24.6 (18.1)	164.3 (71.5)	0.01 (2.8)
Combined scores of UPDRS● tasks	1.7 (2.5)	-2.0 (0.5)	0.01 (2.0)	-0.7 (2.0)	0.8 (1.2)	0.16 (0.9)	-1.4 (2.4)	1.7 (1.4)	0.02 (1.5)
Combined scores of tapping and tracing tasks	2.5 (1.6)	-3.1 (1.9)	<0.01 (3.2)	-1.1 (1.6)	1.3 (0.9)	0.02 (1.7)	-2.5 (0.7)	3.0 (3.2)	0.02 (2.5)
Combined scores of recommended tasks	2.1 (2.2)	-2.5 (0.8)	<0.01 (2.7)	-0.8 (2.0)	0.9 (2.4)	0.25 (0.8)	-1.9 (1.5)	2.3 (1.4)	<0.01 (2.9)
Combined scores of all tasks	-7.1 (1.6)	5.9 (4.0)	<0.01 (4.2)	-2.5 (3.0)	3.0 (2.9)	0.01 (1.9)	-5.6 (3.2)	6.7 (4.9)	< 0.01 (3.0)

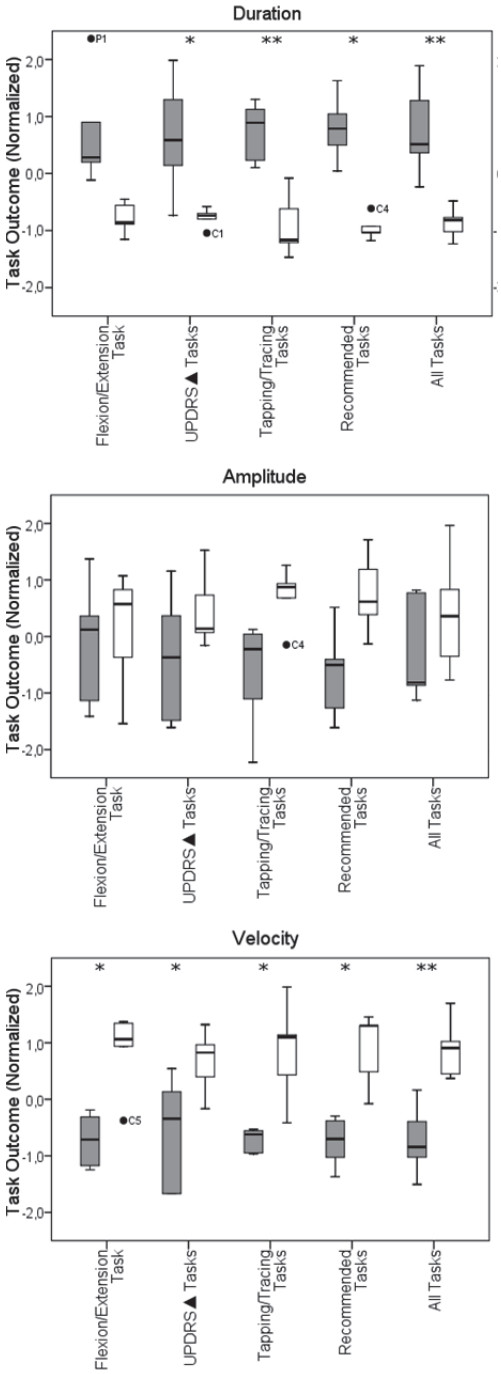

Figure 2: Three sets of boxplots detail differentiability of the outcomes for duration, amplitude and velocity. Data of patients with bradykinesia are grey and data of controls are white. To aid the visual comparability scores were normalized (including the normalized sum scores of the combinations of task outcomes). Scores were reported for the flexion/extension of elbow task and the combined scores of the tasks derived from the UPDRS▲ (hand movements, pronation-supination movement of hands, leg agility, flexion/extension of elbow and gait tasks), of the tapping and drawing tasks (small and large tapping and tracing tasks), the recommended selection, see discussion, of tasks (flexion/extension of elbow, gait, leg agility and pronation-supination movement of hands tasks) and of all tasks (Excluding tasks producing different outcomes, arising from chair and pouring glass task). This figures illustrates that most differentiability is achieved by combining tasks ● Outliers labelled to indicate which group the subject was in and their respective number in the study. ▲ Unified Parkinson's Disease Rating Scale. * Indicates an effect size greater than a Cohen's D of 2.0. ** Indicates an effect size greater than a Cohen's D of 3.0.

Task Outcomes

Mean cycle/stride duration, amplitude and velocity significantly discriminated between patients and controls in four, one and seven tasks respectively. Velocity discriminated most in five of the seven tasks. Duration was most discriminative in the other two tasks.

When task outcomes were combined, only duration and velocity achieved significance, and most discrimination was reported for the combined durations.

Discussion

The majority of the tasks are suitable for assessing bradykinesia instrumentally, as seven of the eleven tasks significantly discriminated patients with bradykinesia from controls. As expected, combining outcomes of different tasks markedly improved discriminative potential.

Other studies reported that gait, arising from chair, leg agility, flexion/extension of the elbow and pro/supination movements of hand tasks are capable of measuring bradykinesia instrumentally (8, 11-18). This is confirmed by our findings and indicates that these tasks are suitable for measuring bradykinesia in long term psychiatric patients, with the exception of the pro/supination task. Granted that the instrument in the study of Patel et al. measured bradykinesia less accurately than tremor and dyskinesia (12).

In the selection process of tasks for the instrumental assessment of bradykinesia, practical aspects should also be considered, see Table 2. The flexion/extension and gait tasks are most feasible, being similar to tasks on validated observer rated scales. Other tasks are less feasible, because (i) they are less practical due to the requirement of additional standardized materials (leg agility, arising from chair, tapping, tracing, pouring, flipping and peppermill). (ii) The tasks could not discriminate patients from controls (hand movements, pronation/supination, pouring and peppermill). (iii) Performance on the tasks depended on more than the underlying construct of bradykinesia. For example, muscle weakness, rigidity, tremor and required accuracy of movements also affect movement speed (24-25). Therefore, confounding could have been an issue in the tapping, tracing, pouring and flipping glass tasks.

Table 2: Tasks feasibility for assessing bradykinesia

Task	Materials	Content Validity	Discriminability
Hand Movement	++	++	-
Gait	++	++	+
Pronation/Supination Movements of hand	++	++	-/+
Leg Agility	-/+	++	+
Flexion/extension of elbow	++	+	++
Arising from chair	-/+	++	++
Pouring water in glass	--	-	--
Tracing (small and large)	--	-	++
Tapping (small and large)	--	-	++
Flipping glass	-	-	++
Peppermill	-	+	-

Overview of practical aspects tasks must meet to be feasible for use in an instrumental assessment. Tasks are scored on the extra materials required to perform the tasks, favoring tasks that do not require any. Content validity indicates to what degree a task measures the underlying construct of bradykinesia. Scores for discriminability were based on the effect sizes found in this study. Scores range from --, -, -/+, + to ++.

Variance in expression of bradykinesia between patients is considerable, partly since severity can differ per region (head/neck/arms/trunk/legs). Observer rated scales rely on the analysis of a broad selection of tasks to achieve adequate content validity. Our results also show that assessing a combination of tasks improves discriminability. Although combining all tasks achieved best discriminability, this is an impractical solution as an assessment would cost too much time, approximately 30 minutes. Therefore, to improve the content validity of the instrumental assessment of bradykinesia a combination of tasks investigating different body parts is required and the selection of tasks should be limited to tasks with a high content validity, adequate discriminability and that are easy to perform and require few additional materials. Thus, the recommended selection of tasks for the design of an instrumental assessment for bradykinesia is the combination of the average cycle/stride velocities on the gait, pronation/supination, leg agility and flexion/extension of elbow tasks. This selection can be performed in less than ten minutes and discriminates very well between patients with bradykinesia and controls, Cohen's D = 2.9.

The external validity of this study could be limited. As this study was limited to male subjects, aged forty to sixty. Although age and gender affect the severity of bradykinesia, they do not affect in which parts of the body bradykinesia is most prominent. In addition, the large effect sizes and the fact that performances on the tasks were based on repeated movements, contribute to a high statistical power. Therefore, this study's findings can likely be generalized to other populations. Investigators were not blinded to the status of the participants, patient or control, or the aim of the study. As patients were compared to healthy controls it was clear which group they were part of. However, data were collected electronically reducing the possibility of estimator bias. Nevertheless, it remains possible that minor variations in instructions between groups resulted in a slight bias.

Instrumental assessment of bradykinesia is ideal for research and monitoring patients, because in contrast to rating scales it is easy to achieve sensitive, reliable and objective measurements without extensive training. An interesting application is instrumentally assessing the Ultra-High Risk (UHR) group for psychosis. There is evidence that in UHR individuals, subtle forms of movement disorders, such as bradykinesia, predict conversion to psychosis (9).

If so, instrumental screening of bradykinesia may be of high clinical value as a biomarker to predict conversion to psychosis in UHR populations.

Conclusion

We confirm that instrumental assessment of bradykinesia is feasible and that content validity can be improved. The selection of tasks considered most feasible for an instrumental assessment was the flexion/extension of elbow, gait, leg agility and pronation/supination tasks. Larger studies are warranted to investigate the validity and reliability of instruments based on these tasks.

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Chapter 7

Efficacy and Safety of Deep Brain Stimulation in Patients With Medication-Induced Tardive Dyskinesia and/or Dystonia:
A Systematic Review

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Abstract

Background: Tardive dyskinesia and dystonia (TDD) are severe side effects of dopamine blocking agents, particularly antipsychotics. While deep brain stimulation (DBS) has proven effective in the treatment of TDD, little is known about the possible psychiatric complications of DBS in psychiatric patients.

Objective: To assess the efficacy and safety, specifically the psychiatric side effects, of DBS in patients with medication-induced TDD.

Data sources: PubMed and EMBASE databases were searched systematically on May 25, 2011, for articles written in English, using the search terms *deep brain stimulation* AND *tardive*.

Study selection: Of the 88 original articles retrieved, 17 studies involving 50 patients with TDD who underwent DBS were included in the review.

Data extraction: Data on the severity of the movement disorders before and after DBS, as rated on the Burke-Fahn-Marsden Dystonia Rating Scale or similar scales, were extracted. Data on psychiatric symptoms before and after DBS were used to calculate the percent improvement per patient per rating scale. Overall improvement and confidence intervals were calculated using a 1-sample, 2-sided Student *t* test.

Results: The mean improvement of TDD of the combined patients 3 to 76 months after implantation was 77.5% (95% CI, 71.4%–83.3%; $P < .000$) on the Burke-Fahn-Marsden Dystonia Rating Scale. Of the 50 patients, 1 experienced an exacerbation of depression, and 1 experienced an exacerbation of psychosis.

