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

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MOVEMENT DISORDERS IN PSYCHIATRY AS SYMPTOM, AS SIDE EFFECT, AND AS RISK FACTOR

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Voor Steven, Thura
mijn ouders
en Marc

Psychiatry is, and should be forever, a science dunked in the milk of human kindness (Kanner, 1942 p. 21)[1].

# Contents

# Chapter 1.

General introduction

Movement abnormalities (MAs) are intrinsically linked to psychiatric disorders[2-5]. Already in the beginning of clinical neurology and psychiatry in the early 19th century, MAs were recognized as a central symptom of psychiatric diagnoses[2, 6]. Two broad diagnostic categories in which disturbed motor behavior are often prominently featured, however not exclusively, are psychotic disorders and autism spectrum disorders (ASD).

The first systematic descriptions of what is currently known as schizophrenia have mentioned MAs[7-9]. Kraepelin dedicated several chapters to movement phenomena in his influential book 'Dementia praecox and paraphrenia' (1919)[7]. He gives, for instance, a lively description of the movement disorder we would now call orofacial dyskinesia: 'The spasmodic phenomena in the musculature of the face and of speech, which often appear, are extremely peculiar disorders. Some of them resemble movements of expression, wrinkling of the forehead, distortion of the corners of the mouth, irregular movements of the tongue and lips, twisting of the eyes, opening them wide, and shutting them tight, in short, those movements which we bring together under the name of making faces or grimacing.'

Also, for autism, from the earliest reports on, MAs have been noted. In the first publication of a case series of eleven children with 'early infantile autism', Kanner (1943, p. 248) observed that 'Several of the children were somewhat clumsy in gait and gross motor performances'[10].

The recognition of movement disorders in psychiatric disorders is important from both a clinical and research perspective. Movement disorders (MDs) occur frequently in patients with psychotic disorders[11, 12]. In patients at long-stay wards using antipsychotics, in whom MDs are most pronounced, up to 74% display at least one MD[12-14]. MDs can hinder patients in their daily activities[15], may cause feelings of shame[16] and can diminish patients' quality of life[17, 18]. In psychotic disorders, parkinsonism has been associated with less physical activity and more sedentary behavior[19], and parkinsonism and dyskinesia with a poorer psychiatric prognosis[11], cognitive deterioration[20, 21], worse global and social functioning[11, 22-25], and a shortened life expectancy[26, 27]. Furthermore, MDs occurring as side effect of antipsychotic medication may cause diminished treatment adherence[28,29].

MAs are highly prevalent in children with autism spectrum disorders (ASD), with 33%- 100% showing some form of motor delay in comparison with neurotypical children[30, 31]. Motor stereotypies are also common, in particular in children with greater severity of ASD and lower IQ[32, 33]. Motor abilities, social-communicative

and linguistic skills, and physical activity have been demonstrated to mutually influence each other in the development of children with ASD[34-37]. Thus, including motor skills in treatment may ameliorate various ASD-related and physical health outcomes[38]. Indeed, trials into exercise-based interventions such as sport and active play[39], creative yoga[40] and therapeutic horseback riding[41] show promising results.

Psychiatric disorders in general are complex, heterogeneous in etiology and presentation, and not well understood. Especially in psychotic disorders and ASD, more insight into movement disorders and their interactive connection with other symptoms and domains of functioning might improve our understanding[35, 42]. Knowledge of underlying networks has great potential for discovering new targets for pharmacological intervention and non-invasive brain stimulation[2, 43]. In the context of psychotic disorders, other promising clinical applications of MD measurement include predicting clinical outcomes and providing opportunities for personalized medicine[11, 43-45]. Furthermore, emerging evidence shows that some forms of motor disturbances may serve as a direct target for novel interventions[46].

## Movement disorders

A broad range of motor phenomena has been recognized in psychiatric disorders with different paradigms using their own terminology and interpretations[31, 47]. For example, in the schizophrenia literature, extrapyramidal syndromes, movement disorders, motor deficits, abnormal involuntary movements, neurological soft signs, psychomotor slowing and catatonia are referring to partly distinct and partly overlapping concepts. In research into motor behavior in ASD yet another terminology is generally used, like sensorimotor deficits, motor coordination, motor proficiency, motor skills, motor abilities, movement problems, and motor abnormalities[31].

Despite this wide variety of motor phenomena, the scope of this thesis encompasses three MDs most commonly referred to in the schizophrenia literature: dyskinesia, parkinsonism, and akathisia. The definitions given below are based on Van Harten (1998)[48]. Because dystonia is mentioned several times in the General Introduction and in the General Discussion, a definition of dystonia is also included. The term ‘movement disorders’ (MDs) in this thesis is used to refer to these phenomena.

*Dyskinesia* is a hyperkinetic movement disorder characterized by involuntary, writhing, irregular movements which are often fluid and choreatic but may occur as rapid jerking or slow and extended muscle spasms. The core sign is orofacial dyskinesia consisting of involuntary movements of the tongue, jaw, lips or face which manifest as twisting curling of protrusion of the tongue, chewing or lateral jaw movements, pursing, sucking, pouting or puckering of the lips, facial tics, and frequent eye blinking. Choreiform purposeless movement may also be present in the trunk and/or limbs, such as writhing movements of the fingers ('piano-playing fingers'), irregular toe movements, rotation of wrists, arms, ankles, and legs, head nodding, trunk movements, and pelvic thrusting. The respiratory system may also be included leading to symptoms of irregularity in the rate and/or rhythm of respiration, gasping, sighing and/or grunting, forceful breathing, and shortness of breath.[48]

*Parkinsonism* is a hypokinetic movement disorder consisting of bradykinesia, rigidity, tremor at rest and postural instability.

Bradykinesia (slowness of movement) and hypokinesia (reduced movement) or akinesia (lack of movement) are the most frequent and can be the only signs of parkinsonism. They result in monotonous speech, a reduction in facial expression and the rate of eye blinking, muscle fatigue or weakness, stooped posture, and slow walking with short steps and decreased arm swing. Sialorrhea may appear when saliva is not swallowed as fast as it is produced. Furthermore, dysarthria (difficulty with speaking) and dysphagia (swallowing difficulties) may be present.

Rigidity is characterized by a persistent increased tone of the muscles, which renders the muscles continuously or intermittently firm and tense and seems to be most prominent in the large flexor muscle groups.

Tremor at rest is a rhythmic tremor with a frequency of 3 – 5 Hz. The movement is a pronation and supination of the hands sometimes referred to as a pill-rolling tremor. Most often, it is localized in both hands but it can also be in one hand. Jaw, lips, head and limbs can be affected too. When the jaw is affected, it is called 'Rabbit syndrome'.

*Akathisia* is characterized by subjective feelings of inner restlessness, often accompanied by mental distress, and objective motor movement. The subjective sensation of restlessness is usually most prominent in the legs although some patients may experience a general feeling of unease in their body. The objective signs typically involve movement of the legs such as pacing when standing,

rocking from foot to foot, shuffling of the legs, or swinging of one leg while sitting. These movements are described as a response to an irresistible urge to move, but the movement alleviates the urge and distress only temporarily. The restlessness can preoccupy the patient's thinking and may be very difficult to endure.

*Dystonia* is a syndrome defined by sustained involuntary muscle contractions, frequently causing twisting and repetitive movements or abnormal postures. Usually, muscles of the upper part of the body are involved, the eyes (e.g., blefarospasm), neck (e.g., torticollis), face, jaw and or tongue (e.g., oromandibular dystonia), trunk, arms or hands. Sometimes legs, feet or pelvic muscles are also involved[49].

## Movement disorders as symptom, as side effect and as prognostic and risk factor

A complicating factor in the study of MDs is that MDs can occur as a symptom of a psychiatric disorder, as a side effect of antipsychotic medication[50], or as a result of MDs that have arisen as symptoms and have been modified by antipsychotics[4, 51]. Indeed, research has shown that antipsychotic medication can induce MDs, or improve, worsen, or left unchanged pre-existing MDs[51].

*Movement disorders as symptom in the psychosis spectrum and in ASD*

Evidence that MDs can be a symptom of psychotic disorders comes from the presence of MDs in I) antipsychotic naïve patients with schizophrenia. As mentioned above, MDs were described in the classic schizophrenia literature predating the neuroleptic era[7-9], and the occurrence of MDs in antipsychotic-naïve patients has been confirmed in more recent publications[52-54]. II) antipsychotic- naïve adolescents at clinical high risk of psychosis[55-57] and III) non-affected siblings of patients with schizophrenia[58]. MDs in the latter two groups tend to be more subtle in nature than in patients with schizophrenia and may only be detectable with instrumental measurements[44, 58].

A growing body of evidence suggests that psychosis may be conceptualized as a continuum with psychotic-like experiences in the absence of a psychiatric disorder on one end, and full-blown schizophrenia on the other end[59-63]. However, debate is ongoing to what extent this paradigm holds true and how psychotic-like experiences are related to diagnosable disorders[64-67]. Paramount in this context is research into auditory verbal hallucinations (AVH) in healthy individuals[64, 68, 69]. Knowledge about MDs in individuals with AVH can be another piece of the puzzle

in characterizing this population and can be informative on the broader question into the scope of the continuum paradigm[70].

In ASD, a broad spectrum of spontaneous MAs has been described including neurological soft signs, abnormal involuntary movements, catatonia, repetitive and/or stereotyped patterns of behavior, clumsy gait, poor muscle tone, imbalance, and impairment of motor skills[2, 71]. The prevalence of neurological soft signs, abnormal involuntary movements, and catatonia are estimated at 74%-100%, 18%-25% and 4%-7% respectively.[2] However the estimates about abnormal involuntary movements, which included parkinsonism, were based on only two studies[33, 72]. Moreover, there is a paucity of research into parkinsonism and dyskinesia in ASD in general, i.e., studies on prevalence, course, correlates with other symptoms, neurobiological substrates etc. are lacking[2].

*Movement disorders as side effect of antipsychotic medication*

Well-functioning motor control is dependent on extensive brain circuitry including cortico-striatal-thalamic-cortico loops moderated by dopamine[73]. Therefore, any dopamine-blocking drug can potentially induce MDs. The antiemetic metoclopramide for example, can cause MDs, irrespective of whether a patient has a psychiatric disorder or not[74-77]. As all currently licensed antipsychotic drugs block striatal D2 receptors[78], it is not surprising that they can cause or perpetuate MDs. Indeed, since the introduction of the first antipsychotic drug in 1952, MDs have been noted as side effect[79, 80] and the propensity of antipsychotic drugs to induce MDs has been demonstrated by numerous studies ever since[12, 50, 81-84]. In the decades following the advent of antipsychotic agents, the focus on MDs as a side effect grew stronger, even to the extent that interest in MDs as symptom almost disappeared[47].

This is exemplified by Diagnostic and Statistical Manual for Mental disorders (DSM) IV and 5, where parkinsonism, acute and tardive akathisia and dystonia, and tardive dyskinesia are defined as MDs caused by antipsychotic treatment[85, 86].

In the context of side effects, a distinction is made between acute and tardive (late onset) MDs. Acute MDs appear in the first few days or weeks of treatment or following an increase in the dose of an antipsychotic. They can be subdivided into acute akathisia, parkinsonism and dystonia. Tardive MDs develop after months or years of antipsychotic use and consist of tardive dyskinesia, tardive akathisia, and tardive dystonia[48].

For both acute and tardive MDs, important medication-related risk factors include type and dose of the antipsychotic. Antipsychotics with a higher affinity for the dopamine D2 receptor (high potency) and higher doses carry a greater risk[87-90]. For tardive dyskinesia, duration of antipsychotic treatment [89-91] and the number of interruptions are additional risk factors[92]. In general, second generation antipsychotics (SGAs) have a lower affinity for the D2 receptor than first generation antipsychotics (FGAs)[93] and many of the SGAs have antagonistic effects on the serotonin 5HT2 receptor[94] and anticholinergic properties[95]. Due to these characteristics, SGAs have a lower likelihood of inducing MDs than FGAs[96]. However, even in patients primarily treated with SGAs, the incidence of MDs remains substantial[97-99]. A recent overview of reviews and meta-analyses about fifteen SGAs and two FGAs compared the prevalence rates of acute MDs in randomized controlled trials. SGAs were associated with rates ranging from 3%-16% for akathisia, 1%-15% for dystonia, 2%- 29% for parkinsonism, and 0.2%-28% for tremor, depending on the type of SGA. The prevalence for these MDs associated with the two FGAs were 16%-25%, 11%-17%, 21%-23% and 19%-22% respectively[100]. A meta-analysis on the prevalence of tardive dyskinesia associated with antipsychotics reported rates of 30% for current FGA treatment versus 21% for current SGA treatment, and 7% for FGA-naïve patients treated with SGAs[98] . The 7% prevalence of tardive dyskinesia for FGA-naïve patients who are prescribed SGAs may be explained by the lower propensity of SGAs compared to FGAs to induce tardive dyskinesia[101]. Furthermore, the prevalence of 7% is at the lower end of the prevalence rates for spontaneous dyskinesia, which have been estimated to range from 4%-40% dependent on age[102]. This observation may point at an ameliorating effect of SGAs on pre-existing dyskinesia in some cases[51].

Patients with schizophrenia are often prescribed two or more antipsychotic drugs simultaneously with prevalences varying from 13%-70%, depending on treatment setting and country[103-105]. With exposure to two or more antipsychotics, patients are at a higher risk of multiple side effects including MDs[105, 106]. Antipsychotic polypharmacy is associated with prescription of high total doses[104, 107-110] which may be a mediating factor in increasing the risk of treatment emergent MDs[111].

In addition to the use in the treatment of psychotic disorders, antipsychotics are also increasingly prescribed for other indications including off-label for borderline personality disorder (BPD)[112, 113]. However, systematic reviews or meta-analyses on antipsychotic-related MDs in BPD have been lacking.

As mentioned above, it is important to note that in the context of antipsychotic medication, MDs in patients with psychiatric illnesses likely represent a com-

bination of spontaneous and drug-induced MDs. A conceptualization that has recently become more popular is that antipsychotic medication act upon and may modify (a vulnerability for) MDs which may have arisen as a result of the underlying pathophysiology[4, 51]. Thus, although we refer in part II. of this thesis to MDs as side effects for reasons of readability, the reality is more complex. Unfortunately, it is in most cases impossible to differentiate primary from drug-induced MDs in patients using antipsychotic medication.

*Movement disorders as prognostic factor and risk factor for mortality in psychotic disorders*

MAs have been shown to be predictive of clinical and functional outcome over time across the psychosis spectrum[19, 22]. A recent systematic review of 68 studies found that neurological soft signs, parkinsonism and dyskinesia were related to a worse outcome in terms of symptomatic course and global and social functioning[11]. These findings pertained to subjects with clinical high risk of developing a psychotic disorder, patients with first episode psychosis, and patients with schizophrenia, although the predictive value of the specific MAs varied over the different populations.

Another important outcome in individuals with psychotic disorders and specifically those with a chronic course and functional impairment classifying as severe mental illness (SMI), is mortality. Patients with SMI have a shortened life expectancy of 9-25[114-117] years, thus the identification of risk factors is of utmost importance. Some studies suggest that MDs may be a risk factor but not much research into this topic has been conducted, and results have been inconclusive[27, 118-120].

## Measurement of movement disorders

For the assessment of MDs, three approaches can be used: clinical examination, rating scales, and instrumental measurement. Traditionally, the former two have been applied most often in both clinical practice and research[121]. Rating scales are observation-based, ordinal scales with defined anchor points for severity classification. Although rating scales are frequently used, they have several disadvantages including substantial interrater variability, lack of linearity (a score twice as high may not correspond to an MD twice as severe), and limited sensitivity which may hamper the detection of subclinical MDs[49, 121]. Furthermore, adequate use requires time-consuming training.

Because MDs are directly observable – in contrast to other psychiatric symptoms–they are suitable for instrumental measurement techniques. In the past

decades, several instruments for the measurement of MDs and movement have been developed such as instruments which measure variation in exerted pressure[49, 122-125], techniques for the assessment of handwriting kinematics[126, 127], apps measuring tremor[128], and actigraphy[19, 129]. With instrumental measurements, the shortcomings of ratings scales are overcome, i.e., instrumental measurements are highly reliable, linearly related to severity, and they are very sensitive and able to detect subclinical MDs[58, 121, 122, 130]. However, an advantage of rating scales over most instrumental measurement technique is that with rating scales, all relevant body parts are assessed whereas instruments typically measure only one body part.

Since an instrument measuring finger dyskinesia, tremor, and bradykinesia has been used in two of the studies in this thesis, this instrument will be introduced further.

*Mechanical measurement of dyskinesia, tremor, and bradykinesia*

In the studies described in chapter 2 and 3 a mechanical instrument was used designed by Koning (2011)[49] based on the same principles as an earlier instrument developed by Caligiuri and Lohr (1990, 1992)[122, 125].

Dyskinesia of the fingers and tremor were assessed by measuring force variability (FV) with a task in which the participant attempts to exert a constant pressure on a button attached to a load cell (Fig 1.). The load cell is connected to a monitor showing a real-time graph indicating the target force and actual force applied (Fig 2.). The target force was set to an equivalent of 3 Newton[131]. FV in the 0-3 frequency range was used to measure dyskinesia as this is thought to reflect

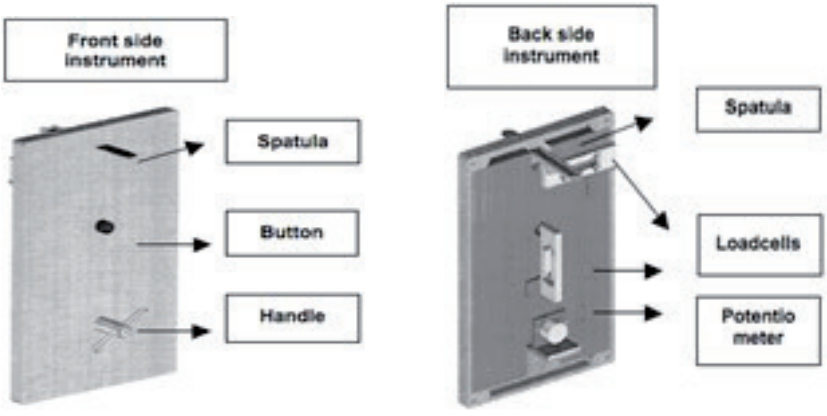


Figure 1. Mechanical instrument for measuring force variability and velocity scaling

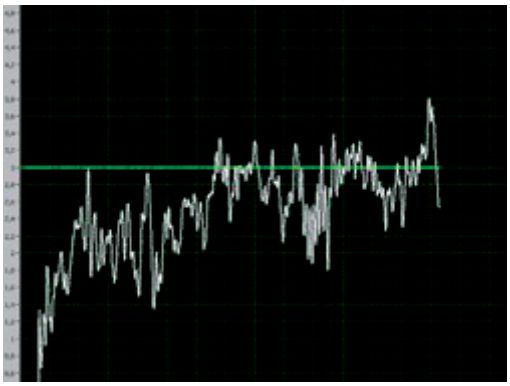

Figure 2. Test for force variability, as seen on the computer screen
*Example subject's force variability when trying to match the target pressure of 3N.*

dyskinesia[123] and is unaffected by resting tremor[58, 132]. This approach has been validated for finger dyskinesia in subjects with psychotic disorders[122, 130, 131, 133, 134]. For the measurement of tremor, FV in the 4-6 frequency ranged was used[58, 132].

Bradykinesia was determined by quantifying the ability to adjust the velocity of movement to changing distances[58, 125-127]. When the distance between two fixed targets is increased, healthy individuals (i.e., those without parkinsonism) typically increase their movement speed. Individuals with bradykinesia, on the other hand, have difficulty adjusting their movement speed and require more time to cover longer distances. The task measuring velocity scaling (VS) consisted of flexing a handle with the wrist as fast and as accurately as possible in order to move a flexible cursor presented on the monitor to a target cursor located at 25 degrees and 45 degrees from the midline of the wrist flexion[125] (Fig 3.). The handle is con-

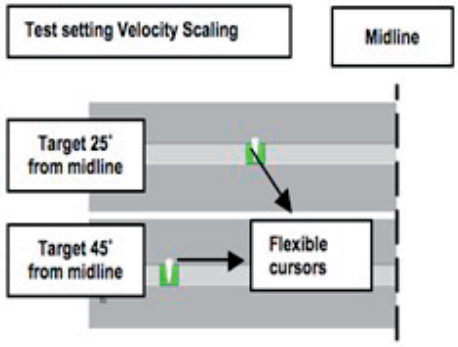


Figure 3. Test for velocity scaling

nected to a potentiometer attached to a monitor showing in real-time the target and the cursor. VS is measured in degree per second per degree (deg/s/deg). This technique has been validated for antipsychotic-induced bradykinesia[125, 126].

## Outline of this thesis

### Part I. Movement disorders as symptom

In chapter 2, we studied spontaneous dyskinesia in individuals with auditory verbal hallucinations (AVH) in the absence of a psychotic disorder. MDs are an intrinsic part of psychotic disorders[43, 48, 50, 135]. However, little is known about the occurrence of MDs in subjects with psychotic-like experiences who are not under psychiatric care[70]. If (subclinical) MDs are related to psychotic-like symptoms in otherwise healthy individuals, this would lend further evidence for the link between psychosis and spontaneous MDs. Furthermore, such a finding would support the concept of psychosis as a continuous phenomenon. As dyskinesia in healthy individuals with AVH may be more subtle in nature than in patients with psychotic disorders, we used the instrument described above to provide sensitive measurements of dyskinesia.

The study described in chapter 3 aimed to investigate if parkinsonism and dyskinesia are present in children and adolescents with ASD. Various MAs and developmental delays in motor milestones have been described in ASD but few studies assessed parkinsonism and dyskinesia[2]. Given the genetic overlap between schizophrenia and ASD[136, 137], similar MDs might occur in both populations. We studied subjects with ASD aged 6-26 years and compared them with age, sex and IQ matched healthy children and adolescents. Both rating scales and instrumental measurements of parkinsonism and dyskinesia were used to establish if these MDs were more prevalent in ASD than in typically developing subjects.

### Part II. Movement disorders as side effect

Chapter 4 aims to estimate the risk of acute antipsychotic-induced MDs in BPD. A large proportion of BPD patients receive off-label antipsychotic medication, predominantly SGAs. Since the 1990's up until around 2010 prescriptions of antipsychotics for BPD have been rising and they seem to have been more or less stable since then[112]. The most recent figures show that around one third of BPD outpatients and around 69% of BPD inpatients in Europe are prescribed an antipsychotic drug[112, 113].

We performed a meta-analysis on data of MDs from randomized controlled trials on efficacy and side effects of SGAs in BPD.

Chapter 5 comprises the first report of a trial into the effects of switching a combination of FGA(s) and SGA(s) to one antipsychotic in long-stay patients with SMI. Antipsychotic polypharmacy is common in schizophrenia, particularly in patients at long stay wards[138]. However, most guidelines advise against antipsychotic polypharmacy[139, 140] and evidence of its effectiveness is inconsistent[141-144]. Furthermore, patients who are prescribed antipsychotic polypharmacy are at increased risk of multiple side effects including MDs[105, 106]. We conducted a randomized controlled trial to study the effects of switching to one antipsychotic on relapse, psychotic symptoms, quality of life and side effects. In chapter 5, the first article of this study which focused on relapse and psychotic symptoms is delineated.



## Part III. Movement disorders as risk factor for mortality

The study described in Chapter 6 aims to shed light on the association of parkinsonism, akathisia, and dyskinesia with mortality in patients with SMI. As mentioned above, the lifespan of SMI patients is 9-25 years shorter than in the general population. Several factors are known to contribute to this huge difference, such as smoking, an unhealthy life style[145] and access to and quality of physical healthcare[146]. Some studies have suggested that MDs may be an additional risk factor[26, 120]. Tardive dyskinesia has received the most research attention in this respect, but results have been inconclusive[26, 119, 120, 147]. Furthermore, studies into the association between parkinsonism and akathisia and mortality are very scarce[27, 119, 120]. To investigate the potential role of MDs in mortality, we used data from the Curacao Extrapyramidal Syndromes Study. In this study, patients with SMI from the only psychiatric hospital on the island of Curacao were followed for a period of eighteen years. At baseline and seven follow-ups, tardive dyskinesia, parkinsonism and akathisia were assessed with validated rating scales. Because of the long follow-up period and multiple measurements of MDs, these data offered a unique opportunity to determine the association between MDs and mortality.

## References


1. Kanner L. Exoneration of the feebleminded. *Am J Psychiatry* 1942;99(1):17-22.
2. Hirjak D, Meyer-Lindenberg A, Fritze S, Sambataro F, Kubera KM, Wolf RC. Motor dysfunction as research domain across bipolar, obsessive-compulsive and neurodevelopmental disorders. *Neuroscience and biobehavioral reviews* Dec 2018;95:315-335.
3. van Harten PN, Tenback DE. Letter to the Editor: Movement disorders should be a criterion for schizophrenia in DSM-V. *Psychol Med* 2009;39(10):1754-1756.
4. Peralta V, Cuesta MJ. Motor Abnormalities: From Neurodevelopmental to Neurodegenerative Through "Functional" (Neuro)Psychiatric Disorders. *Schizophrenia bulletin* Sep 1 2017;43(5):956-971.
5. Bernard JA, Mittal VA. Updating the research domain criteria: the utility of a motor dimension. *Psychological medicine* Oct 2015;45(13):2685-2689.
6. Berrios GE, Marková IS. Historical and conceptual aspects of motor disorders in the psychoses. *Schizophrenia research* Oct 2018;200:5-11.
7. Kraepelin E. Dementia praecox and paraphrenia: LWW; 1921.
8. Bleuler E. *Dementia praecox oder Gruppe der Schizophrenien.* Vol 4: Deuticke; 1911.
9. Reiter PJ. Extrapyramidal motor disturbances in dementia praecox. *Acta Psychiatrica et Neurologica (KjøBenhavn)* 1926;1:287-304.
10. Kanner L. Autistic disturbances of affective contact. *Nervous Child* 1943;2(3):217-250.
11. Pieters LE, Nadesalingam N, Walther S, van Harten PN. A systematic review of the prognostic value of motor abnormalities on clinical outcome in psychosis. *Neuroscience and biobehavioral reviews* Jan 2022;132:691-705.
12. van Harten PN, Matroos GE, Hoek HW, Kahn RS. The prevalence of tardive dystonia, tardive dyskinesia, parkinsonism and akathisia. The Curaçao Extrapyramidal Syndromes Study: I. *Schizophr Res* 1996;19(195-203).
13. Bakker PR, de Groot IW, van Os J, van Harten PN. Long-Stay Psychiatric Patients: A Prospective Study Revealing Persistent Antipsychotic-Induced Movement Disorder. *PLoS One* 2011;6(10):e25588.
14. Parksepp M, Ljubajev U, Taht K, Janno S. Prevalence of neuroleptic-induced movement disorders: an 8-year follow-up study in chronic schizophrenia inpatients. *Nordic Journal of Psychiatry* 2016;70(7):498-502.
15. Fujimaki K, Morinobu S, Yamashita H, Takahashi T, Yamawaki S. Predictors of quality of life in inpatients with schizophrenia. *Psychiatry research* May 30 2012;197(3):199-205.
16. Brotchie J, Bezard E, Jenner P. *Pathophysiology, pharmacology and biochemistry of dyskinesia.* Vol 98: Academic Press; 2011.
17. McEvoy J, Gandhi SK, Rizio AA, Maher S, Kosinski M, Bjorner JB, Carroll B. Effect of tardive dyskinesia on quality of life in patients with bipolar disorder, major depressive disorder, and schizophrenia. *Qual Life Res* Dec 2019;28(12):3303-3312.
18. Adrianzén C, Arango-Dávila C, Araujo DM, Ruíz I, Walton RJ, Dossenbach M, Karagianis J. Relative association of treatment-emergent adverse events with quality of life of patients with schizophrenia: post hoc analysis from a 3-year observational study. *Human psychopharmacology* Aug 2010;25(6):439-447.