Conclusions: DBS seems to be effective and relatively safe for patients with treatment resistant TDD; however, the results should be interpreted with caution, as most of the data are from case reports and small trials.

Medication-induced tardive dyskinesia and tardive dystonia (TDD) are characterized by twisting or jerking movements that typically occur after long-term treatment with dopamine-blocking agents, mostly antipsychotics(1), but also with certain antiemetics (metoclopramide and prochlorperazine) and antidepressants(2). The prevalence of tardive dyskinesia in patients treated with antipsychotics ranges from 32.4% for first-generation antipsychotics to 13.1% for second-generation antipsychotics(3), while the prevalence of tardive dystonia ranges from 0.4%–9%[4], depending on the population and type of antipsychotic used. Both conditions may occur in the same patient[1.] Tardive syndromes, especially when dystonic features are present, can become socially or even physically disabling or painful. The most recent Cochrane review4 did not find sufficient evidence from randomized controlled trials to support one specific treatment option, although there was some evidence from other types of studies that the following treatment strategies may provide benefit: lowering the dosage or stopping antipsychotics, switching to clozapine or another second-generation antipsychotic, or adding tetrabenazine[4]. For dystonia, particularly focal dystonia, injections of botulinum toxin may be helpful[1]. Unfortunately, some patients with severe forms of TDD do not benefit from pharmacologic interventions(1,3,5), even after the offending medication has been discontinued(4,6,7).

Deep brain stimulation (DBS) is a surgical technique that has been successfully used to treat movement disorders such as Parkinson's disease, tremor, and primary dystonia(8-11), although results are less clear-cut for secondary dystonia (eg, after traumatic brain injury and cerebrovascular accidents)(12). Preliminary research indicates that patients with TDD benefit from DBS(8,11,13-15), whereas patients with other forms of secondary dystonia do not(8). Moreover, clinicians may be reluctant to use DBS, not only because of the lack of evidence for randomized controlled trials supporting its effectiveness, but also because it might give rise to psychiatric side effects in patients who already have psychiatric problems and because it requires clinicians to change their mindset and seek a surgical rather than medical solution(16). Most studies of DBS excluded patients with a history of severe depression or "major psychiatric disorders"(17) because of the presumed high risk of psychiatric side effects such as manic symptoms, depression, impulse-control problems, and attempted suicide, which had been observed in some patients with Parkinson's disease after electrode implantation(18,19). However, the subthalamic nucleus is usually stimulated in patients with Parkinson's disease, a site that is associated with a higher risk of psychiatric side effects than is the globus pallidus internus (GPi), the most common stimulation target in TDD(18-20).

The goal of this systematic review was to evaluate the efficacy of DBS in the GPi on medication-induced TDD and the risk of psychiatric complications.

Method

Search Strategy

On May 25, 2011, the PubMed and EMBASE databases were searched, using the search terms *deep brain stimulation* AND *tardive*, with the limitations that studies must involve humans and be written in English (PubMed) and must be original articles (EMBASE). No date limitations were used. The references of retrieved articles were also screened. For inclusion, studies had to report the severity of the movement disorders before and after DBS electrode implantation, measured in individual patients by means of rating scales.

In total, 112 articles were identified, of which 88 remained after duplicates were excluded. A further 66 articles were excluded because (1) the patients did not have medication induced TDD (19 articles), (2) DBS was not the intervention treatment (16 articles), (3) the article was a review (30 articles), or (4) the stimulation target was not the GPi (1 article). The full text of the remaining 22 articles was reviewed, which led to the exclusion of a further 5 articles that did not match our inclusion criteria. Two other articles were identified from the reference lists, so that 17 articles were included (Table 1).

To ensure that the same patient was not entered more than once in multiple publications by the same author group, patient data regarding date of birth, ages at onset, and symptom ratings were compared. As noted in Table 1, 3 patients were published twice, in both Gruber et al(14) and Trottenberg et al(32). Another patient was included twice because the patient had undergone 2 separate procedures: in 1 report(30), the stimulation leads had stopped functioning, and in the other(21), the stimulation leads had been reimplanted.

Statistical Analysis

Data were retrieved on TDD severity (Burke-Fahn- Marsden Dystonia Rating Scale [BFMDRS], Abnormal Involuntary Movement Scale [AIMS], and Extrapyramidal Symptom Rating Scale [ESRS]) before and after DBS and, if available, on age at onset of TDD, duration of TDD symptoms, age at surgery, gender, psychiatric diagnosis, psychiatric and nonpsychiatric side effects, rating scale used, duration of follow-up, DBS target, study funding, and study design. Individual data for all patients are available from the corresponding author on request.

The improvement per patient was calculated as a percentage per rating scale. SPSS version 18.0 was used for data analysis; all scores showing improvement were squared, and the subsequent data were checked for normal distribution. The overall improvement and confidence intervals were calculated using a 1-sample, 2-sided Student t test to obtain a mean improvement score and a 95% confidence interval (CI). The effect of patient characteristics on changes in BFMDRS total score was evaluated with a Pearson coefficient when possible. When assumptions of linearity were violated, a Spear-

man ϱ was used (age at surgery, age at onset, duration of symptoms, and duration of follow-up). A $\chi 2$ test was used for categorical variables (gender, diagnosis, DBS target, funding, and study design). The *P* value indicating significance was set at < .01 for all tests.

Results

Table 1 shows the characteristics of the patients. Of the 50 patients included in this review, 44 had a known psychiatric diagnosis, and 1 had antiemetic-induced TDD; for 5 patients, no psychiatric diagnosis was reported. Presurgery psychotic symptoms were scored on the Positive and Negative Syndrome Scale (PANSS) in 10 patients(13), mood symptoms were scored on the Montgomery-Asberg Depression Rating Scale (MADRS) for 19 patients(13,14) and on the Beck Depression Inventory (BDI) for 3 patients(28). Some of the studies required patients to have had a stable psychiatric status for at least 6 months.

Motor Improvement

On the BFMDRS, the mean improvement in the movement and disability subscale scores and the total score was 80.9% (95% CI, 74.7%−86.6%), 74.0% (95% CI, 65.0%− 83.3%), and 77.5% (95% CI, 71.4%−83.3%), respectively (all *P* < .000). The same significant (*P* < .000) improvement was seen in the AIMS and ESRS scores, with an average improvement on the AIMS of 71.5% (95% CI, 62.6%−79.3%) and on the ESRS of 67.2% (95% CI, 55.5%−77.2%).

Effect of Covariates on Motor Improvement

None of the *P* values found were significant. The lowest *P* value was .07 for age at surgery. All other covariates reported in the method sections were much higher.

Psychiatric Side Effects

In 12 patients, the presence or absence of psychiatric side effects after the operation was not specifically mentioned in the studies(9,22,25-27,31,33), In 10 of the 50 patients, 1 of whom was included twice(21,30), for whom the presurgery and postsurgery ratings on the PANSS and the MADRS were reported, no significant overall presurgery versus postsurgery difference was found(13). Other studies reported significant mood improvement on the MADRS (9 patients)(14) and the BDI (2 patients)(28). The publications containing the remaining 17 patients reported on psychiatric side effects without the use of a rating scale(10,21,23,24,29,32). One patient with previous depres-

sions developed another depressive episode within a year of the surgery(13), and 1 patient with schizophrenia had a psychotic relapse 6 months after surgery(32).

Table 1: Characteristics of studies included in the review

First author	Publication year	N	Type of motor scale	Type of rating scale blinding	Psychiatric exclusion criteria and rating scales
Capelle (21)	2010	4	BFMDRS	None	No history of major psychosis, antipsychotics discontinued
ChanG(27)	2010	5	BFMDRS, ESRS	Pre- post operative video blinding	Antipsychotics discontinued
Cohen(22)	2007	2	BFMDRS	None	None mentioned
Damier(13)	2007	10	ESRS, AIMS	Stimulation ON/OFF blinding	Stable psychiatric symptoms for 12 months, PANSS, MADRS
Eltahawy(8)	2004	1	BFMDRS	None	None mentioned
Franzini(23)	2005	2	BFMDRS	None	None mentioned
Gruber(14)	2009	9[a]	BFMDRS, AIMS	None	No acute psychiatric symptoms or severe depression in the last 6 months, MADRS
Kefelopoul(28)	2008	1	BFMDRS, AIMS	Stimulation ON/OFF blinding	Controlled psychiatric condition
Kosel(24)	2007	1	BFMDRS	None	None mentioned
Krause(33)	2004	3[b]	BFMDRS	None	BDI
Magarinos-Ascone(10)	2008	1	BFMDRS	None	Absence of psychiatric disturbances
Pretto(9)	2008	1	BFMDRS, AIMS	Pre- post operative video blinding	None mentioned
Sako(29)	2008	6	BFMDRS	None	None mentioned
Schrader(20)	2004	1[a]	AIMS	Stimulation ON/OFF blinding	None mentioned
Trottenberg(25)	2001	1	BFMDRS, AIMS	Stimulation ON/OFF blinding	None mentioned
Trottenberg(30)	2005	5[a]	BFMDRS, AIMS	None	None mentioned
Yianni(26)	2003	1	BFMDRS, AIMS	None	None mentioned

Abbreviations: Burke Fahn Marsden Dystonia Rating Scale (BFMDRS), Abnormal Involuntary Movement Scale (AIMS), Extrapyramidal Rating Scale (ESRS), Positive and Negative Syndrome Score (PANSS), Montgomery-Asberg Depression Rating Scale (MADRS), Becks Depression Inventory (BDI)

[a] Overlap with patients in other studies , [b] 1 patient excluded because follow-up data were not available

Table 2: Patient demographics, symptoms before and after deep brain stimulation (DBS), and psychiatric characteristics

		Non-affective psychosis	Affective psychosis	Other diagnosis	Total
Number of patients		10 (20%)	27 (54%)	13 (26%)	50
Sex, n (5)	Male	7 (70%)	7 (26%)	5 (38%)	19 (38%)
	Female	3 (30%)	20 (74%)	8 (62%)	31 (62%)
Age at surgery	Median (SD)	37 (14.4) (n=10)	48 (11.9) (n=27)	55 (16.4) (n=13)	48 (14.4) (n=50)
Age of onset	Median (SD)	34 (14.9) (n=8)	43,5 (12.9) (n=22)	62 (18.9) (n=8)	44 (15.0) (n=38)
Symptom years	Median (SD)	4.5 (2.7) (n=8)	5 (4.2) (n=22)	4 (2.8) (n=8)	5 (3.6) (n=38)
Follow-up time in months	Median (SD)	9.5 (24)	16 (15)	12 (12)	12 (16)
BFMDRS total Median (SD)	Pre-operative	36 (14) (n=7)	46 (31) (n=20)	48 (25) (n=13)	43 (27) (n=39)
	Post-operative	5 (7) (n=7)	6 (26) (n=20)	16 (21) (n=13)	8 (22) (n=39)
BFMDRS movement Median (SD)	Pre-operative	25 (10) (n=6)	33 (28) (n=17)	36 (20) (n=9)	33 (23) (n=31)
	Post-operative	3 (5) (n=6)	3 (20) (n=17)	9 (8) (n=9)	5 (16) (n=16)
BFMDRS disability Median (SD)	Pre-operative	8 (6) (n=6)	9 (6) (n=17)	9 (6) (n=9)	9 (6) (n=31)
	Post-operative	1 x(4) (n=6)	1 (6) (n=17)	4 (4) (n=9)	2 (5) (n=31)
AIMS Median (SD)	Pre-operative	25 (8) (n=6)	24 (7) (n=14)	22 (10) (n=5)	24 (7) (n=24)
	Post-operative	6 (8) (n=6)	9 (6) (n=14)	5 (4) (n=5)	6 (6) (n=24)
ESRS total Median (SD)	Pre-operative	63 (59) (n=4)	56 (36) (n=10)	31 (-) (n=1)	39 (41) (n=15)
	Post-operative	19 (25) (n=4)	22 (15) (n=10)	16 (-) (n=1)	21 (17) (n=15)

Abbreviations: Abnormal Involuntary Movement Scale (AIMS), Burke Fahn Marsden Dystonia Rating Scale (BFMDRS), Extrapyramidal Rating Scale (ESRS), Globus Pallidus internus (GPi), Standard Deviation (SD), Subthalamic nucleus (STN)

[a] One of the implants in unilateral

Nonpsychiatric Side Effects

One patient had a cerebral infarction in the premotor cortex and thus did not benefit from DBS, although his symptoms did not become markedly worse, either[22]. Many patients had temporary side effects during calibration of the stimulation parameters, and these resolved after the stimulation settings were adjusted. Lasting somatic or implant-related side effects were chest battery infection (2 patients)(22,31), lead reimplantation (1 patient)(13), and adjustment of lead tension (1 patient)(13). One case study reported the loss of 1 electrode and less dexterous hand movements(30).

Discussion

This systematic review shows that DBS greatly improves motor scores in patients with TDD and that the reported, but not systematically assessed, psychiatric side effects are limited. Although based on limited evidence that is not always from randomized controlled trials, this review suggests that DBS is a clinically relevant treatment option for

patients with severe TDD who do not respond to or cannot tolerate pharmacologic interventions. This conclusion is in line with earlier reviews(12,34).

To our knowledge, this is the first review to address the psychiatric side effects of DBS in patients with TDD. Unfortunately, most of the studies included in the review did not systematically measure the patients' psychiatric status before and after DBS, and therefore findings might be biased. Of the 44 patients with a psychiatric diagnosis before DBS, only 2 (5%) experienced an exacerbation of their symptoms, and no patients developed new symptoms. If DBS were truly dangerous to the psychiatric health of patients with TDD, one would expect more reports of psychiatric exacerbations and new symptoms. This finding is consistent with a recent review by Jahanshahi et al(35), which found no evidence that patients with primary dystonia or TDD with severe depression suffered from negative psychiatric effects after DBS of the GPi. A possible explanation for these minimal psychiatric side effects compared with those seen after DBS in patients with Parkinson's disease is the difference in stimulation site, namely, the GPi in patients with TDD and the subthalamic nucleus in patients with Parkinson's disease(18-20).

One review(12) found fewer symptoms and a shorter duration of symptoms before DBS to be independent predictors of improved motor scores after DBS. Our review found various covariates not to affect the outcome, with the lowest *P* value being .07 for age at surgery and age at onset. This lack of effect of covariates might be because a low *P* value (< .01) was used to indicate significance. The *P* value would have been even lower if a Bonferroni correction had been applied (.005 significant *P* value, .010 trend *P* value); however, this would have been inappropriate given the small sample size and low power of the review.

Limitations

This review had a number of limitations that should be considered. For example, publication and observer bias are potentially present in this type of review. Many of the studies included were case reports, which are prone to publication bias, and no effort was made to blind either the clinician (rater) or the patient. To assess for publication bias and observer bias, the studies were scored for blinding and for being part of a larger patient series or study. Neither had an effect on the improvement in motor scores. The psychiatric status of patients before and after DBS was seldom systematically assessed, which could have resulted in reporting bias.

Another potential limitation is that results for tardive dyskinesia and tardive dystonia were not reported separately, but this is probably not a problem, because most patients suffer from both conditions. Also, different motor assessment scales were used (BFMDRS, AIMS, and ESRS), and the duration of follow-up varied widely between studies, ranging from 3 to 76 months; however, covariate analysis showed that the duration of follow-up did not significantly affect motor scores ($P = .20$).

Of the 50 patients included in the review, 5 had no known psychiatric diagnosis, and 1 developed TDD after using dopamine-blocking antiemetics. It is possible that these patients responded differently to DBS than patients with a psychiatric diagnosis; however, exclusion of these patients did not significantly change the improvement in motor scores.

Most patients who developed TDD received antipsychotic treatment for affective disorders with psychotic symptoms (Table 2), and only 20% were treated for a non-affective psychosis. This diagnostic distribution may have been due to selection bias, because some studies used a stable psychiatric status for at least 6 months as an inclusion criterion(13,22.23). Another possibility is that patients with a history of an affective psychiatric disorder are more likely to complain about their movement disorder than patients with schizophrenia, who often suffer from cognitive and negative symptoms. There was no evidence that the patients' diagnosis had an effect on the motor improvement seen after DBS ($P = .57$).

In conclusion, our results indicate that DBS is effective in treating TDD in psychiatric patients and gives rise to few psychiatric side effects. The potential risk of publication and observer bias due to the nature of the papers included means that findings should be interpreted with caution.

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Chapter 8

Discussion

Movement disorders (MD) such as parkinsonism and tardive dyskinesia (TD) are very common in patients with severe mental illness (SMI) (1,2). Parkinsonism is characterized by bradykinesia, rigidity and resting tremor(3) and dyskinesia by involuntary movements in the orofacial region, limbs, trunk and/or respiratory system(4,5). However, little is known about the course of parkinsonism and dyskinesia in SMI and treatment guidelines are often tailored to less severely ill patients who have a lower MD prevalence rate (6,7)

In this thesis we focus on three aspects of MD in SMI: the course, recognition and treatment. Four of the six chapters included (chapters two, three, four and five) in this thesis are derived from the *Curacao Extrapyramidal Syndromes Study* data, which will hence forth be referred to as the Curacao study, and will be discussed first. Chapters six and seven on the treatment of TD and the recognition of parkinsonism using inertial sensors will be discussed separately.

The Curacao Extrapyramidal Syndromes Study

Over the course of an 18 year period, between 1992 and 2009, almost all SMI inpatients and day treatment patients on the Dutch Antilles were included in the Curacao study (8), making it the longest running longitudinal study in MD in the world. The eight measurements over this time period offer a unique opportunity to study the course of MD in SMI patients in a naturalistic setting.

Curacao is an island, thus ensuring a defined catchment area, and because most patients tend to spend their entire lives on the island, dropout is limited and mainly due to death. Another advantage to the island location is that, on Curacao, all inpatient psychiatric care is provided by a single organization making it easy to reduce missing data and to ensure no other treatment is being provided by other health care providers. Reliability of MD rating over the consecutive measurements was high, as the same two highly trained raters rated MD during all eight measurements. Thus ensuring that the definition of MD was the same in 1992 as it was in 2009.

Because of the high MD prevalence found in the Curacao study, we replicated the study in a comparable SMI population the Netherlands (2,9). Similarly high prevalence rates were found with 68% of patients having one or more MD in the Dutch population (2) compared to 74% in the Curacao population(8). The prevalence of the specific MD varied across both populations; parkinsonism and TD had a prevalence of 66% and 37%, and 35% and 54% in the Dutch and the Curacao population, respectively. Medication use of all kinds was also highly similar in both populations, suggesting that the Curacao population is comparable with the Dutch SMI patients.

The course of movement disorders in SMI

Chapters two and three discuss the course of TD, parkinsonism and tremor in the Curacao study. To our knowledge, the Curacao study is unique in its 18-year follow-up compared with previous studies with a maximum follow-up of three years. Schooler and Kane (10) defined the course of TD as either (i) incident (i.e. a MD develops during the study); (ii) persistent (a MD is present at consecutive time points); or (iii) remittent (a MD disappears during the course of the study) (Figure 1) and this definition has been widely used in research since (2,7,9,10) As SMI patients are chronically ill, often for decades (11), long-term follow-up is particularly relevant. About half of the patients in the Curacao study showed a fluctuating course of the MD, with rating scale scores alternating above and below the cut off required for an MD diagnosis (Figure 2). These findings strongly suggest that future studies with a long-term follow-up are warranted. E.g. of the 53 patients with dyskinesia, 26 had a relapsing remitting course (data not published). Graphs for parkinsonism showed a similar distribution with just under half of the patients showing a relapsing remitting course.