19. Pieters LE, Deenik J, Tenback DE, van Oort J, van Harten PN. Exploring the Relationship Between Movement Disorders and Physical Activity in Patients With Schizophrenia: An Actigraphy Study. *Schizophrenia bulletin* Jul 8 2021;47(4):906-914.
20. Cuesta MJ, Sánchez-Torres AM, García de Jalón E, Campos MS, Ibáñez B, Moreno-Izco L, Peralta V. Spontaneous Parkinsonism Is Associated With Cognitive Impairment in Antipsychotic-Naive Patients With First-Episode Psychosis: A 6-Month Follow-up Study. *Schizophr Bull* September 1, 2014 2014;40(5):1164-1173.
21. Chen L, Ascher-Svanum H, Lawson A, Stauffer VL, Nyhuis A, Haynes V, Schuh K, Kinon BJ. Movement disorder profile and treatment outcomes in a one-year study of patients with schizophrenia. *Neuropsychiatr Dis Treat* 2013;9:815-822.
22. Nadesalingam N, Chapellier V, Lefebvre S, et al. Motor abnormalities are associated with poor social and functional outcomes in schizophrenia. *Compr Psychiatry* 2022/05/01/ 2022;115:152307.
23. Cuesta MJ, García de Jalón E, Campos MS, Moreno-Izco L, Lorente-Omeñaca R, Sánchez-Torres AM, Peralta V. Motor abnormalities in first-episode psychosis patients and long-term psychosocial functioning. *Schizophrenia research* Oct 2018;200:97-103.
24. Mittal VA, Jalbrzikowski M, Daley M, Roman C, Bearden CE, Cannon TD. Abnormal movements are associated with poor psychosocial functioning in adolescents at high risk for psychosis. *Schizophr Res* 2011;130(1-3):164-169.
25. Ascher-Svanum H, Zhu B, Faries D, Peng X, Kinon BJ, Tohen M. Tardive dyskinesia and the 3-year course of schizophrenia: results from a large, prospective, naturalistic study. *The Journal of clinical psychiatry* Oct 2008;69(10):1580-1588.
26. Ballesteros J, Gonzáles-Pinto A, Bulbena A. Tardive dyskinesia associated with higher mortality in psychiatric patients: results of a meta-analysis of seven independent studies. *J Clin Psychopharmacol* 2000;20(2):188-194.
27. Schoepf D, Uppal H, Potluri R, Heun R. Physical comorbidity and its relevance on mortality in schizophrenia: a naturalistic 12-year follow-up in general hospital admissions. *Eur Arch Psychiatry Clin Neurosci* 2014;264(1):3-28.
28. Fenton WS, Blyler CR, Heinssen RK. Determinants of medication compliance in schizophrenia: empirical and clinical findings. *Schizophr Bull* 1997;23(4):637-651.
29. Lohr JB, Eidt CA, Abdulrazzaq Alfaraj A, Soliman MA. The clinical challenges of akathisia. *CNS Spectr* Dec 2015;20 Suppl 1:1-14; quiz 15-16.
30. Green D, Charman T, Pickles A, Chandler S, Loucas T, Simonoff E, Baird G. Impairment in movement skills of children with autistic spectrum disorders. *Dev Med Child Neurol* Apr 2009;51(4):311-316.
31. Damme TV, Simons J, Sabbe B, van West D. Motor abilities of children and adolescents with a psychiatric condition: A systematic literature review. *World J Psychiatry* 2015;5(3):315-329.
32. Melo C, Ruano L, Jorge J, Pinto Ribeiro T, Oliveira G, Azevedo L, Temudo T. Prevalence and determinants of motor stereotypies in autism spectrum disorder: A systematic review and meta-analysis. *Autism* Apr 2020;24(3):569-590.
33. Campbell M, Locascio JJ, Choroco MC, Spencer EK, Malone RP, Kafantaris V, Overall JE. Stereotypies and tardive dyskinesia: Abnormal movements in autistic children. *Psychopharmacol Bull* 1990;26(2):260-266.

34. MacDonald M, Lord C, Ulrich DA. The relationship of motor skills and social communicative skills in school-aged children with autism spectrum disorder. *Adapt Phys Activ Q* Jul 2013;30(3):271-282.
35. Ohara R, Kanejima Y, Kitamura M, Izawa KP. Association between Social Skills and Motor Skills in Individuals with Autism Spectrum Disorder: A Systematic Review. *Eur J Investig Health Psychol Educ* Dec 12 2019;10(1):276-296.
36. Mody M, Shui AM, Nowinski LA, Golas SB, Ferrone C, O'Rourke JA, McDougle CJ. Communication Deficits and the Motor System: Exploring Patterns of Associations in Autism Spectrum Disorder (ASD). *J Autism Dev Disord* 2017/01/01 2017;47(1):155-162.
37. Pusponegoro HD, Efar P, Soedjatmiko, Soebadi A, Firmansyah A, Chen HJ, Hung KL. Gross Motor Profile and Its Association with Socialization Skills in Children with Autism Spectrum Disorders. *Pediatr Neonatol* Dec 2016;57(6):501-507.
38. Yu CCW, Wong SWL, Lo FSF, So RCH, Chan DFY. Study protocol: a randomized controlled trial study on the effect of a game-based exercise training program on promoting physical fitness and mental health in children with autism spectrum disorder. *BMC Psychiatry* Feb 27 2018;18(1):56.
39. Najafabadi MG, Sheikh M, Hemayattalab R, Memari AH, Aderyani MR, Hafizi S. The effect of SPARK on social and motor skills of children with autism. *Pediatr Neonatol* Oct 2018;59(5):481-487.
40. Kaur M, Bhat A. Creative Yoga Intervention Improves Motor and Imitation Skills of Children With Autism Spectrum Disorder. *Phys Ther* Nov 25 2019;99(11):1520-1534.
41. Gabriels RL, Pan Z, Dechant B, Agnew JA, Brim N, Mesibov G. Randomized Controlled Trial of Therapeutic Horseback Riding in Children and Adolescents With Autism Spectrum Disorder. *J Am Acad Child Adolesc Psychiatry* Jul 2015;54(7):541-549.
42. Moura BM, van Rooijen G, Schirmbeck F, et al. A Network of Psychopathological, Cognitive, and Motor Symptoms in Schizophrenia Spectrum Disorders. *Schizophr Bull* 2021;47(4):915-926.
43. Mittal VA, Walther S. As Motor System Pathophysiology Returns to the Forefront of Psychosis Research, Clinical Implications Should Hold Center Stage. *Schizophrenia bulletin* Apr 25 2019;45(3):495-497.
44. Dean DJ, Walther S, Bernard JA, Mittal VA. Motor clusters reveal differences in risk for psychosis, cognitive functioning, and thalamocortical connectivity: evidence for vulnerability subtypes. *Clin Psychol Sci* Sep 1 2018;6(5):721-734.
45. van Harten PN, Pieters LE. Clinical Consequences of Motor Behavior as Transdiagnostic Phenomenon. *Schizophrenia bulletin* Mar 17 2022.
46. Schülke R, Straube B. Transcranial Direct Current Stimulation Improves Semantic Speech-Gesture Matching in Patients With Schizophrenia Spectrum Disorder. *Schizophrenia bulletin* Apr 25 2019;45(3):522-530.
47. Walther S, Strik W. Motor Symptoms and Schizophrenia. *Neuropsychobiology* 2012;66(2):77-92.
48. Van Harten PN. *Movement disorders associated with neuroleptics. The Curacao extrapyramidal syndromes study.* Utrecht, Universiteit Utrecht; 1998.
49. Koning JP. Movement disorders in patients with schizophrenia and their siblings; symptoms, side effects and mechanical measurements. *Utrecht: Psychiatry* 2011.

50. van Harten PN, Bakker PR, Mentzel CL, Tijssen MA, Tenback DE. Movement Disorders and Psychosis, a Complex Marriage. *Frontiers in Psychiatry* 2015-January-09 2015;5(190).
51. Peralta V, Cuesta MJ. The effect of antipsychotic medication on neuromotor abnormalities in neuroleptic-naive nonaffective psychotic patients: a naturalistic study with haloperidol, risperidone, or olanzapine. *Prim Care Companion J Clin Psychiatry* 2010;12(2).
52. Koning JP, Tenback DE, van Os J, Aleman A, Kahn RS, van Harten PN. Dyskinesia and parkinsonism in antipsychotic-naive patients with schizophrenia, first-degree relatives and healthy controls: a meta-analysis. *Schizophr Bull* 2010;36(4):723-731.
53. Pappa S, Dazzan P. Spontaneous movement disorders in antipsychotic-naive patients with first-episode psychoses: a systematic review. *Psychol Med* 2009;39(07):1065-1076.
54. Ayehu M, Shibre T, Milkias B, Fekadu A. Movement disorders in neuroleptic-naïve patients with schizophrenia spectrum disorders. *BMC Psychiatry* Oct 9 2014;14:280.
55. Dean DJ, Mittal VA. Spontaneous parkinsonisms and striatal impairment in neuroleptic free youth at ultrahigh risk for psychosis. *NPJ Schizophr* 2015;1:14006-.
56. Mittal VA, Neumann C, Saczawa M, Walker EF. Longitudinal progression of movement abnormalities in relation to psychotic symptoms in adolescents at high risk of schizophrenia. *Archives of General Psychiatry* 2008;65(2):165-171.
57. Dean DJ, Bernard JA, Damme KSF, O'Reilly R, Orr JM, Mittal VA. Longitudinal Assessment and Functional Neuroimaging of Movement Variability Reveal Novel Insights Into Motor Dysfunction in Clinical High Risk for Psychosis. *Schizophrenia bulletin* Dec 1 2020;46(6):1567-1576.
58. Koning JP, Kahn R, Tenback DE, van Schelven LJ, van Harten PN. Movement disorders in nonpsychotic siblings of patients with nonaffective psychosis. *Psychiatry Res* 2011;188(1):133-137.
59. van Os J, Hanssen M, Bijl RV, Ravelli A. Strauss (1969) revisited: a psychosis continuum in the general population? *Schizophr Res* 2000;45(1-2):11-20.
60. Kelleher I, Jenner JA, Cannon M. Psychotic symptoms in the general population - an evolutionary perspective. *The British Journal of Psychiatry* 2010-09-01 00:00:00 2010;197(3):167-169.
61. van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychol Med* 2009;39(02):179-195.
62. Kelleher I, Wigman JTW, Harley M, et al. Psychotic experiences in the population: Association with functioning and mental distress. *Schizophr Res* 2015;165(1):9-14.
63. DeRosse P, Karlsgodt KH. Examining the Psychosis Continuum. *Current behavioral neuroscience reports* 2015;2(2):80-89.
64. Daalman K, Boks MPM, Diederen KM, de Weijer AD, Blom JD, Kahn RS, Sommer IEC. The same or different? A phenomenological comparison fo auditory verbal hallucinations in healthy and psychotic individuals. *The Journal of clinical psychiatry* 2010;72(2):320-325.
65. Linscott RJ, van Os J. Systematic reviews of categorical versus continuum models in psychosis: evidence for discontinuous subpopulations underlying a psychometric

continuum. Implications for DSM-V, DSM-VI, and DSM-VII. *Annu Rev Clin Psychol* 2010;6:391-419.
66. Sommer IE. The continuum hypothesis of psychosis: David's criticisms are timely. *Psychol Med* 2010;40(12):1959-1961.
67. David AS. Why we need more debate on whether psychotic symptoms lie on a continuum with normality. *Psychol Med* 2010;40(12):1935-1942.
68. Sommer IEC, Daalman K, Rietkerk T, Diederen KM, Bakker S, Wijkstra J, Boks MPM. Healthy Individuals With Auditory Verbal Hallucinations; Who Are They? Psychiatric Assessments of a Selected Sample of 103 Subjects. *Schizophr Bull* May 1, 2010 2010;36(3):633-641.
69. Baumeister D, Sedgwick O, Howes O, Peters E. Auditory verbal hallucinations and continuum models of psychosis: A systematic review of the healthy voice-hearer literature. *Clin Psychol Rev* Feb 2017;51:125-141.
70. Mittal VA, Dean DJ, Pelletier A, Caligiuri M. Associations between spontaneous movement abnormalities and psychotic-like experiences in the general population. *Schizophr Res* 2011;132:194-196.
71. Vaquerizo-Serrano J, Salazar De Pablo G, Singh J, Santosh P. Catatonia in autism spectrum disorders: A systematic review and meta-analysis. *Eur Psychiatry* Dec 15 2021;65(1):e4.
72. Starkstein S, Gellar S, Parlier M, Payne L, Piven J. High rates of parkinsonism in adults with autism. *Journal of neurodevelopmental disorders* 2015;7(1):29.
73. DeLong MR, Wichmann T. Circuits and circuit disorders of the basal ganglia. *Arch Neurol* 2007;64(1):20-24.
74. Rao AS, Camilleri M. Review article: metoclopramide and tardive dyskinesia. *Aliment Pharmacol Ther* Jan 2010;31(1):11-19.
75. Chauhan G, Nayar P, Kashyap C. Metoclopramide-induced akathisia. *J Anaesthesiol Clin Pharmacol* Oct 2012;28(4):548-549.
76. Al-Saffar A, Lennernäs H, Hellström PM. Gastroparesis, metoclopramide, and tardive dyskinesia: Risk revisited. *Neurogastroenterol Motil* Nov 2019;31(11):e13617.
77. Lai CH, Yeh YC, Chen YY. Metoclopramide as a prokinetic agent for diabetic gastroparesis: revisiting the risk of Parkinsonism. *Ther Adv Drug Saf* 2019;10:2042098619854007.
78. Howes OD, Kapur S. The Dopamine Hypothesis of Schizophrenia: Version III - The Final Common Pathway. *Schizophr Bull* May 1, 2009 2009;35(3):549-562.
79. Steck H. [Extrapyramidal and diencephalic syndrome in the course of largactil and serpasil treatments]. *Ann Med Psychol (Paris)* Dec 1954;112(2 5):737-744.
80. Delay J, Deniker P. Chlorpromazine and neuroleptic treatments in psychiatry. *J Clin Exp Psychopathol* Jan-Mar 1956;17(1):19-24.
81. Malhotra AK, Litman RE, Pickar D. Adverse effects of antipsychotic drugs. *Drug Saf* Dec 1993;9(6):429-436.
82. van Harten PN, Hoek HW, Matroos GE, van Os J. Incidence of tardive dyskinesia and tardive dystonia in African Caribbean Patients on long-term antipsychotic treatment: the Curaçao Extrapyramidal Syndromes Study V. *The Journal of clinical psychiatry* 2006;67:1920-1927.
83. Gao K, Kemp DE, Ganocy SJ, Gajwani P, Xia G, Calabrese JR. Antipsychotic-induced extrapyramidal side effects in bipolar disorder and schizophrenia. A systematic Review. *J Clin Psychopharmacol* 2008;28(2):203-209.

84. Kapur S, Zipursky RB, Jones C, Remington G, Houle S. Relationship between dopamine D2 occupancy, clinical respons, and side effects: a double-blind PET study of first episode schizophrenia. *Am J Psychiatry* 2000;157(4):514-520.
85. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th ed.); 2000.
86. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.); 2013.
87. Sachdev P. The epidemiology of drug-induced akathisia: Part I. Acute akathisia. *Schizophrenia bulletin* 1995;21(3):431-449.
88. Miller CH, Fleischhacker WW. Managing antipsychotic-induced acute and chronic akathisia. *Drug Saf* Jan 2000;22(1):73-81.
89. Van Harten PN. *Bewegingsstoornissen door antipsychotica; diagnostiek en behandeling*. Amsterdam: Boom; 2000.
90. Tenback DE, van Harten PN, Slooff CJ, Belger MA, van Os J. Effects of antipsychotic treatment on tardive dyskinesia: a 6-month evaluation of patients from the European Schizophrenia Outpatient Health Outcomes (SOHO) Study. *The Journal of clinical psychiatry* Sep 2005;66(9):1130-1133.
91. Stegmayer K, Walther S, van Harten P. Tardive Dyskinesia Associated with Atypical Antipsychotics: Prevalence, Mechanisms and Management Strategies. *CNS drugs* Feb 2018;32(2):135-147.
92. van Harten PN, Hoek HW, Matroos GE, Koeter M, Kahn RS. Intermittent neuroleptic treatment and risk for tardive dyskinesia: Curaçao Extrapyramidal Syndromes Study III. *The American journal of psychiatry* Apr 1998;155(4):565-567.
93. Seeman P, Corbett R, Van Tol HHM. Atypical Neuroleptics Have Low Affinity for Dopamine D2 Receptors or Are Selective for D4 Receptors. *Neuropsychopharmacology* 1997/02/01 1997;16(2):93-110.
94. Meltzer HY, Li Z, Kaneda Y, Ichikawa J. Serotonin receptors: their key role in drugs to treat schizophrenia. *Progress in neuro-psychopharmacology & biological psychiatry* Oct 2003;27(7):1159-1172.
95. Chew ML, Mulsant BH, Pollock BG, et al. A model of anticholinergic activity of atypical antipsychotic medications. *Schizophr Res* 2006;88(1-3):63-72.
96. Sykes DA, Moore H, Stott L, Holliday N, Javitch JA, Lane JR, Charlton SJ. Extrapyramidal side effects of antipsychotics are linked to their association kinetics at dopamine D(2) receptors. *Nat Commun* Oct 2 2017;8(1):763.
97. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* Sep 14 2013;382(9896):951-962.
98. Carbon M, Hsieh CH, Kane JM, Correll CU. Tardive Dyskinesia Prevalence in the Period of Second-Generation Antipsychotic Use: A Meta-Analysis. *The Journal of clinical psychiatry* Mar 2017;78(3):e264-e278.
99. Kahn RS, Fleischhacker WW, Boter H, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet* Mar 29 2008;371(9618):1085-1097.
100. Martino D, Karnik V, Osland S, Barnes TRE, Pringsheim TM. Movement Disorders Associated With Antipsychotic Medication in People With Schizophrenia: An Overview of Cochrane Reviews and Meta-Analysis. *Can J Psychiatry* Jan 1 2018;63(11):706743718777392.

101. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. *The American journal of psychiatry* Mar 2004;161(3):414-425.
102. Fenton WS. Prevalence of spontaneous dyskinesia in schizophrenia. *The Journal of clinical psychiatry* 2000;61 Suppl 4:10-14.
103. Barbui C, Nose M, Mazzi MA, et al. Persistence with polypharmacy and excessive dosing in patients with schizophrenia treated in four European countries. *International clinical psychopharmacology* Nov 2006;21(6):355-362.
104. Igbinomwanhia NG, Olotu SO, James BO. Prevalence and correlates of antipsychotic polypharmacy among outpatients with schizophrenia attending a tertiary psychiatric facility in Nigeria. *Therapeutic advances in psychopharmacology* Jan 2017;7(1):3-10.
105. Westaway K, Sluggett JK, Alderman C, Procter N, Roughead E. Prevalence of multiple antipsychotic use and associated adverse effects in Australians with mental illness. *International journal of evidence-based healthcare* Sep 2016;14(3):104-112.
106. Gallego JA, Nielsen J, De Hert M, Kane JM, Correll CU. Safety and tolerability of antipsychotic polypharmacy. *Expert opinion on drug safety* Jul 2012;11(4):527-542.
107. Correll CU, Rummel-Kluge C, Corves C, Kane JM, Leucht S. Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. *Schizophrenia bulletin* Mar 2009;35(2):443-457.
108. Procyshyn RM, Honer WG, Wu TK, Ko RW, McIsaac SA, Young AH, Johnson JL, Barr AM. Persistent antipsychotic polypharmacy and excessive dosing in the community psychiatric treatment setting: a review of medication profiles in 435 Canadian outpatients. *The Journal of clinical psychiatry* May 2010;71(5):566-573.
109. Sim K, Su A, Fujii S, et al. Antipsychotic polypharmacy in patients with schizophrenia: a multicentre comparative study in East Asia. *Br J Clin Pharmacol* Aug 2004;58(2):178-183.
110. Ghio L, Natta W, Gotelli S, Ferrannini L. Antipsychotic utilisation and polypharmacy in Italian residential facilities: a survey. *Epidemiology and psychiatric sciences* Jun 2011;20(2):171-179.
111. Carnahan RM, Lund BC, Perry PJ, Chrischilles EA. Increased risk of extrapyramidal side-effect treatment associated with atypical antipsychotic polytherapy. *Acta psychiatrica Scandinavica* Feb 2006;113(2):135-141.
112. Pascual JC, Martín-Blanco A, Soler J. Twenty-Year Trends in the Psychopharmacological Treatment of Outpatients with Borderline Personality Disorder: A Cross-Sectional Naturalistic Study in Spain. *CNS drugs* Sep 2021;35(9):1023-1032.
113. Bridler R, Häberle A, Müller ST, Cattapan K, Grohmann R, Toto S, Kasper S, Greil W. Psychopharmacological treatment of 2195 in-patients with borderline personality disorder: A comparison with other psychiatric disorders. *Eur Neuropsychopharmacol* Jun 2015;25(6):763-772.
114. Laursen TM. Life expectancy among persons with schizophrenia or bipolar affective disorder. *Schizophr Res* 2011;131(1-3):101-104.
115. Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, Haukka J. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *The Lancet* 2009/8/28/ 2009;374(9690):620-627.

116. Crump C, Winkleby MA, Sundquist K, Sundquist J. Comorbidities and Mortality in Persons With Schizophrenia: A Swedish National Cohort Study. *Am J Psychiatry* 2013;170(3):324-333.
117. Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and mortality in bipolar disorder: A swedish national cohort study. *JAMA psychiatry* 2013;70(9):931-939.
118. Ballesteros J, González-Pinto A, Bulbena A. Tardive dyskinesia associated with higher mortality in psychiatric patients: results of a meta-analysis of seven independent studies. *J Clin Psychopharmacol* 2000;20(2):188-194.
119. Modestin J, Vogt Wehrli M, Stephan PL, Agarwalla P. Relationship between Neuroleptic Extrapyramidal Syndromes and Patients' All-Cause Mortality. *Pharmacopsychiatry* 2009;42(02):57-60.
120. Chong S-A, Tay JAM, Subramaniam M, Pek E, Machin D. Mortality Rates Among Patients With Schizophrenia and Tardive Dyskinesia. *J Clin Psychopharmacol* 2009;29(1):5-8.
121. van Harten PN, Walther S, Kent JS, Sponheim SR, Mittal VA. The clinical and prognostic value of motor abnormalities in psychosis, and the importance of instrumental assessment. *Neuroscience and biobehavioral reviews* Sep 2017;80:476-487.
122. Caligiuri MP, Lohr JB. Fine force instability: a quantitative measure of neuroleptic-induced dyskinesia in the hand. *J Neuropsychiatr* 1990;2:395-398.
123. Lohr JB, Caligiuri MP. Quantitative instrumental measurement of tardive dyskinesia: a review. *Neuropsychopharmacology* 1992;6(4):231-239.
124. Caligiuri MP, Lohr JB, Rotrosen J, Adler L, Lavori P, Edson R, Tracy K. Reliability of an instrumental assessment of tardive dyskinesia: results from VA Cooperative Study #394. *Psychopharmacology* Jul 1997;132(1):61-66.
125. Caligiuri MP, Lohr JB, Ruck RK. Scaling of movement velocity: A measure of neuromotor retardation in individuals with psychopathology. *Psychophysiology* 1998;35(4):431-437.
126. Caligiuri MP, Teulings HL, Filoteo JV, Song D, Lohr JB. Quantitative measurement of handwriting in the assessment of drug-induced parkinsonism. *Human movement science* Oct 2006;25(4-5):510-522.
127. Caligiuri MP, Teulings H-L, Dean CE, Niculescu Iii AB, Lohr JB. Handwriting movement kinematics for quantifying extrapyramidal side effects in patients treated with atypical antipsychotics. *Psychiatry Res* 2010;177:77-83.
128. Kubben PL, Kuijf ML, Ackermans LP, Leentjens AF, Temel Y. TREMOR12: An Open-Source Mobile App for Tremor Quantification. *Stereotact Funct Neurosurg* 2016;94(3):182-186.
129. Tahmasian M, Khazaie H, Golshani S, Avis KT. Clinical application of actigraphy in psychotic disorders: a systematic review. *Curr Psychiatry Rep* Jun 2013;15(6):359.
130. Cortese L, Caligiuri MP, Malla AK, Manchanda R, Takhar J, Haricharan R. Relationship of neuromotor disturbances to psychosis symptoms in first-episode neuroleptic-naive schizophrenia patients. *Schizophr Res* 2005;75(1):65-75.
131. Dean CE, Russel JM, Kuskowski MA, Caligiuri MP, Nugent SM. Clinical rating scales and instruments. How do they compare in assessing abnormal involuntary movements? *Journal of clinical psychopharmacology* 2004;24:298-304.
132. Stein RB, Oguztoreli MN. Tremor and other oscillations in neuromuscular systems. *Biological cybernetics* 1976;22(3):147-157.

133. Caligiuri MP, Lohr JB. A disturbance in the control of muscle force in neuroleptic-naive schizophrenic patients. *Biological psychiatry* Jan 15 1994;35(2):104-111.
134. Caligiuri MP, Lohr JB, Vaughan RM, McAdams L. Fluctuation of tardive dyskinesia. *Biol Psychiatry* 1995/09/01/ 1995;38(5):336-339.
135. Hirjak D, Meyer-Lindenberg A, Kubera KM, Thomann PA, Wolf RC. Motor dysfunction as research domain in the period preceding manifest schizophrenia: A systematic review. *Neuroscience & Biobehavioral Reviews* 2018/04/01/ 2018;87:87-105.
136. Burbach JP, van der Zwaag B. Contact in the genetics of autism and schizophrenia. *Trends Neurosci* Feb 2009;32(2):69-72.
137. Forsyth JK, Nachun D, Gandal MJ, Geschwind DH, Anderson AE, Coppola G, Bearden CE. Synaptic and Gene Regulatory Mechanisms in Schizophrenia, Autism, and 22q11.2 Copy Number Variant-Mediated Risk for Neuropsychiatric Disorders. *Biological psychiatry* Jan 15 2020;87(2):150-163.
138. Gallego JA, Bonetti J, Zhang J, Kane JM, Correll CU. Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. *Schizophrenia research* Jun 2012;138(1):18-28.
139. NICE National institute for Health and Care Excellence, Schizophrenia Clinical guideline.
140. Stuurgroep multidisciplinaire richtlijnontwikkeling GGZ. Multidisciplinaire richtlijn schizofrenie (Dutch Clinical guideline for Schizophrenia). 2012.
141. Correll CU, Rummel-Kluge C, Corves C, Kane JM, Leucht S. Antipsychotic Combinations vs Monotherapy in Schizophrenia: A Meta-analysis of Randomized Controlled Trials. *Schizophr Bull* 2009;35(2):443-457.
142. Galling B, Roldan A, Hagi K, et al. Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis. *World psychiatry : official journal of the World Psychiatric Association (WPA)* Feb 2017;16(1):77-89.
143. Katona L, Czobor P, Bitter I. Real-world effectiveness of antipsychotic monotherapy vs. polypharmacy in schizophrenia: to switch or to combine? A nationwide study in Hungary. *Schizophrenia research* Jan 2014;152(1):246-254.
144. Tiihonen J, Taipale H, Mehtälä J, Vattulainen P, Correll CU, Tanskanen A. Association of Antipsychotic Polypharmacy vs Monotherapy With Psychiatric Rehospitalization Among Adults With Schizophrenia. *JAMA psychiatry* May 1 2019;76(5):499-507.
145. Heald A, Pendlebury J, Anderson S, Narayan V, Guy M, Gibson M, Haddad P, Livingston M. Lifestyle factors and the metabolic syndrome in Schizophrenia: a cross-sectional study. *Annals of General Psychiatry* 2017;16(1):12.
146. De Hert M, Correll CU, Bobes J, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World psychiatry : official journal of the World Psychiatric Association (WPA)* 2011;10:52-77.
147. Dean CE, Thuras PD. Mortality and tardive dyskinesia: long-term study using the US National Death Index. *The British Journal of Psychiatry* 2009-04-01 00:00:00 2009;194(4):360-364.