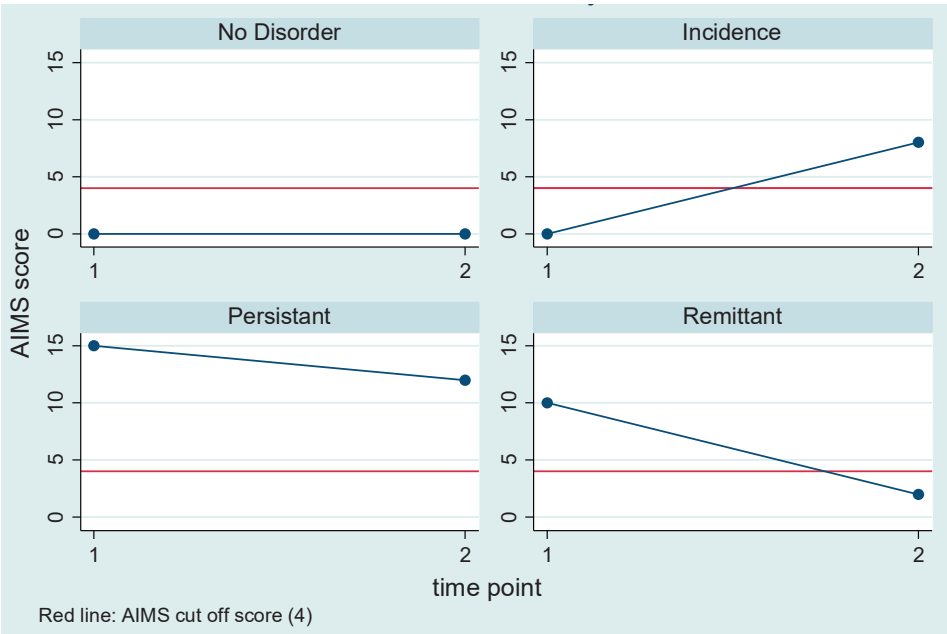

Figure 1: Movement sidorders as defined by Scooler and Kane

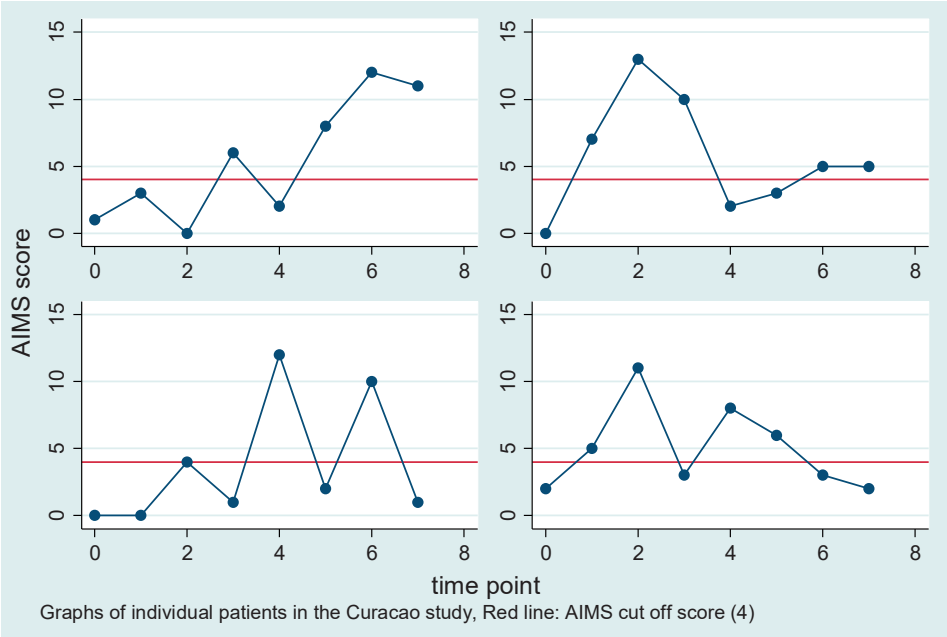

Figure 2: AIMS score over consecutive measurements

These results show that, in the long term, movement disorders fluctuate in severity from not clinically detectable to highly visible in a single patient. Indicating that in the long-term a more accurate description of the course of MD would be 'relapsing remitting' instead of either persistent, incident or remitting as this implies the MD has a steady state after the end of the study.

In chapter four we found that parkinsonism increased all cause mortality with a hazard ratio of 1.4, although akathisia and TD did not have a significant association with mortality, highlighting the clinical relevance of MD. To our knowledge only Modestin et al. (12) have published on mortality while correcting for all three MD. There results were similar, stressing the importance of detecting parkinsonism as a risk factor. With this study it was not possible to find out if parkinsonism is a causal risk factor for mortality or that other factors, related to parkinsonism, are accountable. Therefore, more replication studies are needed, especially because most studies focus only on the relationship between TD and mortality which have produced mixed results(12–15)

Recognition of movement disorders

The diagnosis of MD is clinical, sometimes supported with rating scales to describe type and severity. They have several advantages; their validity and reliability has been studied, they have been used extensively in research on MD, and no specific equip-

ment is required (16). However these rating scales differ in i) comprehensiveness, ii) number of items, iii) severity rating and iv) definition of the described MD, and are not always interchangeable. Also, extensive training is required to use them correctly in a clinical setting and to achieve an inter rater reliability suitable for research purposes. Furthermore, the ordinal scale in most rating scales limits the interpretation of movement disorder severity and change over time (16,17)

In the last decade several Instrumental Measurements (IM) have been developed, allowing objective measures of MD on a continuous scale with minimal training (17,18). However, IMs are expensive and each MD requires a different IM. Therefore, at the moment, IMs are rarely used in clinical practice.

Chapters five and six focus on parkinsonism in SMI patients. Both studies used the Unified Parkinson's Disease Rating Scale (UPDRS) as a gold standard for the diagnosis of parkinsonism, but as chapter six used a Dutch SMI population, it will be discussed later.

Blink rate

In chapter five we hypothesized that blink rate can detect parkinsonism in SMI patients, as the use of blink rate has been shown to help in the identification of patients with Parkinson's disease (19). Blink rate per minute of conversation can easily be assessed with a stopwatch and requires little training. In the Curacao population, standardized blink rate at each of the eight measurements showed a strong correlation between blink rate per minute of conversation and parkinsonism ($p<0.001$). Though, the explained variance of the blink rate was 2.5%, making it unsuitable for clinical screening for parkinsonism in SMI patients. However, combining blink rate with other simple measures, e.g. a finger tapping test, a resting tremor test and one or more gross motor tests such as the timed up and go test may result in a higher explained variance. Such a test battery could be programmed into an easy to use app for clinicians and patients.

Treatment of movement disorders

Most studies on treatment interventions for drug-induced MD are randomized controlled clinical trials (RCT), which offer important information about efficacy. However, most of these studies have stringent inclusion criteria often excluding patients comorbidities or certain medication combinations (20–23). This hampers extrapolation of the results to real world SMI populations. Thus, along with the short study duration and idealized treatment settings, it is likely that these results are not representative of a real world SMI-treatment setting. It is therefore necessary to replicate these results in a naturalistic setting to ensure they translate to clinical practice, as has been done in chapters two and three.

Parkinsonism and tremor

Parkinsonism (including resting tremor) and action tremor are considered a dose-dependent drug-induced side effects (5,16) and therefore most treatment algorithms advise lowering the dose or, where possible, stopping the offending drug entirely (24,25). If that is not possible, adding an anti-tremor or anti-Parkinson drug may be considered (5,25). In chapters two and three we tested the efficacy of this treatment approach. The results for action tremor were in line with what was expected; having action tremor was positively associated with action tremor inducing medication (OR 4.5), and negatively associated with a beta blocker (OR 0.08).

Resting tremor, which is part of the parkinsonism triad along with rigidity and bradykinesia (26), showed no relationship with the use of antipsychotics. Indeed, 11% of patients without antipsychotics had resting tremor (data not published) that showed a relapsing remitting course. In many cases the tremor disappeared when antipsychotic medication were administered at a later time point, thus making it unlikely that these patients had developed Parkinson's disease. Neither did resting tremor show a relationship with antipsychotic type or dose, despite it also being considered a drug-induced side effect.

Stopping antipsychotics reduced parkinsonism severity as a whole on the UPDRS by about a third. Reducing antipsychotic dose or changing the type of antipsychotic drugs had no effect, which concur with the results found by Bakker et al. (9), i.e. a small but significant effect of antipsychotic dose, but no effect of the type of antipsychotic drug.

These results are not in line with the assumption that both parkinsonism and resting tremor are dose dependent drug-induced side effects. If parkinsonism is solely caused by antipsychotic medication, then stopping antipsychotic drugs should result in a near complete remission of the parkinsonism symptoms and not a severity reduction of about a third. A change in antipsychotic dose would also be expected to have some impact. Having resting tremor outside of the use of antipsychotic medication is also not in line with the dose dependent side effect assumption. There are a number of possible explanations for these unexpected results.

Firstly, parkinsonism in psychotic disorders could also, in part, be a symptom of the psychotic syndrome, as evidence shows that both clinically recognisable MD and subtle movement abnormalities are an integral part of the neuropathology of psychiatric illnesses (16,27–31) and slower movements and lack of movement initiation have long been reported as symptoms of psychotic disorders(5).

Second, long-term treatment with antipsychotics may be related to persistent parkinsonism due to irreversible changes in the basal ganglia, more specifically a persistent dysfunction of the D2 receptor by the offending drug. Studies in rodents indicate a direct neurotoxic effect of haloperidol (32,33) leading to a decreased dopamine turnover(33), and other studies have observed permanent effects of haloperidol on the equivalent of the basal ganglia in rat brains (34,35) As for human, results found for

structural brain changes by antipsychotics are not consistent (36,37) On the other hand, previous studies suggest that drug-induced parkinsonism can persist even with a normal DAT imaging. (38). These results could be an indication that there can be neurotoxic effects of medication influencing dopamine transmission, including antipsychotics, inducing permanent effects in humans as well as rodents.

Third, apathy caused by negative symptoms could be misclassified on the UPDRS items for speech, facial expression and global spontaneity, and both stupor (defined as: no psychomotor activity; not actively relating to environment) and waxy flexibility (defined as: slight and even resistance to positioning by examiner)(39) in catatonia could be misclassified as bradykinesia and rigidity scored on the UPDRS. However, resting tremor does not overlap negative symptoms or catatonia and therefore cannot be misclassified, making this explanation less likely.

Fourth, it could be that some patients developed Parkinson's disease during the study. This is unlikely as Parkinson's disease has a low incidence (around 1% after age 60) and is a progressive disorder that would have eventually been recognised over the study's 18 years follow-up. Also, spontaneous remission of resting tremor makes Parkinson's disease unlikely.

The most likely explanations are that parkinsonism is, at least in part, a symptom of the psychotic disorder and that long-term antipsychotic treatment may induce structural changes in the basal ganglia leading to an irreversible form of parkinsonism, warranting a revision of the concept that acute drug-induced MD are reversible and tardive often persistent.

Tardive dyskinesia

Treatment guidelines for TD vary from country to country, possibly owing to inconsistent results of treatment studies (5,40). While there is sound evidence for regarding TD as a side effect of antipsychotics (5,16), there does not seem to be a dose dependent effect, and symptoms can continue long after the offending drugs have stopped. Also, there is sound evidence that dyskinetic movements, such as those seen in TD, are inherent to psychotic disorders with subtle dyskinetic movements sometimes appearing in untreated ultra high risk (UHR) individuals before the development of full blown psychotic symptoms(28,29). Indeed, dyskinetic movements in drug-naïve first episode psychotic disorders or UHR predict worse psychiatric outcome (29–31,41) .

In the Curacao study, cessation of antipsychotics or changing antipsychotic type had little effect on TD symptom severity. Contrary to expectations, an increase in antipsychotic dose or adding another antipsychotic type resulted in a decrease of dyskinesia symptom severity and not an increase. In their seminal paper, Schooler and Kane (10) first described the "masking" effect of TD lasting up to three months after an increasing antipsychotic dose. As our measurements are spaced approximately two years apart the "masking" effect continues after 3 months.

Different hypotheses of the pathogenesis of TD exist, such as the dopamine supersensitivity, the striatal neurodegeneration, the maladaptive synaptic plasticity, the enhanced serotonin (5HT2) signalling, and the striatal dopamine-D3 up regulation. However, none of them sufficiently explains all aspects of TD(16,42). All the models have dopamine dysregulation in the basal ganglia induced by D2-blocking agents, such as antipsychotics, in common. Moreover, future studies may help elucidate common pathways in the development of MD. At any rate, irrespective of the pathological mechanism, increasing antipsychotic dose can improve TD symptoms over a substantial period.

Chapters related to other study populations

Treatment of tardive dyskinesia and or dystonia with deep brain stimulation

As has been mentioned above, trials on the treatment of TD have yielded mixed results (5,40). In chapter seven we describe the effect of deep brain stimulation (DBS) in the Globus Pallidus internus on TD severity. The results of the review were very promising with a 70-80% reduction of TD severity after DBS treatment. Not all patients included in the review were SMI patients, but those who had SMI achieved similar results to other patients. As DBS directly affects the output of the Globus Pallidus internus (4,43)the effect does not depend on the etiology of the MD, i.e. drug-induced or MD as symptoms of a psychotic syndrome.

Assessing bradykinesia with inertial sensors

In chapter six inertial sensors are used to assess the speed of patients on 16 different tasks. Four were considered promising for future study both for their ability to differentiate patients from controls and for their simplicity, namely: (i) stride length and speed; (ii) arm pronation and supination velocity; (iii) the velocity of leg tapping while seated; and (iv) the velocity of arm flexion and extension at the elbow. These four tasks have been validated in a larger patient sample in a subsequent study (44). While the sensors are capable of diagnosing bradykinesia in certain settings they are expensive (however they are becoming cheaper) and are not widely available. Also the operation program was custom made for these sensors, making it difficult to transfer to other types of inertial sensors. Despite the drawbacks, the ease of use, the continuous scale, and the lack of inter-rater reliability issues make these sensors attractive for use in research settings for screening large populations or tracking bradykinesia over time.

Future directions

As shown in this thesis, the long-term follow-up of MD in SMI patients in the well-defined catchment area of Curacao offers a wealth of real-world data, which can be used to evaluate the advice given in treatment guidelines. It illustrates that guidelines based on knowledge of the pathophysiology and RTCs on homogenous patient groups with relatively short follow-up times may not always translate well to long-term daily clinical practice in SMI patients. Therefore, it is important to check the efficacy of theory-based guidelines and replicate the results of these RCTs in real world naturalistic studies.

As has been mentioned previously, compelling evidence exists that MD can be both drug-induced and be a symptom of psychotic disorders (after excluding patients with MD based on neurological or other disorders). Our data in chapters two and three seem to support this hypothesis. For daily clinical practice it is less important to differentiate which part of a MD is drug-induced and which part is related to the psychotic disorder, than it is in knowing how to treat the MD. However, understanding what parts of MD are related to the psychotic disorder and how they differ between different patient groups with schizophrenia could provide important information on the underlying neuropathology of the schizophrenia itself. Furthermore, if MD are predictive of which patients will develop SMI or predict the onset of a psychotic relapse it could be of great value to clinical practice. Unfortunately, antipsychotic-naïve SMI patients are rare (8). There are almost no studies on patients with psychotic disorders who remain antipsychotic naïve, making it almost impossible to disentangle which part of MD is due to antipsychotics and which part is related to the underlying neuropathology of mental disorders. However, the Curacao study shows that during long term follow-up MD fluctuate substantially. A long term follow-up study that measured psychiatric symptoms in addition to medication and MD severity might provide more insight. Both the short-term (over day or weeks) and long-term (over years) fluctuations could yield important information. Both cases would require a prospective trial with movement disorder measurements, information on medication use and severity measures for the psychiatric illness.

Another important future development are IMs that can be used to diagnose and assess the presence of a MD and its severity. As has been stated before, the current rating scales have important practical drawbacks, as do the IMs that have currently been developed. As requirements for MD diagnosis and severity description differ between clinical and research settings, the development of different IMs for these specific settings will likely be necessary. An IM for clinical practice should be easy to use, reliable and inexpensive. With accelerometers and gyroscopes integrated into smartphones, mobile applications that measure motor abnormalities have already been developed (e.g., assessment of tremor). With available pressure-sensitive displays, applications that can measure other motor abnormalities such as dyskinesia will be developed in the near future. The trade off of the relatively cheap sensors in mobile phones

is that they are not as precise as the more expensive sensors. However, for clinical purposes high level precision in MD tracking may be less important.

For research purposes IMs may need to be more precise than the information sensors in a mobile phone can provide, while cost restrictions might be less stringent and acquiring specialised equipment might be more of an option. Using IMs would be an important improvement over rating scales in a research setting. It is often tedious to rate a large number of these scales, especially on videos, and to reach sufficient inter-rater reliability is often an issue. Also the lack of linearity of rating scales and their inability to detect subtle movement disorders are important drawbacks. For research precision an inter-rater reliability is relatively more important, and price and ease of use relatively less important than in clinical practice, making sensors like those used in chapter six a good choice.

Conclusions

To conclude, MD are very common in SMI patients, with dyskinesia and parkinsonism being the most common in our study population. Tremor also occurred frequently in the population, with resting tremor being more common than action tremor. Over the years these MD showed a relapsing and remitting course. This was less related to the change of medication than expected. Also, parkinsonism, but not TD or akathisia, was related to all cause mortality.

For action tremor we found that either stopping tremor inducing medication or adding propranolol was highly effective. This is in line with current treatment recommendations. For resting tremor, however, changing antipsychotic type or dose had no significant effect. In fact, for parkinsonism we found that the treatment recommendations of dose reduction or switching from an antipsychotic with a high D2-affinity to a low affinity did not lead to a significant reduction in parkinsonism severity. For dyskinesia, starting antipsychotic treatment or increasing the dose or changing from current SGA to FGA treatment led to a reduction in severity. Neither of these treatment strategies is mentioned in current guidelines. Treatment guidelines are often based on RCT's, but results from studies in a naturalistic setting add important information that should be incorporated in treatment guideline recommendations. The results are in line with research indicating that MD can be caused by the psychotic disorder, as well as being side-effects of antipsychotics or other (psychiatric) medication.

We also studied the association between blink rate and parkinsonism blink rate and found a strong association. However, the positive predictive value of blink rate was not suitable as a screening tool to detect parkinsonism. Inertial sensors had a much higher positive predictive value; however, they require specialised equipment making them more suitable for research than for clinical applications.

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Summary

Plain Language Summary

This thesis focuses on movement disorders in patients that have a severe mental illness (SMI). The main goals are to (i) identify the course of movement disorders over the decades, (ii) develop methods that make it easier to recognise and diagnose movement disorders, and (iii) to assess the effectiveness of current treatment methods of movement disorders.

Due to prescribed medications, and often as an effect of the disorders themselves, movement disorders occur frequently in SMI patients. Visible and uncontrollable, they are often a source of shame and frustration in patients, and as such, tend to have a large impact on their daily lives. They have also been linked to a poorer psychiatric prognosis, reduced treatment adherence, are more likely to have a physical illness and a higher risk of death. Previous research has shown that, despite the large impact on a patient's life, the movement disorders are rarely noted in a patient's file, and seem to receive little attention from treating physicians.

There are four important movement disorders that occur frequently in patients with SMI;

- **Parkinsonism** (also referred to as drug-induced parkinsonism). This tends to look a lot like its namesake, Parkinson's disease. Core symptoms are (i) bradykinesia (slower and/or smaller movements than usual), (ii) rigidity (muscle stiffness, difficulty moving muscles), (iii) resting tremor (the rhythmic moving of a body part such as a hand or head when it is inactive - for example, when resting a hand on a table), and (iv) postural instability.
- **Action tremor** (also known as postural tremor). This is the rhythmic movement of a body part when it is active. A tremor of the hand can, for example, be seen when reaching for a cup.
- **Akathisia.** This literally means the inability to sit still. It consists of both a subjective feeling of restlessness, as well as objective movements (movements that can be seen by other people), typically occurring in the legs.
- **Tardive dyskinesia (TD).** This presents itself in involuntary movements of any body part, with the face and limbs being affected most often. Movements are generally fluid (sometimes called choreatic) and happen continually. They can be very subtle (such as a slight movement of the fingers, as though playing the piano) or very noticeable (such as the continual movement of the tongue, in which it regularly pokes out of the mouth), depending on the severity of the disorder.

Many chapters in this thesis are based on data from the *Curacao Extrapyramidal Syndromes Study;* a cohort of all 223 SMI patients in the former Dutch Antilles. Over the course of 18 years, eight consecutive assessments were done measuring movement disorders and medication use in patients, making it the longest running study in

movement disorders in SMI patients to date. The consecutive assessments allow us to calculate which part of the changes in movement disorders is due to changes in medication.

Chapter 2
The effect of switching antipsychotic dose or type on parkinsonism and TD

This chapter of the thesis focuses on the efficacy of current treatment guidelines for parkinsonism and TD in patients with SMI. Using the data from the *Curacao Extrapyramidal Syndromes Study*, we calculated the effect of switching antipsychotic type and/or dose on the scores of: (i) the Unified Parkinson's Disease Rating Scale (UPDRS; that measures parkinsonism); and (ii) the Abnormal Involuntary Movement Scale (AIMS, that measures TD). To this end, antipsychotics were twice divided into two groups. They were divided depending on (i) whether they were a first generation antipsychotic (FGA) or a second generation antipsychotic (SGA), and they were divided depending on (ii) whether they had a high affinity for the dopamine 2 (D2) receptor (thought to be the most important receptor for both antipsychotic effect and parkinsonism).

The statistical analysis showed a significant reduction in TD severity for (i) starting an FGA or an antipsychotic with a high D2-receptor affinity or (ii) for adding an SGA to current FGA treatment. There was also a severity reduction when an SGA was added on top of current FGA use.

For parkinsonism, only ceasing all antipsychotic medication led to a reduction of the symptoms severity. Starting antipsychotics led to an increase in symptom severity only when antipsychotics were divided according to D2 receptor severity. Finally, dose reduction had no significant effect on parkinsonism symptoms.

These results do not concur with current treatment guidelines for movement disorders in patients with psychotic disorders. This suggests that movement disorders in patients with SMI react differently to antipsychotic treatment than other patients with a psychotic disorder. Therefore it is important that treatment guidelines are adapted for SMI patients.

Chapter 3
Risk factors for tremor in patients with SMI

This chapter focuses on risk factors and treatment of different forms of tremor in patients with SMI. It is also a base on data from *Curacao Extrapyramidal Syndromes Study*. Over a third of patients had a tremor at some point during the study, with resting tremor occurring more frequently (17%) than action tremor (5.2%).

There was a statistically significant association between receiving medication with anticholinergic properties (anticholinergic medication is often prescribed as a treatment for parkinsonism, of which resting tremor is a part) and developing resting tremor at the next measurement. For action tremor, receiving a beta-blocker reduced the risk of having an action tremor at the next measurement.

These results show that many patients with SMI suffer from tremors and that it is important to differentiate between the different tremor types, as both types of tremor have different risk factors and treatment strategies.