# Part I.

## Movement disorders as symptom

# 2

# Chapter 2.

## Instrumental measurements of spontaneous dyskinesia and schizotypy in subjects with auditory verbal hallucinations and healthy controls

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## Abstract

Spontaneous dyskinesia is associated with non-affective psychosis. Few studies investigated dyskinesia in individuals with subclinical psychotic experiences. We examined dyskinesia using instrumental measurements of force variability in 34 individuals with frequent auditory verbal hallucinations but without a clinical psychotic disorder and 31 matched healthy controls. Schizotypy was assessed using the Schizotypal Personality Questionnaire. We found a positive correlation between dyskinesia and schizotypy in the total group. In addition, when using a cut-off point based on the 95$^{th}$ percentile of force variability in the control group, we found a greater proportion of subjects with dyskinesia in the group with auditory verbal hallucinations than in the control subjects. Current findings are in agreement with the concept of psychosis as a continuous phenomenon and with movement disorders being an integral part of psychosis.

# 1. Introduction

Psychotic symptoms occur along a continuum, ranging from mild and subclinical to severe and associated with dysfunction. Furthermore, the continuum theory implies that psychotic symptoms can occur in the absence of a psychotic disorder, and are more prevalent than psychotic disorders themselves[1-3]. One way to study the validity of the continuum concept is to investigate if similar correlations between symptom dimensions are present for the subclinical manifestation as are known to exist in psychotic disorders[1, 2]. Indeed, correlations between the positive dimension and negative and affective dimensions have been found[2, 4].

Movement disorders are also known to be part of the clinical picture of psychosis[5], however, not much research has been done on movement disorders in relation to subclinical psychotic experiences.

The relationship between movement disorders and schizophrenia has been well established[5]. Movement abnormalities are prevalent in antipsychotic naive patients with schizophrenia[6], adolescents with schizotypal personality disorder[7] and non-affected siblings of schizophrenia patients, who have a heightened genetic risk to develop a psychotic disorder[6, 8, 9]. Movement disorders have even been suggested as a core symptom of schizophrenia[5]. One of these motor symptoms is dyskinesia, which is a hyperkinetic movement disorder characterized by involuntary writhing and purposeless, irregular choreatiform movements[10]. In schizophrenia, these movements frequently occur in the orofacial region and the distal extremities[11]. Research suggests that dyskinesia is related to aberrant striatopallidal activity giving rise to reduced output in the globus pallidus interna and disinhibition of thalamocortical pathways[12]. It has been hypothesized that both dyskinesia and psychotic symptoms depend on dysfunction in striatal dopaminergic transmission[13-15]. Dyskinesia ranges in severity from subtle to severe and more subtle forms can only be measured mechanically[8].

Persons who experience auditory verbal hallucinations in the absence of a clinically relevant psychotic disorder can be considered a population with (at least one) non-clinical psychotic symptom. A sample of these persons has been brought together by Sommer et al.[16]. Sommer and colleagues found more schizotypy, a heightened delusional tendency, more disorganized speech[17] and a lower global level of functioning in individuals with auditory verbal hallucinations compared to matched healthy controls[16]. They suggested that the hallucinations in these individuals are part of a general vulnerability to psychosis[16]. Following this line

of reasoning, we regard these individuals as a group with a generally heightened expression of the psychosis phenotype.

In the present study we examined instrumentally measured dyskinesia as a sign of non-affective psychosis in a subset of these subjects with auditory verbal hallucinations and a healthy control group. We hypothesized that:

1. in the group with auditory verbal hallucinations and the control group together, dyskinesia and schizotypy are positively correlated. 2. individuals with auditory verbal hallucinations show more dyskinesia than healthy controls.

## 2. Methods

### 2.1 Participants

The current study was part of a larger study on subjects experiencing auditory verbal hallucinations without a diagnosis of a psychotic disorder[16]. Subjects with auditory verbal hallucinations and healthy controls were recruited using a website with information about hearing voices.

Inclusion criteria for subjects with auditory verbal hallucinations were: 1) voices were distinct from thoughts with a 'hearing' quality, 2) voices were experienced at least once a month, 3) no diagnosis or treatment for psychiatric disorders other than depressive or anxiety disorders in remission, 4) no alcohol or drug abuse for at least 3 months, 5) no chronic somatic disorder, 6) 18 years of age or older, 7) 4 Dutch-born grandparents 8) no current use of psychotropic medication. Healthy control subjects had to fulfill criteria 3-8. The procedure of selection of nonpsychotic individuals with auditory verbal hallucinations and healthy controls is described in more detail elsewhere[16].

### 2.2 Demographic and psychiatric assessments

Relevant demographic variables for all participants for the present study were gender, age, total years of education. DSM IV axis I disorders were assessed in all subjects by independent psychiatrist using the Comprehensive Assessment of Symptoms and History (CASH) interview[18]. The subjects with auditory verbal hallucinations were additionally assessed for personality disorders with the Structured Clinical Interview for Personality Disorder (SCID II)[19]. Urine samples were taken to screen for use of cannabis, amphetamine, cocaine, heroin and methadone. A positive screen of one or more of these substances would lead to exclusion.

## 2.3 Measurement of dyskinesia and schizotypy

Mean force variability was taken as a proxy for upper extremity dyskinesia and measured with a mechanical instrument designed by Koning et al.[8] based on a similar instrument developed by Caligiuri[20].

The task for subjects consisted of pressing a button with constant pressure, first with the index finger of their dominant hand and then with the index finger of their non-dominant hand. The button was connected to a load cell attached to a monitor showing a graph indicating the pressure exerted, providing participants with immediate feedback. The target force was set at an equivalent of 3 Newton. The force generated was measured continuously (12 bit sampling at 2.5 kHz, digital low pass filtering, storage, and further analysis at 100 Hz). The task was performed 3 times per hand for a duration of 20 seconds each, separated by 5-second rest periods. The first trial was used to accustom subjects to the test. Data of the two subsequent tests for both hands, regardless of handedness, were used for analysis. The average pressure was calculated for each 20-second test period. This mean was subtracted from the signal and then Fourier transformed. Total power in the 0 to 3 Hz range was determined and converted to calculate the standard deviation for the 0 to 3 Hz signal components. The standard deviation was presented as the percentage of error (standard deviation divided by mean force). Force in the 0 – 3 Hz frequency range was used as this measures dyskinesia best and is unaffected by resting tremor which manifests itself in the 4 – 6 Hz frequency band[8]. This procedure has been used and validated earlier[8, 21]. Dyskinesia was defined as a force variability score higher than the 95$^{th}$ percentile of the control group[8, 22].

Schizotypal tendency was assessed by means of the Schizotypal Personality Questionnaire[23], a self-report questionnaire containing 74 questions.

## 2.4 Analyses

Depending on the type and distribution of the data, t-tests, Mann Whitney U, Chi-square and Fisher's exact tests were used to test for differences between groups. Spearman's rho was calculated to assess the correlation between force variability and schizotypy.

# 3. Results

## 3.1 Demographic and psychiatric characteristics

Data were collected for 34 individuals with auditory verbal hallucinations and 31 healthy control subjects. Participants with auditory verbal hallucinations and healthy controls did not differ with regard to gender, age or total years of education which was to be expected because both groups were matched on these variables (table 1). There were no personality disorders in the hallucinating group. In the control group, one subject had a diagnosis of a single depressive episode, partially in remission, 3 had a recurrent depressive disorder in complete remission and 1 a depressive disorder NAO. In the hallucinating group was 1 person with a single depressive episode, 1 with a single depressive episode partially in remission, 5 with a single depressive episode in complete remission and 2 with a recurrent depressive disorder in complete remission. There were no positive screens for cannabis, amphetamine, cocaine, heroin or methadone.

*Table 1. Demographic characteristics*

| | Control group (*n*= 31) | AVH group (*n*= 34) | Statistic | *P* Value |
|---|---|---|---|---|
| Gender % man | 48.4 | 38.2 | *Chi square*(1) = 0.68 | 0.41 |
| Age in years mean (sd) | 45.9 (15.0) | 45.4 (11.9) | *t*(63) = 0.137 | 0.89 |
| Total years of education mean (sd) | 13.0 (2.6) | 13.8 (1.9) | *t*(53*)*= -1.45 | 0.15 |

*AVH: auditory verbal hallucinations*

## 3.2 Force variability and schizotypy

Data for force variability in both groups were skewed to the left and not normally distributed. In addition, In the group with auditory verbal hallucinations the kurtosis was relatively high (table 2.). The cut-off score for force variability derived from the 95$^{th}$ percentile in the control group was 3.11. Based on this criterion, 1 individual (3,2 %) in the control group and 8 (23,5%) in the group with hallucinations showed dyskinesia. These percentages were significantly different (Fisher's Exact Test *1-sided p=0,019)*

*Table 2. Characteristics of the data for force variability and schizotypy*

| | Force Variability | | Schizotypy | |
|---|---|---|---|---|
| | Control group n = 31 | AVH group N = 34 | Control group n = 31 | AVH group n = 34 |
| Mean (SD) | 1.89 (0.61) | 2.49 (1.38) | 10.2 (5.7) | 27.4 (11.3) |
| Median | 1.79 | 2.06 | 10.0 | 24.5 |
| Skewness (SE) | 0.85 (0.43) | 1.56 (0.40) | 0.29 (0.43) | 0.13 (0.40) |
| Kurtosis (SE) | -0.16 (0.83) | 1.97 (0.79) | -0.83 (0.83) | -0.34 (0.79) |

*AVH: auditory verbal hallucinations*

Data for schizotypy were normally distributed in the group with hallucinations but did not have a normal appearance in the control group. There was a significant difference between the groups (Mann Whitney U = 940.00 p=.000 see table 2 for means and medians per group).

The correlation between force variability and schizotypy measured with Spearman's rho was .32 (p= 0.005) in the total group.

## 4. Discussion

The present findings show that spontaneous dyskinesia in the upper extremities and schizotypy are positively related in a combined sample of non-clinical individuals with auditory verbal hallucinations and healthy controls. Secondly, we found that spontaneous dyskinesia occurs in a greater proportion of subjects with auditory verbal hallucinations compared to a matched control group.

Our findings concur with results of Mittal et al. (2011), who found significant differences in instrumentally measured finger dyskinesia between groups of the normal population that scored high versus low on non clinical psychosis (NCP)[13, 24, 25]. Results are also in line with the study of Koning et al. (2011a) showing differences in instrumentally measured dyskinesia between siblings of patients with schizophrenia and healthy controls.

Mittal et al. reported positive correlations between force variability and psychotic-like symptoms in two studies in students with high and low(er) NCP with magnitudes ranging from .16 (force variability– prodromal questionnaire brief total)[24] to .26 (force variability – Community Assessment of Psychic Experiences (CAPE) positive symptoms) and .48 (force variability – CAPE negative symp-

toms)[25]. In addition, Koning et al.[9] found a correlation in nonpsychotic siblings of patients with schizophrenia of .51 between positive schizotypy and spontaneous dyskinesia. In this study by Koning et al., traditional rating scales were used and the correlation was found in siblings who showed at least a minimal sign of a movement disorder[9].

Interestingly, positive correlations between spontaneous dyskinesia and psychotic-like symptoms are found in studies using different designs and populations. At this point it is difficult to assess to what extent differences in strength between correlations are attributable to methods of sample selection or choice of questionnaires measuring psychotic-like phenomena although both probably have some influence.

The underlying neurobiological mechanism of the relation between hallucinations and dyskinesia should be found in the overlap of the pathophysiology of each symptom. For auditory verbal hallucinations, a wealth of findings have been published but for dyskinesia (modern) neuroimaging studies are scarce. One study investigated neural correlates of spontaneous dyskinesia in subjects with non-clinical psychosis and showed smaller bilateral putamen compared to a healthy control group. Furthermore, a correlation between force variability and striatal abnormalities was reported [25]. Other neuroimaging studies on dyskinesia focused on tardive dyskinesia (TD) in patients with schizophrenia. Inconsistent results were found in abnormalities in the basal ganglia[11, 26]. In addition, reduced gray matter in cortical areas [27] and microstructural abnormalities in white matter[28] have been observed.

With regard to the neurobiology of auditory verbal hallucinations several brain areas have suggested including the superior temporal gyrus, middle temporal gyrus, prefrontal, premotor, cingulate, cerebellar, and subcortical regions[29]. In addition, microstructural changes in the arcuate fasciculus, which connects frontotemporal language production and perception areas, have been reported [30]. In a recent structural imaging study, Van Lutterveld and colleagues examined cortical thickness in non-clinical subjects with auditory verbal hallucinations which came from the same project as the present investigation, patients with a psychotic disorder and auditory verbal hallucinations, and healthy controls[31]. They found that in the left paracentral lobule, left pars orbitalis, right fusiform gyrus and right inferior temporal gyrus, patients had the lowest thickness, controls had the highest thickness, and the non-clinical subjects with auditory verbal hallucinations were in between. Patients and non-clinical individuals with auditory verbal hallucinations showed less cortical thickness compared to controls

in the right insula. Moreover, with the use of rank order analysis, the authors demonstrated that the order of mean cortical thickness for the three groups was for 88% of the areas such that the thickness was highest in the controls, followed by the non-clinical subjects with auditory verbal hallucinations and finally the patients with a psychotic disorder and auditory verbal hallucinations. These areas included the right superior frontal gyrus and bilateral pars orbitalis (which is part of the inferior frontal gyrus).

In summary, largely different brain regions seem to be involved in dyskinesia and auditory verbal hallucinations although reduced gray matter in the right superior frontal gyrus and bilateral inferior frontal gyrus have been reported for both symptoms[27, 31].

A limitation of the present study was the selection procedure of subjects by means of a website as individuals with strong paranoid tendency may be unlikely to engage. It is unclear if this has affected the results. However, the way in which our results concur with findings in other studies suggests that they were not caused by our method of subject selection. Another limitation was that nicotine use was not measured, while this may influence dyskinesia[32].

In the present study, results of Mittal et al. and Koning et al. are replicated in a different population, which, in contrast to their samples, was selected on the presence of one clear non-clinical psychotic symptom. Furthermore, in contrast to the studies of Mittal, participants in our study were extensively examined with regard to the absence of Axis I and II disorders by a psychiatrist. Results can be explained by regarding auditory verbal hallucinations, schizotypy and spontaneous dyskinesia all as part of a psychosis vulnerability implying that they are all in part mediated by the same underlying neurobiological mechanism, although the exact nature of this mechanism remains elusive. Our results supports the earlier conclusion of Sommer et al.[16] that auditory verbal hallucinations in this population, are part of a general vulnerability for psychosis.

Present findings of a correlation between spontaneous dyskinesia and schizotypy in our total sample, and a higher proportion of dyskinesia in persons with auditory verbal hallucinations in comparison to healthy controls are in accordance with psychosis as a continuous phenomenon.

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## References


1. van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychol Med* 2009;39(02):179-195.
2. van Os J, Hanssen M, Bijl RV, Ravelli A. Strauss (1969) revisited: a psychosis continuum in the general population? *Schizophr Res* 2000;45(1-2):11-20.
3. Kelleher I, Jenner JA, Cannon M. Psychotic symptoms in the general population - an evolutionary perspective. *The British Journal of Psychiatry* 2010-09-01 00:00:00 2010;197(3):167-169.
4. Stefanis NC, Hanssen M, Smirnis NK, Avramopoulos DA, Evokimidis IK, Stefanis CN, Verdoux H, Van Os J. Evidence that three dimensions of psychosis have a distribution in the general population. *Psychol Med* 2002;32(2):347-358.
5. van Harten PN, Tenback DE. Letter to the Editor: Movement disorders should be a criterion for schizophrenia in DSM-V. *Psychol Med* 2009;39(10):1754-1756.
6. Koning JP, Tenback DE, van Os J, Aleman A, Kahn RS, van Harten PN. Dyskinesia and parkinsonism in antipsychotic-naive patients with schizophrenia, first-degree relatives and healthy controls: a meta-analysis. *Schizophr Bull* 2010;36(4):723-731.
7. Mittal VA, Neumann C, Saczawa M, Walker EF. Longitudinal progression of movement abnormalities in relation to psychotic symptoms in adolescents at high risk of schizophrenia. *Archives of General Psychiatry* 2008;65(2):165-171.
8. Koning JP, Kahn R, Tenback DE, van Schelven LJ, van Harten PN. Movement disorders in nonpsychotic siblings of patients with nonaffective psychosis. *Psychiatry Res* 2011;188(1):133-137.
9. Koning JP, Tenback DE, Kahn RS, Vollema MG, Cahn W, van Harten PN. Movement disorders are associated with schizotypy in unaffected siblings of patients with nonaffective psychosis. *Psychol Med* 2011;41(10):2141-2147.
10. Koning JP. Movement disorders in patients with schizophrenia and their siblings; symptoms, side effects and mechanical measurements. *Utrecht: Psychiatry* 2011.
11. Walther S. Psychomotor symptoms of schizophrenia map on the cerebral motor circuit. *Psychiatry Research: Neuroimaging* 2015;233(3):293-298.
12. Obeso JA, Rodriguez-Oroz MC, Stamelou M, Bhatia KP, Burn DJ. The expanding universe of disorders of the basal ganglia. *The Lancet* 2014/8/15/ 2014;384(9942):523-531.
13. Mittal VA, Daley M, Shiode MF, Bearden CE, O'Neill J, Cannon TD. Striatal volumes and dyskinetic movements in youth at high-risk for psychosis. *Schizophr Res* 2010;123(1):68-70.
14. DeLong Mr WT. CIrcuits and circuit disorders of the basal ganglia. *Archives of Neurology* 2007;64(1):20-24.
15. Perez-Costas E, Melendez-Ferro M, Roberts RC. Basal ganglia pathology in schizophrenia: dopamine connections and anomalies. *J Neurochem* 2010;113(2):287-302.
16. Sommer IEC, Daalman K, Rietkerk T, Diederen KM, Bakker S, Wijkstra J, Boks MPM. Healthy Individuals With Auditory Verbal Hallucinations; Who Are They? Psychiatric Assessments of a Selected Sample of 103 Subjects. *Schizophr Bull* May 1, 2010 2010;36(3):633-641.

17. Sommer IE, Derwort AMC, Daalman K, de Weijer AD, Liddle PF, Boks MPM. Formal thought disorder in non-clinical individuals with auditory verbal hallucinations. *Schizophr Res* 2010;118(1-3):140-145.
18. Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment for Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. *Arch Gen Psychiatry* 1992;49:615-623.
19. First MB, Spitzer RL, Gibbon M. Structured Clinical Interview for Personality Disorder (SCID-II): multi-site test-retest reliability study. *J Pers Disorder* 1995;9:92-104.
20. Caligiuri MP, Lohr JB. Fine force instability: a quantitative measure of neuroleptic-induced dyskinesia in the hand. *Journal of Neuropsychiatry* 1990;2:395-398.
21. Lohr JB, Caligiuri MP. Quantitative instrumental measurement of tardive dyskinesia: a review. *Neuropsychopharmacology* 1992;6(4):231-239.
22. Cortese L, Caligiuri MP, Malla AK, Manchanda R, Takhar J, Haricharan R. Relationship of neuromotor disturbances to psychosis symptoms in first-episode neuroleptic-naive schizophrenia patients. *Schizophr Res* 2005;75(1):65-75.
23. Raine A. The SPQ: A Scale for the Assessment of Schizotypal Personality Based on DSM-III-R Criteria. *Schizophr Bull* January 1, 1991 1991;17(4):555-564.
24. Mittal VA, Dean DJ, Pelletier A, Caligiuri M. Associations between spontaneous movement abnormalities and psychotic-like experiences in the general population. *Schizophr Res* 2011;132:194-196.
25. Mittal VA, Orr JM, Turner JA, Pelletier AL, Dean DJ, Lunsford-Avery J, Gupta T. Striatal abnormalities and spontaneous dyskinesias in non-clinical psychosis. *Schizophr Res* 2013;151(1-3):141-147.
26. Hirjak D, Wolf RC, Wilder-Smith EP, Kubera KM, Thomann PA. Motor Abnormalities and Basal Ganglia in Schizophrenia: Evidence from Structural Magnetic Resonance Imaging. *Brain Topogr* 2015;28(1):135-152.
27. Li C-T, Chou K-H, Su T-P, Huang C-C, Chen M-H, Bai Y-M, Lin C-P. Gray Matter Abnormalities in Schizophrenia Patients with Tardive Dyskinesia: A Magnetic Resonance Imaging Voxel-Based Morphometry Study. *PLoS One* 2013;8(8):e71034.
28. Bai YM, Chou K-H, Lin C-P, Chen IY, Li C-T, Yang KC, Chou Y-H, Su T-P. White matter abnormalities in schizophrenia patients with tardive dyskinesia: A diffusion tensor image study. *Schizophr Res* 2009;109(1-3):167-181.
29. Allen P, Modinos G, Hubl D, et al. Neuroimaging Auditory Hallucinations in Schizophrenia: From Neuroanatomy to Neurochemistry and Beyond. *Schizophr Bull* July 1, 2012 2012;38(4):695-703.
30. Diederen KMJ, van Lutterveld R, Sommer IEC. Neuroimaging of Voice Hearing in Non-Psychotic Individuals: A Mini Review. *Front Hum Neurosci* 2012;6:111.
31. van Lutterveld R, van den Heuvel MP, Diederen KMJ, et al. Cortical thickness in individuals with non-clinical and clinical psychotic symptoms. *Brain* 2014-10-01 00:00:00 2014;137(10):2664-2669.
32. Quik M, Zhang D, Perez XA, Bordia T. Role for the nicotinic cholinergic system in movement disorders; therapeutic implications. *Pharmacol Ther* 2014;144(1):50-59.

3

# Chapter 3.

## Motor disturbance in ASD: A pilot study showing hypokinetic behavior?

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## Abstract

Data supporting theoretical models linking autism spectrum disorders (ASD) to motor disturbance are inconclusive. In the present study, children and adolescents with ASD (n=44) were compared with a matched group of typically developing individuals (n=49) on both instrumental and observational assessments of motor abnormalities. No group differences were found in the instrumental data. However, more bradykinetic motor behavior was found using an observational scale in the ASD groups. More rigid motor behavior was found in the adolescents with ASD but not in the children. Individuals with ASD show significantly more hypokinetic behavior, which may not be strictly dopaminergic in origin, but may reflect a weak central coherency in neuronal networks related to the motor system in which developmental changes are present.


Key words: autism spectrum disorder, motor disturbance, parkinsonism, dyskinesia

## Introduction

Motor difficulties are highly prevalent in autism spectrum disorder (ASD)[1], yet they are not considered to be part of the core symptoms of ASD. These include persistent deficits in social communication and interaction, and repetitive patterns of behavior[2]. However, social and motor skills are strongly related. Social interactions change as young children learn to walk[3], and through children's play in which motor behavior is essential, social connections are build. Poor motor skills limit these interactions.

The interactive relationship between motor skills, social impairment[4, 5], receptive and expressive language skills[6] has been demonstrated in children with an ASD. Hilton et al. (2012)[7] describe motor impairment in individuals with ASD. Motor skills in unaffected siblings were normal, indicating that motor impairment is a core characteristic of the disorder and not an ASD endophenotype. The question arises whether motor difficulties are indeed part of a symptom cluster in ASD. Dyspraxia is more prevalent in adults with ASD than in controls. Also, in the general population, dyspraxia is associated with higher autistic traits and lower empathy, which could suggest that motor coordination skills are important in empathy and effective social interaction[8]. Several studies have reported benefits of physical exercise on motor skills and social interaction in children with ASD[9, 10]. Sensory-motor therapy is a promising intervention, since improvement on perceptual and social functioning in children with ASD has been found[11]. Altogether, identifying motor problems in individuals with ASD is of great importance, since it enables clinicians to integrate interventions that facilitate motor behavior in care planning. It also contributes to the understanding of the complex nature of this developmental disorder.

Abnormal functioning of the basal ganglia might be a link between movement abnormalities and other symptom clusters in ASD. The basal ganglia are connected with the cortex through several segregated but parallel loops, the so-called cortico-basal-ganglia-thalamocortical circuits. However, besides motor loops, the basal ganglia also contain associative (cognitive), and limbic (emotional) loops. They deal, with the control of behaviour and cognition, together with reward and emotions[12]. Therefore, motor dysfunctions, which are often seen in autism, may directly be related to dysfunctions of behaviour and cognition. Indeed, striatal volume changes in ASD have been observed previously[13].

Motor difficulties in ASD encompass a large range of abnormalities, like problems in coordination and balance, fine and gross motor delays[1]. Because of the

resemblance of some characteristics in both disorders, a potential link between ASD and Parkinson's disorder (PD) has been proposed before[14-16]. Rigid behavior patterns and difficulties in starting and stopping movements are amongst them. However, age at onset is different in both disorders. PD is an age-related progressive neurodegenerative disorder with onset of illness generally between ages of 60-65 and young onset ages <50[17]. ASD is a neurodevelopmental disorder in which, for most children, declines in social interaction are observed during the first years of life[18]. PD is characterized with selective loss of dopaminergic neurons in the substantia nigra[19]. Dysregulation of the dopamine system is also associated with both ASD[20, 21] and motor function[12, 22]. And interesting, the SNP rs167771 of the dopamine-3-receptor gene (DRD3) has recently been found to be associated with repetitive and stereotyped behavior in ASD[21], while the same SNP was earlier reported to be linked to acute risperidone-induced extrapyramidal symptoms in patients with mainly psychotic disorders[23].

Another neuropsychiatric disorder in which movement disorders are an integral part, is schizophrenia[24] and studies indicate that also autism and schizophrenia share genetic factors[25]. These authors suggest that both neuropsychiatric disorders might share pathogenic mechanisms involving altered brain development. Stone and Iguchi[26] (2011) state that ASD and schizophrenia share similarities in genetic components and phenotypes, however, they remain distinct entities with important differences in for example age of onset. Results presented by Koning, et al.[27] could imply that movement disorders are core symptoms of psychotic disorders, since they are strongly associated with dyskinesia and parkinsonism in antipsychotic medication naïve patients. In conclusion, it might then also be possible that movement abnormalities are symptoms of the autism spectrum.

Dyskinesia is a hyperkinetic movement disorder characterized by involuntary writhing and purposeless, irregular movements that may or may not be continuous[28]. Dyskinesia is suggested to arise from aberrant striatopallidal activity, which results in, reduced output in the globus pallidus interna and disinhibition of the thalamocortical pathway[12]. Dyskinesia had also been associated with smaller volumes of the putamen[29, 30]. Parkinsonism is an akinetic rigid syndrome with the following features: rigidity, bradykinesia, resting tremor and postural instability[12]. Parkinsonism is thought to arise from hypodopaminergia in the extrapyramidal motor system, which induces inhibition of thalamocortical projections[12]. Both dyskinesia and parkinsonism can be measured with observational rating scales as well as with mechanical instruments.

The purpose of the present study is to investigate whether movement disorders, as measured with both observational and instrumental assessments, are more prevalent in children and young adults with ASD than in typically developing individuals. We use both observational and instrumental assessments as both present certain advantages. The observational rating scales we choose are widely used in both clinical practice and research. Therefore results are can be easily understood and compared with other research. With observational rating scales dyskinesia or parkinsonism in all body parts are taken into account. Mechanical instruments on the other hand only focus on certain parts of the body and are less widely used, but they are more sensitive and reliable than observational rating scales[28, 31, 32]. Another reason why it is interesting especially for the study of individuals with ASD to use both methods, is that it has been observed before that they perform different on measurements assessing a particular construct, depending on the amount of social interaction needed during testing[33].

It is expected that individuals with ASD experience more movement difficulties than control individuals. We hypothesize to find these difficulties especially in both observational and instrumental assessment of parkinsonism, based on the clinical features often described in this ASD. We do not expect differences in instrumental measurements assessing dyskinesia between the ASD group and controls, since involuntary and purposeless, irregular movements are not typically described for this clinical group. However, since ASD and psychotic disorders share genetic factors, we choose to investigate dyskinesia also.

## Method

### Participants

High functioning children and young adults (age 6-26) with ASD (n = 44) were recruited from the department of child and adolescent psychiatry at the University Medical Centre Utrecht, the Netherlands. Controls (n=49) were recruited through local schools. Inclusion criteria for both groups were age (between 6 and 26 years). All participants had an full scale intelligence quotient (FSIQ) >70, determined by the short form of the Wechsler scales (four subtests: vocabulary, similarities, block design, object assembly).[34, 35] To prevent the inclusion of individuals with possible other causes of movement disorders, the exclusion criteria for both groups were a history of neurological disease, the use of anti-psychotic medication, and substance abuse. Controls with a first- or second-degree relative with developmental disorder were also excluded. The groups were matched for sex, age and FSIQ.