Chapter 4
Movement disorders and mortality in patients with SMI

Patients with SMI die, on average, 15 to 20 years earlier than members of the general population. In *Curacao Extrapyramidal Syndromes Study,* 57% of patients had died after the start of the study 24 years ago. The average age at which a patient died was 68.

Both TD and akathisia had no significant relationship with the risk of death. On the other hand, parkinsonism increased the risk of death by 2% per point on the UPDRS. This would mean that someone with 50 points on the UPDRS (the scale runs from 0 to 52 points) has a 2 times greater risk of death than a patient with no parkinsonism symptoms. As the cause of death in these patients is not specified, it is not possible to tell if patients died because they had parkinsonism, or if they died due to other factors. Therefore, it cannot be said that reducing parkinsonism in patients with SMI will lead to a decrease in the risk of death for patients with parkinsonism.

Chapter 5
Blink rate as a clinical test for parkinsonism

The current gold standard for the diagnosis of parkinsonism is the UPDRS. However, extensive and ongoing training is necessary for a clinician to be able to use this rating scale properly. Because of this, the UPDRS is rarely used in clinical practice. The goal of this study was to see whether or not measuring blink rate per minute of conversation could be used to identify SMI patients with parkinsonism.

There is a very strong statistical association between blink rate and the score on the UPDRS. However, a test using blink rate alone only correctly predicted whether or not patients had parkinsonism in 50% of cases. If other variables such as age, gender and medication use were taken into account, then it was possible to classify 67% of patients correctly. Unfortunately this number is still too low to use blink rate as a screening tool for parkinsonism in clinical practice. However, if blink rate was combined with the instrumental measures in Chapter 6, then it is possible that a viable screening tool could be developed.

Chapter 6
The instrumental assessment of bradykinesia, a comparison between motor tasks

Another way to measure bradykinesia (a core symptom of parkinsonism) is to use sensors to measure the velocity of a patient's movements. In this chapter we assessed what tasks were best at differentiating between SMI patients, with and without bradykinesia. In total we researched eleven tasks. The four deemed most useful were: (i) walking; (ii) rotating the wrist; (iii) stamping a leg on the floor while sitting; and (iv) flexing and extending the elbow. These tasks could be measured using the sensors on a mobile phone and could also be combined with the blink rate during the conversation test from Chapter 6.

Chapter 7
The safety and efficacy of deep brain stimulation as a treatment for TD; a systematic review

In neurological guidelines, deep brain stimulation (DBS) is mentioned as a possible treatment for TD. However, little is known about the possible psychiatric side effects in patients with pre-existing psychiatric disorders. At the time of our search, 17 studies containing 50 patients in total had been published.

On average their movement disorder symptoms improved 77.5% as measured on the Burke-Fahn-Marsden Dystonia Rating Scale (a rating scale for the severity of tardive dyskinesia and dystonia). Of those 50 patients, two had a relapse of a pre-existing psychiatric disorder, and none developed a new disorder. As relapses in psychiatric disorders are not uncommon, we concluded that DBS is most likely safe and effective in psychiatric patients with TD. However, as 50 patients is a relatively small number, the results need to be replicated in larger studies before definite conclusions can be drawn.

Chapter 8
Discussion

Course

In SMI, patients' movement disorders show a relapsing remitting course over the decades. A movement disorder could be severe for a number of years and then disappear for a similar amount of time, only to reappear years later. Changes in medication could only explain a small portion of changes in movement-disorder severity, both for parkinsonism and TD, with action tremor being the noticeable exception. The rest of the variations in severity could possibly be explained by variations in severity of the psy-

chiatric disorder, as research has repeatedly shown a link between movement disorders and the underlying psychopathology of psychiatric disorders.

Recognition

Currently, movement disorders are still mostly diagnosed with observational rating scales. The advantages of these scales are (i) their widespread use in research and (ii) the lack of equipment needed to use them. However, there are also important disadvantages to using rating scales. They require extensive and continuous training of the raters who use them, they are incapable of measuring subtle movement disorders, and it is difficult to interpret movement disorder severity on the ordinal scales they use. Instrumental measures do not have these disadvantages and are therefore more suited for tracking movement disorders over time. With sensors becoming increasingly cheap and accurate, we expect that instrumental measures will become common place in the diagnosis and tracking of movement disorders in the future.

Treatment

In the treatment of parkinsonism it can be useful, if possible, to stop antipsychotic medication or to reduce its dose. However, in patients with SMI this will most likely have only a small impact on the severity of parkinsonism. Resting tremor severity is not significantly reduced by stopping antipsychotic medication, nor does adding anticholinergic medication seem to be effective.

In contrast, action tremor can be treated relatively effectively by either stopping or reducing the dose of the causative drug (usually lithium or antidepressants). When this is not possible, adding a beta-blocker, such as propranolol, often results in the complete remission of the action tremor. It is therefore important to make the distinction between resting and action tremor in patients with SMI, as both require different treatments.

Stopping antipsychotic medication or changing antipsychotic type had no effect on TD severity in our research, despite these being advised by current treatment guidelines. Indeed, increasing antipsychotic dose or adding a second antipsychotic medication type reduced TD severity. If a patient has severe treatment resistant TD, DBS could also be a viable treatment option

Methodological considerations

The majority of this thesis is based on data from *Curacao Extrapyramidal Syndromes Study*. To our knowledge, this is the longest running study on movement disorders in patients with SMI. Because all patients on the former Dutch Antilles were included in the cohort, and the drop out was limited, the results of the *Curacao Extrapyramidal Syndromes*

Study are representative of other real world SMI populations. Over the course of 18 years, patients were rated by the same two people, thus ensuring a consistent rating of movement disorder severity. This makes the study highly useful for testing the effect of medication changes on movement disorders in daily clinical practice.

Traditionally randomized clinical trials (RCTs) are seen as the highest form of evidence. Indeed, they are less susceptible to bias than naturalistic studies. However, in recent years researchers have begun to doubt this view. Often there are problems extrapolating the results from RCTs to a real world setting. As RCTs are comparatively costly and labour intensive, idealised patients who are expected to respond well to treatment are often included. Also RCTs often have idealised treatment settings and high dropout rates (patients will start in the study but for whatever reason will quit before they finish it) making it difficult to predict what the effect of treatment is in a real world setting or for patients that choose to drop out of the study. Currently, treatment guidelines are primarily based on RCTs, therefore it is important to replicate RCT results in a naturalistic setting to ensure that the effect seen in the RCT is also applicable in a real world clinical setting.

Suggestions for future research

Our results show that changes in medication only explains a small part of changes in movement-disorder severity in the long term. This is true for both parkinsonism and TD in patients with SMI. This is important because research shows that movement disorders in patients with psychotic disorders are also related to the psychotic disorder itself. More research into how the movement disorder and the psychotic disorders are related over time could provide important insights, not only into the development and pathophysiology of movement disorders, but also into the underlying pathophysiology of psychotic disorders themselves. A naturalistic study that follows patients over an extended period of time could measure both psychiatric symptoms and movement disorder severity. The data from such a study could shed light on how the relationship between movement disorders and psychiatric symptoms works.

Another important aspect of future research is the development of instrumental measures for movement disorders. For daily clinical practice, an app on a smartphone would be an ideal way to both diagnose movement disorders in patients with SMI and to track movement disorder development over time. A good way of assessing a movement disorder, such as parkinsonism, would be to track it with a number of different, simple tests. For example, the camera of a smartphone could be used to assess blink rate per minute, while the screen could be used to assess finger tapping speed, and the internal sensors could be used to assess tremor and walking speed. For research purposes it may be necessary to have more accurate sensors then those currently available in smartphones. Therefore, using the sensors and tasks developed in Chapter 6 might be better suited.

Samenvatting

Nederlandse samenvatting

Het doel van dit proefschrift is om: (i) het *beloop* van bewegingsstoornissen door de jaren heen bij EPA-patiënten in kaart te brengen, (ii) methodes te ontwikkelen die het makkelijker maken om bewegingsstoornissen te *herkennen*, en (iii) de effectiviteit van *behandelingen* voor bewegingsstoornissen te toetsen.

Bewegingsstoornissen komen veel voor bij patiënten met ernstige psychiatrische aandoeningen (EPA), zowel als gevolg van de aandoeningen zelf als van de medicatie die zij daarvoor gebruiken. Omdat bewegingsstoornissen zo zichtbaar zijn, kunnen ze een bron van schaamte vormen. Ook worden ze geassocieerd met lagere therapietrouw, een slechtere prognose en verhoogde mortaliteit. Ondanks de grote impact op het leven van patiënten is in eerdere onderzoeken naar voren gekomen dat bewegingsstoornissen nauwelijks worden gerapporteerd in patiëntendossiers en ze dus weinig aandacht lijken te krijgen van behandelaren.

Er zijn vier belangrijke bewegingsstoornissen die veel voorkomen bij EPA-patiënten waar dit proefschrift zich op richt. Dit zijn:

- **Parkinsonisme** lijkt in de presentatie op de ziekte van Parkinson en bestaat uit de kernsymptomen (i) bradykinesie (langzaam bewegen met kleinere bewegingen), (ii) rigiditeit (stijfheid), (iii) rusttremor (het trillen van een lichaamsdeel, zoals de hand, als het niet bewogen wordt) en (iv) houdingsinstabiliteit.
- **Actietremor** wordt gekenmerkt door een tremor van een lichaamsdeel als dit tegen de zwaartekracht in wordt gehouden.
- **Acathisie** betekent letterlijk het niet stil kunnen zitten. Het bestaat uit zowel een subjectief gevoel van rusteloosheid als objectieve bewegingen, voornamelijk van de benen.
- **Tardieve dyskinesie (TD)** kenmerkt zich door onwillekeurige vloeiende continue bewegingen. Deze bewegingen kunnen zowel in het gezicht voorkomen als in de ledematen en de romp.

Veel hoofdstukken uit dit proefschrift zijn gebaseerd op de data van de *Curaçao Extrapyramidal Syndromes Study*, een cohort van alle 223 EPA-patiënten op de Nederlandse Antillen. Gedurende achttien jaar zijn bij deze patiënten in totaal acht keer bewegingsstoornissen en medicatiegebruik gemeten. Hierdoor kan het effect van een medicatiewijziging op bewegingsstoornissen in de tijd gevolgd worden.

Hoofdstuk 2
Het effect van het veranderen van de dosis of het type antipsychoticum op parkinsonisme en tardieve dyskinesie

Dit hoofdstuk bekijkt of de effectiviteit van de huidige behandelrichtlijnen voor parkinsonisme en TD bij patiënten die antipsychotica gebruiken, ook van toepassing is op patiënten met EPA. Met behulp van de gegevens van de *Curaçao Extrapyramidal Syndromes Study* is gekeken naar het effect van het wijzigen van het type of de dosis van antipsychotica op: (i) de score van de Unified Parkinsons Disease Rating Scale (UPDRS), die parkinsonisme meet, en (ii) de score van de Abnormal Involuntary Movement Scale (AIMS), die dyskinesie meet. Hiervoor zijn de antipsychotica opgedeeld in eerste- en tweedegeneratie-antipsychotica, alsook in lage en hoge dopamine 2-receptor-affiniteit (D2-affiniteit).