Individuals in the ASD group were diagnosed by a child and adolescent psychiatrist. The ADI-R[36], or the ADOS[37], and in most cases both instruments were available. Ethical approval for the study was obtained and all participants or their parents, if appropriate, gave written informed consent.

## Measures and Materials

### *Data Collection Procedure*

Participants were invited to the UMC Utrecht for an appointment that took approximately 75-90 minutes of their time. The Wechsler scales were administered and the individuals were evaluated with the Abnormal Involuntary Movement Scale (AIMS)[38] for clinical dyskinesia, and the Unified Parkinson Disease Rating Scale (UPDRS)[39] for clinical parkinsonism. Manual dexterity was assessed by observing and questioning participants and/or parents. After that, the mechanical measurements were administered. A research assistant together with a neuropsychologist, both trained by an expert in the field of movement disorders (JK), assessed all scales and tasks. Only one tester was present in the room, the second tester was placed behind a one-way screen. Both testers scored the observational measurement independently. Afterwards, scores were evaluated. Inter rater agreement was 96%. In case both tests had different scores, the lower score was used in the analysis.

## Clinical Assessment of Dyskinesia and Parkinsonism

### *Clinical dyskinesia*

The AIMS divides the body into seven different areas (face, tongue, lips, jaw, upper limbs, lower limbs and neck, shoulders and hips). Each item is scored from 0 to 4 to indicate disorder severity (0 = absent, 1 = questionable, 2 = mild, 3 = moderate, and 4 = severe). Clinical dyskinesia was defined as a score of 2 or greater on any of the seven items of the AIMS, based on the research criteria for dyskinesia[40].

### *Clinical Parkinsonism*

The motor examination part of the UPDRS was used to assess speech, facial mobility, resting tremor (face and each limb), rigidity (neck and each limb), rapid hand and foot movements, rising from chair, posture, gait, postural stability and body bradykinesia. Each item is scored from 0 to 4 to indicate disorder severity (0 = absent, 1 = questionable, 2 = mild, 3 = moderate, and 4 = severe). Clinical parkinsonism was considered a case when any item was scored at least “mild” (a score of 2 or greater) on the UPDRS[39].

## Mechanical Assessment of Dyskinesia and Parkinsonism (Resting tremor and Bradykinesia)

*Dyskinesia using mechanical measurement*

Dyskinesia is a hyperkinetic movement disorder characterized by involuntary writhing and purposeless, irregular movements that may or may not be continuous[28]. When present in the hands, this leads to instability in tasks requiring the exertion of a constant pressure. Variability in exerted force [force variability (FV)] in the lower (< 3Hz) frequency range can therefore be used as a quantification of dyskinesia[31]. An instrument based on this principle was used to assess dyskinesia mechanically by measuring the FV, as indicated by the individual's attempt to exert constant pressure on a load cell and measuring the variations in the force applied over time. Participants were asked to exert constant target pressure, first by pushing a button with the index finger of their dominant hand, then of their non-dominant hand[27]. The button was connected to a cell attached to a monitor showing a real-time graph indicating target and actual force applied. The strength required to achieve the target height on the graph was set to an equivalent of 3 N for the index finger[41]. All participants performed each exercise three times for duration of 20 s each, separated by 5-s rest periods. The first trial was used to accustom the test taker to the procedure. Mean data of the two subsequent measurement trials were used for analysis. The force generated was measured continuously and presented graphically to the subject with virtually no delay. The average force was calculated for each 20-s test period. After subtracting this mean from the signal, it was Fourier transformed. Total power in the 0 to 3 Hz range was calculated and converted to find the standard deviation for the 0 to 3 Hz signal components. This standard deviation is technically equivalent to the one found after a very sharp 3 Hz low-pass filtering of the force signal. The standard deviation was presented as the percentage of error, or coefficient of variation (CV, standard deviation divided by mean force). For dyskinesia, only force measured in the 0 to 3 Hz frequency range was used as this reflects dyskinesia best[32] and is unaffected by resting tremor (which is measured at the 4 to 6 Hz frequency band)[42]. This technique has been extensively validated for finger dyskinesia[32]. For a more detailed explanation of the procedure/apparatus, we refer to "Appendix". Examples of force variability/force variation are presented in Illustration 1, 2 and 3.

*Parkinsonism (Resting Tremor and Bradykinesia) Using Mechanical Measurement*

The data generated in the preceding procedure were also used to mechanically evaluate resting tremor, by calculating the amount of variability in the force applied, with the difference that now only total force in the 4 to 6 Hz frequency

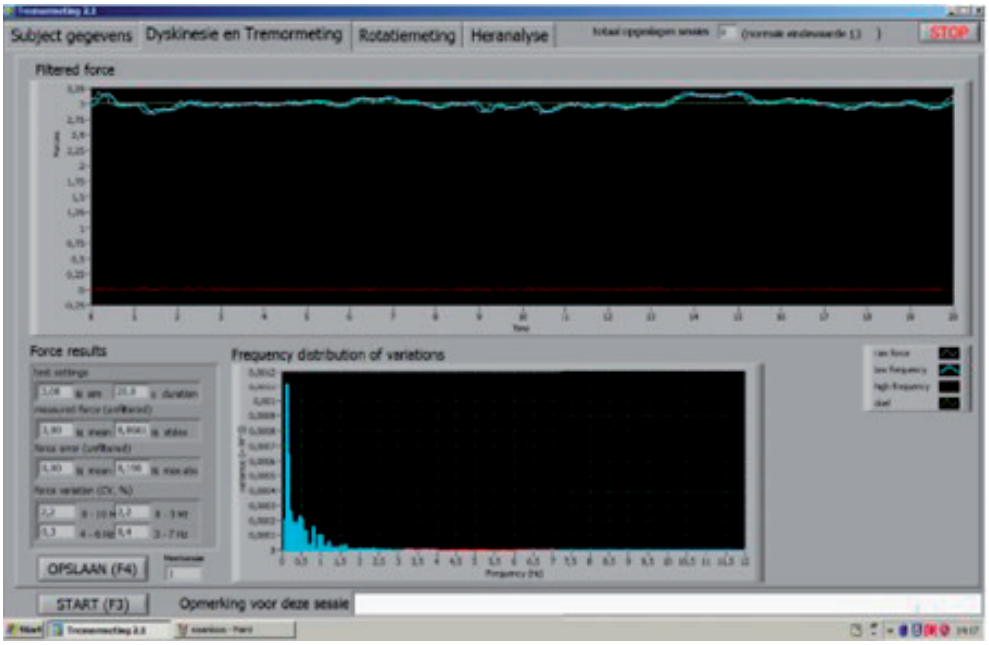


**Illustration 1**. Subject: no dyskinesia, no tremor. This is an example of force variability. The bluish/green line indicates the actual force applied over time in the 0-3 Hz frequency range. In the box you can see the frequency distributions of the variations. There have been norm scores for normal healthy subjects, and they resemble this line, so here there is "no dyskinesia" and "no tremor"

range was used, as this frequency reflects resting tremor best[42] and movements in this range are unaffected by dyskinesia.

Bradykinesia can be mechanically quantified by measuring the ability to adjust movement velocity to changing distances[43, 44]. Participants with bradykinesia (Parkinson's disease or drug induced parkinsonism) are less able to scale their movement velocity and require more time as distances increase. Velocity scaling (VS) scores are expressed as degrees per second per degree (º/s/º). Participants were instructed to flex a handle with their wrist as fast but as accurately as possible in order to move a flexible cursor presented on the computer screen to a target cursor located at 25º and 45º from the midline of the wrist flexion[43]. The handle was connected to a potentiometer attached to a monitor showing in real-time the target and flexible cursor. Participants started with the dominant hand and then switched to the non-dominant hand and performed 32 movement measurements, consisting of 16 measurements for each of the two randomly presented target locations, for each hand, for a total of 64 movements[43].

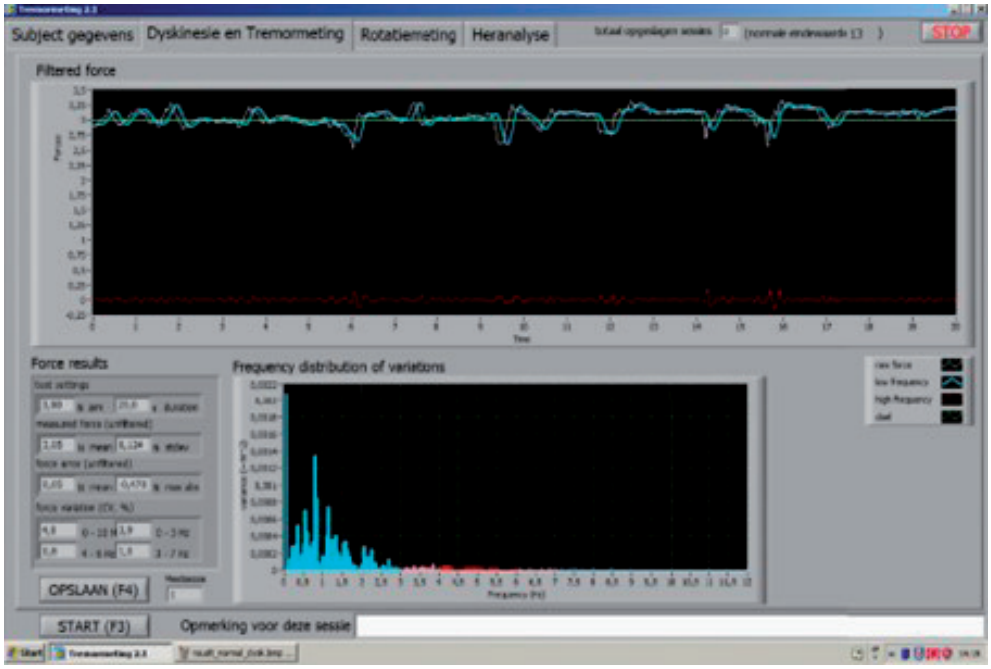


**Illustration 2**. Subject: with dyskinesia, but no tremor. As depicted in the blue line (low frequency) and bars, a person with dyskinesia shows more variation around the green target line. If we look at the frequency distributions of the force variation, you will see a little (blue) peak emerging in the 0–3 Hz frequency range

## Data Analysis

Statistical analyses were performed using SPSS-24®. A *p*-value <.05 was deemed significant. A chi square analysis was conducted to test whether the two groups differed relative to gender and manual dexterity. Age and FSIQ were analyzed using a t-test for independent groups. A series of analyses of variance were performed to test for differences between the ASD and the control group in the mechanical assessments of parkinsonism (tremor, bradykinesia) and dyskinesia separately. Although this resulted in smaller groups, we choose two different age groups i.e. children (age 6–12 years, n=44) and adolescents/young adults (age 13–26 years, n=49) since developmental effects on motor behavior are expected to be high. Outliers were identified by using bivariate scatterplots for each group and was scored an outlier with Z-score > 3.29 (p<.001, two tailed). Evaluation of the data led to the conclusion that present extreme scores were proper part of our sample, and were therefore not removed. Data were transformed using log transformation in order to pull outliers closer to the center of the distribution.

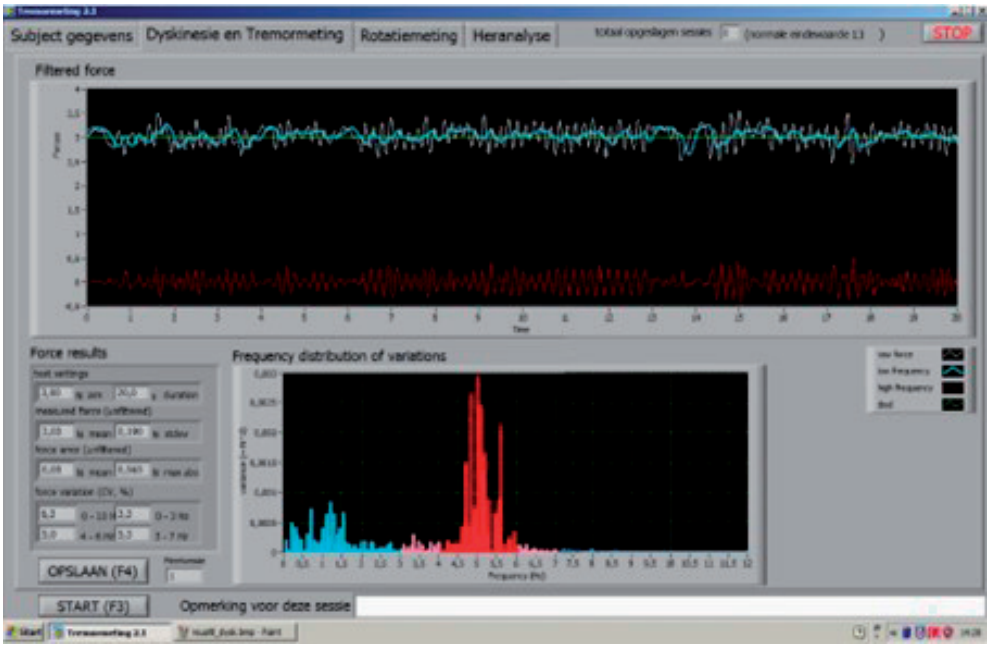


**Illustration 3.** Subject: with resting tremor, but no dyskinesia. If we look at the same graph of a person with resting tremor, but no dyskinesia, it looks like this. As you can see, red line shows oscillations in the 4–6 Hz frequency range. The blue line shows some variation around the target line, but less extensive compared to the former person with dyskinesia. So you can see that this method can differentiate between resting tremor and dyskinesia. If we look at the frequency distributions of the force variation, you will see a little peak emerging in the 4–6 Hz frequency range, and a very little one in the 0–3 Hz frequency range

***Differences between groups on the clinical assessments are calculated with Mann Whitney U tests.***

For the mechanical measurements, power was adequate (0.80) for the detection of medium effect sizes f=.029. For the rating scales we were able to detect large effect sizes. In the children group, a power of 0,8 was reached at effect size d = 0,87 and for the adolescents at effect size d = 0,84.

# Results

## Descriptive statistics

Demographic characteristics of the participants are presented in Table I. In both the child and adolescent/young adult group, the individuals with ASD and controls did not differ relative to age, gender, FSIQ and handedness.