In de analyses werden significante associaties gevonden tussen een vermindering van de ernst van de TD en zowel (i) het starten van of switchen naar een eerstegeneratie-antipsychoticum, als (ii) het starten van of switchen naar een antipsychoticum met hoge D2-affiniteit, alsook (iii) het toevoegen van een tweedegeneratie-antipsychoticum aan een eerstegeneratie-antipsychoticum.

Bij parkinsonisme voorspelde alleen het stoppen van antipsychotica een vermindering van de ernst van de bewegingsstoornis; een toename van de ernst werd gezien bij het starten van een middel met een hoge D2-affiniteit.

Deze bevindingen waren niet in lijn met de behandelrichtlijnen voor beide bewegingsstoornissen. Dit suggereert dat EPA-patiënten anders reageren dan op basis van de richtlijn verwacht wordt en dat de richtlijnen mogelijk aangepast moeten worden voor deze specifieke groep.

Hoofdstuk 3
Risicofactoren voor tremor bij EPA-patiënten

In dit hoofdstuk wordt er gekeken naar de prevalentie, risicofactoren en behandeling van tremoren bij patiënten met EPA. Ook deze studie heeft gebruikgemaakt van data uit de *Curaçao Extrapyramidal Syndromes Study*. Daarbij is er een onderscheid gemaakt tussen rusttremor en actietremor, die beide gemeten zijn met de UPDRS.

Ruim een derde van de patiënten had op enig moment gedurende de studie een tremor. Rusttremor kwam gemiddeld vaker voor (17%) dan actietremor (5,2%).

In de analyses was er een significante associatie tussen het krijgen van anticholinerge medicatie (anticholinergica worden vaak gegeven als behandeling voor parkinsonisme waar rusttremor bij hoort) en het ontwikkelen van rusttremor bij de volgende meting.

Bij actietremor was bij het krijgen van een bètablokker de kans op een tremor bij de volgende meting juist lager.

Deze resultaten laten zien dat tremoren veel voorkomen bij EPA-patiënten en dat het belangrijk is om onderscheid te maken tussen rust- en actietremor, omdat deze twee varianten verschillende risicofactoren hebben en een verschillende behandeling behoeven.

Hoofdstuk 4
Bewegingsstoornissen en mortaliteit bij EPA-patiënten

Gemiddeld leven mensen met EPA 15 tot 20 jaar korter dan mensen uit de algemene bevolking. In de *Curaçao Extrapyramidal Syndromes Study* was na 24 jaar 57% van de patiënten op gemiddeld 68-jarige leeftijd overleden.

TD en acathisie hadden geen significante relatie met het tijdstip van overlijden. Parkinsonisme gaf wel een verhoogd risico op vroegtijdig overlijden. Per punt op de UPDRS werd het risico op overlijden 2% hoger. Dat zou betekenen dat iemand met 50 punten een twee keer zo groot risico heeft om binnen een bepaalde periode te overlijden dan iemand zonder parkinsonisme. Dit laat zien dat bewegingsstoornissen een belangrijke impact kunnen hebben op de overleving van patiënten. Een verhoogd risico op vroegtijdig overlijden bij patiënten met parkinsonisme versus patiënten zonder parkinsonisme wil nog niet zeggen dat het overlijden direct een gevolg is van deze stoornis. Er kunnen ook andere factoren verbonden zijn met overlijden en met parkinsonisme. Bijvoorbeeld: als patiënten met parkinsonisme vaker vallen of zich vaker verslikken dan patiënten zonder parkinsonisme, en vallen en verslikken hangen samen met een verhoogd risico op vroegtijdig overlijden, dan is het effect van parkinsonisme op overlijden indirect.

Hoofdstuk 5
Knipperfrequentie van de oogleden als klinische test voor parkinsonisme

Momenteel wordt de UPDRS vaak gebruikt om de ernst van het parkinsonisme te meten. De schaal is uitgebreid onderzocht bij de ziekte van Parkinson en is ook heel bruikbaar bij parkinsonisme. De beoordelaars moeten echter uitvoerig getraind zijn, wat een belangrijke beperking is bij het gebruik van deze schaal in de klinische praktijk. Het doel van deze studie was om te onderzoeken of het meten van de knipperfrequentie van de oogleden tijdens conversatie een goede screeningsmethode was voor parkinsonisme.

Er bleek een zeer sterke associatie tussen knipperfrequentie en het aantal punten op de UPDRS. Een test met alleen knipperfrequentie zou echter ongeveer 50% van de patiënten correct classificeren. Dit percentage stijgt tot slechts 67% wanneer de knipperfrequentietest uitgevoerd wordt samen met klinische variabelen, zoals leeftijd, ge-

slacht en medicatiegebruik. Dit percentage is te laag om deze test als screeningstest te gebruiken voor parkinsonisme in de praktijk. Mogelijk kan de knipperfrequentietest gecombineerd worden met de tests in het volgende hoofdstuk om zo een betere totale test te krijgen.

Hoofdstuk 6
Het instrumenteel meten van bradykinesie: een vergelijking tussen verschillende taken

Een andere manier om parkinsonisme bij EPA-patiënten te meten is met sensoren die de snelheid van een beweging kunnen meten. Deze sensoren kunnen (met klittenband) om de ledematen bevestigd worden, maar kunnen bijvoorbeeld ook in smartphones zitten. In dit hoofdstuk wordt gekeken welke taken het best onderscheid maken tussen mensen met en mensen zonder parkinsonisme. In totaal zijn er elf taken onderzocht, waarvan de volgende vier het meest bruikbaar waren: (i) lopen, (ii) draaien van de pols, (iii) stampen met de voeten en (iv) buigen en strekken van de elleboog. Deze taken zouden bijvoorbeeld met de knipperfrequentietest gecombineerd kunnen worden.

Hoofdstuk 7
De veiligheid en effectiviteit van diepe hersenstimulatie als behandeling voor tardieve dyskinesie en/of dystonie: een systematische review

Diepe hersenstimulatie (DBS) is opgenomen in neurologische richtlijnen als optie voor het behandelen van TD. Er is echter weinig bekend over de mogelijke psychiatrische bijwerkingen van DBS bij mensen met een psychiatrische stoornis (in de voorgeschiedenis). Daarom hebben we een systematische zoekopdracht gedaan. In totaal zijn zeventien studies naar DBS bij TD met in totaal vijftig patiënten gevonden.

Gemiddeld verbeterde de bewegingsstoornis van patiënten met 77,5% op de Burke-Fahn-Marsden Dystonia Rating Scale (een schaal die de ernst van de dystonie/dyskinesie meet). Van de vijftig patiënten kregen er twee een terugval van een eerdere psychiatrische stoornis en ontwikkelde niemand een nieuwe psychiatrische stoornis. Omdat het terugvallen van een eerdere stoornis ook zonder DBS niet ongebruikelijk is, concludeerden we dat DBS waarschijnlijk een effectieve en relatief veilige behandeling is voor TD. Omdat vijftig patiënten echter een klein aantal is, moeten deze resultaten gerepliceerd worden in een groter onderzoek.

Hoofdstuk 8
Discussie

De belangrijkste conclusies uit dit proefschrift zijn onder te verdelen in het beloop, de herkenning en de behandeling van medicatiegeïnduceerde bewegingsstoornissen.

Beloop

Bij EPA-patiënten zijn bewegingsstoornissen wisselend aanwezig over de loop van de twintig tot veertig jaar waarin patiënten psychiatrisch ziek zijn. Een bewegingsstoornis kon gedurende een aantal jaren ernstig zijn, daarna een aantal jaren nauwelijks aanwezig zijn, en jaren later weer verschijnen. Medicatiewisselingen verklaarden maar een klein deel van de bewegingsstoornissen, zowel bij parkinsonisme als bij TD. Mogelijk komt dit doordat bewegingsstoornissen ook gerelateerd zijn aan de onderliggende psychiatrische aandoening.

Herkenning

Momenteel worden bewegingsstoornissen in de regel nog gediagnosticeerd en gevolgd met observatieschalen. Deze schalen hebben als voordeel dat ze onderzocht zijn op hun validiteit en betrouwbaarheid en dat ze vaak zijn gebruikt in onderzoek. Ze hebben echter als nadeel dat onderzoekers herhaaldelijk uitgebreid getraind moeten worden, dat ze subtiele bewegingsstoornissen niet detecteren en dat de ernst van een bewegingsstoornis moeilijk te interpreteren is omdat deze schalen ordinaal zijn. Instrumentele metingen hebben deze nadelen niet, en kunnen worden gebruikt voor het meten van de oogknipperfrequentie of de snelheid van een beweging. Wij verwachten dat de introductie van instrumenteel meten een snelle opmars zal beleven, omdat de sensoren goedkoper worden en meer geïntegreerd zullen zijn in smartphones.

Behandeling

Het kan zinvol zijn om bij parkinsonisme en rusttremor, indien mogelijk, antipsychotica te stoppen of de dosis te verlagen. De ernst van parkinsonisme neemt met gemiddeld 30% af als antipsychotica gestopt worden. De ernst neemt echter met (gemiddeld) nog geen 10% af als de dosis verlaagd wordt. Rusttremor neemt nauwelijks af bij dosisverlaging, en neemt opmerkelijk genoeg zelfs toe bij het toevoegen van anticholinergica, een interventie die in de richtlijn opgenomen is als behandeling voor parkinsonisme.

Actietremoren zijn daarentegen heel goed te behandelen. Dosisverlaging of stoppen van de medicatie die de tremor veroorzaakt (vaak antidepressiva of lithium), zorgt er meestal voor dat de tremor weggaat. Als dat niet kan vanwege risico op terugval van de psychiatrische aandoening, of als dit onvoldoende werkt, is het toevoegen van een

bètablokker (bijvoorbeeld propranolol) heel effectief. Het is dus belangrijk om bij een patiënt met een tremor onderscheid te maken tussen een actie- en een rusttremor.

Bij TD had, in ons onderzoek, het stoppen van antipsychotica of het veranderen van het soort antipsychoticum (zoals geadviseerd in de behandelrichtlijn) geen effect op de ernst van de bewegingsstoornis. Integendeel, het verhogen van de dosis van het antipsychoticum of het toevoegen van een tweede antipsychoticum leidde juist tot een vermindering van de ernst van de symptomen. Mocht TD farmacologisch onbehandelbaar zijn en een groot effect hebben op de kwaliteit van het leven van een patiënt, dan kan DBS overwogen worden.

Methodologische overwegingen

Het grootste deel van dit proefschrift is gebaseerd op de data van de *Curaçao Extrapyramidal Syndromes Study*. Voor zover bekend is dit de langstlopende studie naar bewegingsstoornissen ter wereld, en omdat alle patiënten van het eiland zijn opgenomen in de studie, zijn de resultaten goed te vertalen naar andere EPA-populaties. Patiënten zijn gedurende achttien jaar gevolgd en telkens door dezelfde twee psychiaters beoordeeld, waardoor de bewegingsstoornissen betrouwbaar zijn vastgelegd. Hierdoor is de studie geschikt om te beoordelen wat het effect van medicatieveranderingen op bewegingsstoornissen is in de dagelijkse klinische praktijk.

Traditioneel worden gerandomiseerde (interventie)onderzoeken (randomized controlled trials (RCT's)) gezien als de hoogste vorm van evidentie. Er zijn echter problemen met het vertalen van de resultaten van RCT's naar de dagelijkse praktijk. RCT's hebben vaak strenge inclusiecriteria in vergelijking met naturalistische studies, en deze patiëntengroepen zijn daarom niet altijd representatief voor de patiënten die de clinicus in de praktijk ziet. Daarnaast hebben deze studies vaak een hoge drop-out (patiënten beginnen wel aan de studie, maar stoppen voor ze afgelopen is), waardoor het moeilijk te bepalen is wat het middel doet bij de patiënten die de studie niet afmaken. Aangezien richtlijnen gemaakt worden op basis van RCT's, is het zinvol de RCT-resultaten te vergelijken met die van de naturalistische studies. Zo kan worden nagegaan of de resultaten uit RCT's ook van toepassing zijn in de klinische praktijk.

Suggesties voor toekomstig onderzoek

Onze resultaten laten zien dat medicatie en wijzigingen in de medicatie maar een deel van het voorkomen van parkinsonisme en TD bij patiënten met EPA kunnen verklaren. Interessant is dat onderzoek laat zien dat bewegingsstoornissen bij patiënten met een psychotische stoornis gerelateerd zijn aan de psychotische stoornis zelf. Meer onderzoek op dit gebied zou zowel inzicht geven in de onderliggende ziektemechanismes van psychotische stoornissen als in die van bewegingsstoornissen. Een langlopende prospectieve studie die in kaart brengt of bewegingsstoornissen inderdaad fluctueren in

samenhang met de psychiatrische symptomen, zou hier een belangrijke bijdrage aan kunnen leveren.

Een andere belangrijke ontwikkeling is het instrumenteel meten van bewegingsstoornissen. Voor de klinische praktijk zou een app op een mobiele telefoon een ideale manier zijn om bewegingsstoornissen bij een patiënt in de loop van de tijd objectief te meten. Een bewegingsstoornis zou mogelijk goed in kaart gebracht kunnen worden door een aantal korte testen te combineren, zoals knipperfrequentie, tremor, de snelheid van het tikken op het scherm en de snelheid van het lopen. Voor onderzoeksdoeleinden zullen mogelijk nauwkeurigere sensoren nodig zijn dan die in smartphones. Daarom zouden de sensoren die beschreven zijn in hoofdstuk 6 een goede manier zijn om parkinsonisme vast te stellen voor toekomstig onderzoek.

Valorisation

Relevance

Patients with severe mental illness (SMI) are often ill for decades. They have a lower quality of life and much higher morbidity and mortality, both in comparison to the general population and other patients with mental disorders (1). It is estimated that there are around 281,000 patients with SMI in the Netherlands (2). The socio-economic cost has not been calculated, but it is expected to be high, as patients with SMI often need ongoing psychiatric care and rarely have paid employment(3).

This thesis focuses on patients with SMI and specifically the long-term course, recognition, and treatment of movement disorders. Thus enabling us to i) identify which factors influence movement disorders over the course of a multidecade illness, ii) develop easier and more cost-effective ways of recognizing movement disorders, and iii) test if current treatment guidelines are effective in SMI patients. The *Curacao Extrapyramidal Syndromes Study* is well suited for this kind of research as it is the longest running study on movement disorders and it includes all patients with SMI on the island of Curacao thus limiting bias.

Studies have shown that over 80% (4,5)of SMI patients have at least one movement disorder and movement disorders are associated with lower quality of life (6), poor treatment adherence(7), and increased mortality (8–10). However, there is a paucity of research into movement disorders in psychiatric patients in general and movement disorders in SMI patients specifically. Currently, most treatment guidelines mentioning movement disorders do not differentiate between SMI and non-SMI. This differentiation is important because guidelines are often based on randomized controlled trials (RCTs) performed in populations that are less severely ill, younger, respond better to treatment and have fewer co-morbidities than SMI patients. Severity and duration of illness, co-morbidity, age, and duration of illness, are all factors known to influence the risk of developing movement disorders and their reaction to treatment. That is why multiple research groups have advocated to test RCT-based treatment recommendations in psychiatry with naturalistic studies (11,12).

Target groups

First and foremost this thesis is intended to improve the lives of patients with SMI and to inform the professionals who treat them on the prevalence and treatment options of movement disorders. This thesis is part of the movement for increased attention for SMI patients that started with the 2014 "Over de brug" report by the Kenniscentrum Phrenos. SMI patients have been receiving increased attention over the years as it has become clear that they are frequently at a disadvantage compared to other members of the population (Kenniscentrum Phrenos, 'Over de brug' report) both in the socio-economic realm as in

the medical realm. For instance, Dutch SMI patients have been shown to face stigmatization from health care professionals such as general practitioners and even doctors in training (13). Also the recent PHAMOUS study showed that patients with SMI have persistent low rates of treatment for various metabolic disorders (14).

This research has already been presented on multiple occasions both nationally and internationally and received the 2nd Prize for the best poster presentation from the Nederlandse Vereniging voor Psychiatrie (NNVP). It will also be presented to the Dutch organization for psychiatric patients and the organization for parents of psychiatric patients.

This thesis is of specific interest for the developers of treatment guidelines that cover SMI patients and policy makers connected to SMI patients, both in mental health organizations themselves and in the health insurance companies. To this purpose the members of committee that published the Dutch Schizophrenia treatment guideline have already been informed of the results of the article that show that the effect of switching antipsychotics and dose reduction on movement disorders is different in SMI patients compared to other psychiatric patients using antipsychotics.

Activities/Products

Wearables and other electronic monitoring devices are becoming more and more common in clinical and psychiatric practice. They have several important advantages over clinical rating scales and self report scales, firstly they offer an objective measurement thus reducing bias, secondly they can record patients symptoms in their daily life where they are most relevant and finally because they involve patients in their own treatment. As wearables are becoming cheaper and easier to use it is expected that they will become common place in psychiatric treatment

Originally we investigated blink rate because it would be easy to integrate into an app for a mobile phone. However, blink rate alone cannot sufficiently differentiate between patients with and without parkinsonism. Combining the blink rate with the tasks developed in chapter six (walking, foot stamping, wrist rotation, and bending and extending the elbow) could drastically improve the sensitivity and specificity of such an app. This app could be developed by a researcher within the MHeNS or by an external company.

On a broader scale the knowledge generated by this thesis has also been used to improve national training programs on movement for residents in psychiatry and nurse practitioners. Thus improving treatment for patients all over the Netherlands.

Innovation

This thesis is the first to focus on the very long term course of movement disorders in psychiatric patients. Whereas previous studies lasted, at most, three to five years this thesis has an 18 year follow-up making it unique. This offers new insight into how movement orders develop and fluctuate over the decades. Over the course of 10 to 20 years movement disorders relapse and remit multiple times within a single patient, even when no changes in medication are made.

This thesis, along with other research(15,15–22), challenges the theory that movement disorders in SMI patients are entirely based on medication or, more specifically for tardive dyskinesia and parkinsonism, antipsychotic use. This is important because it has an enormous impact on how to treat these movement disorders and well as how to prevent them. When the assumption is that movement disorders are solely caused by antipsychotic medication research and treatment guidelines will focus on stopping medication and dose reduction. When movement disorders are considered part of the psychiatric disorder their treatment could be either focused on managing the movement disorders themselves or on optimally treating the psychiatric disorder. Either way they are much more likely to be effective if the base assumption is correct. This is reflected in our findings in chapter two in which recommendations in treatment guidelines did not affect movement disorders in patients with SMI as predicted but had no effect or in some cases made the movement disorder worse.

Another way in which this thesis in innovative is the use of instrumental measures to diagnose and track movement disorders. As has been mentioned previously instrumental measures have important advantages over the clinical rating scales that are currently used in both research and clinical practice. They are objective and can be used with minimal training in many different settings. They use a continuous as opposed to an ordinal scale which means they are easier to interpret and better suited for tracking a movement disorder over time. And finally they are more sensitive and can be used to identify subtle movement disorders which current rating scales cannot do.

Schedule & Implementation

As a continuation of this thesis a new thesis will be started at the end of this year, with the aim to develop an integrated set of measures for movement disorders. This set will be implemented in the yearly screening and medication review of the SMI patient ward of GGz Centraal in Amersfoort.

Also the new thesis aims to create a longitudinal naturalistic database with data of movement disorders, quality of life, psychiatric symptoms, and medication use. This data will be made publically available thus enabling both researchers from GGz Centraal as well as researchers from other Dutch institutions to replicate guidelines recommendations in a naturalistic real world clinical setting. The results from these repli-

cations for patients with SMI can be integrated into current diagnosis based treatment guidelines. Thus enabling treatment guidelines to have recommendations and information specific to SMI patients.

In the long-term treatment guidelines specifically for SMI patients could be developed, thus making more tailored treatment possible for this patient group.

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Curriculum vitae

Charlie (Charlotte) Liduine Mentzel was born in Heerlen, Netherlands on June 22nd, 1984. She was raised in the Netherlands, Canada and Great Britain, and took part in a ten month exchange program in Japan during high school.

She obtained her Bachelors degree in biomedical sciences from the Universiteit Utrecht and in 2011 completed the Selective Utrecht Medical Master (SUMMA) program – a dual Masters degree granting the title of Medical Doctor and Clinical Researcher.

Following this she began training as a Psychiatry Registrar at GGZ centraal under Dr. H. J. G. M. van Megen (Head of Psychiatry residency program at GGZ centraal). She started her PhD program under Prof. P. N. van Harten (specialist in Movement Disorders in Psychosis at Maastrict University), as well Prof. M. de Koning-Tijssen (specialist in Movement Disorders in Neurology) and Dr. P. R. Bakker.

She has currently completed her basic training as Psychiatry Registrar, and will complete her senior training with the Waikata District Health Board in New Zealand. By the end of 2019, she plans to have completed her psychiatry training.

She is married to Christopher Pole, with whom they have two children, Elijah and Freya Pole.