Table I: demographic characteristics

| | 6-12 | | | 13-26 | | |
|---|---|---|---|---|---|---|
| | ASD (n=22) | Controls (n=22) | p | ASD (n=23) | controls (n=26) | p |
| Age in years (M/sd) | 10,4 (1,7) | 10,3 (1,8) | .84 | 18,7 (4,6) | 20,2 (4,1) | .25 |
| Sex (n male) | 17 | 17 | .99 | 17 | 20 | .81 |
| FSIQ (M/sd) | 113,7(17,0) | 114,6 (15,0) | .87 | 107,7 (19,8) | 113,5 (14,6) | .26 |
| Handedness (n right) | 21 | 21 | .99 | 19 | 25 | .23 |

### *Clinical assessment of dyskinesia and Parkinsonism*

Results are presented in Table 2. Non-parametric analysis showed no significant differences in dyskinesia between the ASD and control group. However, significantly more bradykinetic motor behavior using the observation scales (UPDRS) for parkinsonism ($p<0.0001$) was present in children and adolescents with an ASD. More rigid motor behavior was found in the adolescent group, as compared to controls. This was not present in the younger age group.

Table II A: Cases of dyskinesia and parkinsonism based on clinical assessment

| | 6-12 | | | 13-26 | | |
|---|---|---|---|---|---|---|
| | ASD (n = 22) Cases n (%) | Controls (n = 22) Cases n (%) | *p | ASD (n = 23) Cases n (%) | Controls (n = 26) Cases n (%) | *p |
| Dyskinesia | 4 (18.2) | 1 (4.5) | .546 | 4 (17.4) | 0 | .093 |
| Parkinsonism | 12 (54.5) | 1 (4.5) | .000 | 17 (73.9) | 3 (11.5) | .000 |
| Bradykinesia | 11 (50.0) | 1 (4.5) | .000 | 15 (65.2) | 2 (7.7) | .000 |
| Rigidity | 1 (4.5) | 0 | .325 | 7 (30.4) | 0 | .000 |
| Tremor | 2 (9.1) | 0 | .144 | 4 (17.4) | 1 (3.8) | .439 |

Cases are defined as a score of 2 or higher on any item on the AIMS for dyskinesia and the UPDRS for parkinsonism. For bradykinesia, rigidity and tremor, a score of 2 or higher on one or more items pertaining to the relevant domain was used for case definition.
* p-values from Mann Whitney U tests

### *Mechanical Assessment of Dyskinesia and Parkinsonism (Resting Tremor and Bradykinesia)*

The results are presented in Table 3. A series of analyses of variance revealed no significant main effects of group membership (ASD versus controls), on mechanical tests for parkinsonism and dyskinesia. There were main effects for age for dyskinesia and resting tremor in both hands, the adolescents/young adults showed less dyskinesia and tremor than the children. Bradykinesia did not show a main effect for age. There was no significant effects for group x age. These results indicate there was no difference between the ASD group and controls on mechanical measurements for dyskinesia, resting tremor and bradykinesia.

Table III: mechanical assessment of dyskinesia and parkinsonism; ANOVA results

| | Group | | | Age | | | Group x Age | | |
|---|---|---|---|---|---|---|---|---|---|
| | F | p | η2p | F | p | η2p | F | p | η2p |
| Dyskinesia | | | | | | | | | |
| Right hand | 0.668 | .416 | .008 | 30.181 | .000 | .276 | 0.133 | .717 | .002 |
| Left hand | 0.321 | .573 | .004 | 34.816 | .000 | .306 | 0.044 | .834 | .001 |
| Parkinsonism | | | | | | | | | |
| Tremor right hand | 0.227 | .635 | .003 | 21.530 | .000 | .214 | 0.103 | .749 | .001 |
| Tremor left hand | 0.292 | .591 | .004 | 15.715 | .000 | .166 | 0.121 | .729 | .002 |
| Bradykinesia right hand | 0.033 | .857 | .000 | 1.229 | .271 | .015 | 0.327 | .569 | .004 |
| Bradykinesia left hand | 0.357 | .552 | .005 | 0.960 | .330 | .012 | 0.035 | .852 | .000 |
| Bradykinesia towards | 0.025 | .876 | .000 | 0.003 | .953 | .000 | 0.051 | .822 | .001 |
| Bradykinesia reverse | 0.079 | .78 | .001 | 0.188 | .666 | .002 | 0.582 | .448 | .007 |

### *Correlations between observational and mechanical measurements*

Considering the discrepant findings of the observational rating scales versus the mechanical measurements, we calculated Pearson's correlations between their corresponding items/results. For dyskinesia, the correlation between item 5 of the AIMS (5 (dyskinesia of the upper extremities: arms, wrists, hands, fingers) and FV was .17 (p=0.132) for the ASD group and .42 (p=0.002) for the control group. For bradykinesia of the arms/hands UPDRS item 24 (hand movements: patient opens and closes hands in rapid succession) and 25 (Rapid alternating movements of the hands: Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible) were combined and correlated with VS. R was .06 (p=0.362) and for the ASD group and -.07 (p=0.331) for the control group.

## Discussion

We found differences between the ASD group and controls with a rating scale assessing parkinsonism, but not with a mechanical instrument measuring force variability and movement velocity. With the rating scale, we observed more bradykinesia in both age groups with ASD compared to the typically developing control groups. In the adolescents/young adults with ASD, but not in the children, more rigidity was found than in the control group. Resting and action tremors were not observed using the mechanical instrument and the rating scales. For dyskinetic movements, the difference between the ASD group and the control group did not reach significance in the children but was significant at trend level in the adolescent/young adult group.

Surprisingly, our groups performed similar on the mechanical measurements assessing movement velocity, a quantification of bradykinesia. Effect sizes for the effect of group and the group x age were very small (partial $\eta^2 \leq 0.008$ for all measurements) indicating that results could not be explained by a lack of power in our analyses. These findings are unexpected, since we found higher rates of bradykinesia in children and young adults with ASD, compared to controls, using the observational instrument. Individuals in the ASD group showed rapid fatiguing, slowness in performed movements, speaking in soft monotone voices and little facial expression. These symptoms were scored in the mild range. Notably, slowness and rapid fatiguing were also seen in hand movement, whereas ASD groups performed normally on the instrumental task requiring rapid hand movements. We also found higher rates of rigidity in the ASD group compared to the control group in the adolescents/young adults. In the children, there was somewhat more rigidity as well with the difference between the groups showing a small to intermediate effect size, which probably may have reached significance if we had had larger groups. Higher rates of parkinsonism in individuals with ASD, and thus partly in line with our results, were found by Starkstein, et al. (2015)[45]. Also using the UPDRS, higher rates of tremor, rigidity, bradykinesia and postural instability were found in older adults (age > 39 years) with an ASD. The participants in that study were older, had lower IQ's and several were on neuroleptic medication. These factors, especially the use of neuroleptics[46], influence motor performance. Human perception of movement is highly complex and mechanical measurements as used might not (yet) be able to identify certain attributes of movement. Still, these results are important in the understanding of the clinical presentation of motor disturbance and underlying pathology in ASD and offer material for future research.

Our results are in contrast with a study in siblings of patients with non-affective psychosis, in which parkinsonism and dyskinesia were observed with instrumental measurements, but were not observed with rating scales. The authors concluded that the mechanical instrument provided more sensitive measures of dyskinesia and parkinsonism[47]. It is therefore remarkable that in a disorder in which dopaminergic involvement is assumed[13, 20], no differences in task performance could be detected on instrumental measurements. An explanation for these contrasting findings might be that the movement disorders seen in ASD are different in nature than those seen in the psychosis spectrum. Where movement disorders in the latter are thought to stem from abnormalities in dopaminergic transmission in the striatum, in ASD they may be caused by other neurobiological mechanisms.

We did not find an increase in instrumentally measured dyskinetic movements in individuals with ASD compared to healthy control participants. With the AIMS we observed slightly more dyskinesia in the ASD groups. In the children group, the difference had a small effect size and was not significant. However, in the adolescent/young adult group, the difference had a medium effect size and was significant at trend level. To the best of our knowledge, there a no other publications on spontaneous dyskinesia in patients with ASD.

The fact that significant differences in bradykinesia, and on a trend level dyskinesia, were found with the UPDRS and AIMS respectively, but not with the mechanical instrument, was unexpected. To gain more insight into this finding, correlations between the instrumental measurements and items from the observational ratings scales thought to measure bradykinesia and dyskinesia were determined. We were surprised by the absence of a correlation between the items of the UPDRS determining bradykinesia of the hands, and VS in the ASD and control group. An explanation might be that different constructs are being measured. Caligiuri et al. (1998) argue that FV measures predominantly neuromotor retardation, while with observational ratings, both psychomotor and neuromotor slowing are being taken into account[43]. For dyskinesia, a significant intermediate to strong correlation between dyskinesia of the upper extremities on the AIMS and FV was found for the control group while the correlation in the ASD group was weak to intermediate and not significant. This might be understood by looking at research suggesting that individuals with ASD perform better under conditions in which social interaction is minimized. Computerized versions of cognitive tasks will be discussed in more depth later in our discussion.

Taken together, our findings may reflect movement abnormalities caused by other neurobiological processes than those seen in psychotic disorders. Rather

than disturbed dopaminergic transmission, an alternative, more appealing explanation for the movement abnormalities observed in ASD may be provided when linking the results to the vast literature on impaired functional and structural connectivity. Due to under[48] or over connectivity of brain regions, among which are fronto-striatal connections and the basal ganglia[49], problems in coordination of motor, cognitive and social activities occur in ASD. In a computational approach, abnormalities were found in two areas in motor behavior; poor integration of information for efficient motor planning and increased variability in basis sensory input and motor outputs. Motor learning was relatively intact[50]. Mounting evidence suggests that brain connectivity might be altered in ASD. Most findings show a decrease in long range connectivity whereas findings on proposed local over-connectivity have been inconsistent [51, 52]. Evidence also suggests that connectivity is related to symptom severity in ASD[53]. Recent work shows an anti-correlation, or under connectivity between anterior and posterior brain regions in individuals with ASD[54]. Functional connectivity has also been linked to behavior in ASD; higher scores on the ADI-R were correlated with weaker functional connectivity.[55, 56]

Regarding networks related to motor behavior, hyperconnectivity between striatal and cortical regions[57] and in thalamocortical networks[58] have been reported in studies using resting state fMRI paradigms. In school aged children with ASD, Di Martino, et al (2011)[57] found excessive connectivity between striatal subregions and associative and limbic cortex. Woodward, et al (2017)[58] using data from the Autism Brain Imaging Data Exchange (ABIDE) database found hyperconnectivity between the thalamus and cortical regions including motor, somatosensory and prefrontal cortex in ASD. In males with autism a different functional organization of the primary motor cortex, characterized by a lack of differentiation between lower limb/trunk and upper limb/hand parcels has been found[59].

Few studies relating aberrant connectivity directly to motor taks in ASD have been published and studies focused on various different aspects of motor network and used different tasks. Mostofsky, et al. (2007)[60] observed that in children with ASD, increased white matter volume in the primary motor and premotor cortex in the left hemisphere was associated with poorer motor skills, whereas in the control group, increased white matter volume in the primary motor cortex in both hemispheres was associated with better motor performance. In another study, children with ASD showed a slightly different activation pattern and a general decrease in connectivity across the motor network during a finger tapping task compared to typically developing control children[61]. Furthermore, atypical lateralization of motor network connectivity has been reported in children with

ASD, which correlated with motor skill impairment measured with a finger tapping test[62].

Connectivity and developmental trajectory hypotheses could shed light on our findings. Due to under and or over connectivity, the coordination of motor, cognitive and social activity is hypothesized to be problematic. The developmental trajectory hypothesis states that hyperconnectivity is more characteristic in young children with ASD, while hypo- connectivity is more prominent in adolescence and adulthood[63, 64]. In line with this is the suggestion that ASD could be a disorder of aberrant white matter growth patterns at young age and reduced white matter integrity at older age[65]. However, Woodward et al (2017)[58] found that hyperconnectivity between thalamus and motor and temporal cortex was more pronounced in older adolescents than in children/young adolescents and adults. Rigidity, or the resistance to passive movement, has been related to dysfunctional brain connectivity and motor performance in individuals with PD[66]. Hypothetically, it could be possible that the higher degree in rigidity in the adolescent/young adult group in the present study and in the Starkstein, et al. (2015) work[45], might stem from underconnectivity in the brain, which is not yet present in younger children. An important finding in relation to motor impairment is an age-dependent relationship between social adaptability and motor coordination in high functioning children with an ASD[67]. Thus, developmental changes are important to account for.

In their study, Marko, et al. (2015)[68] found that children with an ASD outperformed controls when learning from errors trough proprioception, but underperformed controls when learning form errors through vision. Altered connectivity might play a role in this difference. In our study, motor performance during rating scale observation might be more demanding to individuals with ASD, because there is a high amount of social interaction during assessment. Individuals have to observe the test taker, process this visual, social and motor information and react with motor performance in relation to the test taker. High demands are placed on motor and social networks, and they might interact differently in ASD as they do in healthy controls. Individuals with ASD suffer under more complex circumstances[69]. We argue that the demands on these networks are lower during the mechanical assessment. All individuals receive a training session in which the test instructor shows the computer task. Individuals are asked to follow instruction on the computer screen, lowering the amount of social interaction. After the instruction is given, all individuals perform a solo flight were social information processing is low. This difference has been demonstrated before on set-shifting

tasks. Individuals with an ASD performed better on computerized versions of cognitive tasks in which social interaction is minimized[33].

Of course the new hypothesis that altered connectivity is responsible for our findings is preliminary and must be examined in (RS)-fMRI or EEG studies. However, the use of observational rating scales might mimic expectations of daily live more than a mechanical measurement would in this population. Understanding the role of movement abnormalities in ASD, especially in developing children, is important as it can help to gain insight into the underlying neurobiological processes and the interrelationship of symptom clusters including movement abnormalities. As stated before, a relationship between motor skills and social interaction problems has been demonstrated in ASD, and benefits of physical exercise on motor skills and social interaction in children with ASD have been shown. Another clue that motor problems might be part of a symptom cluster is that dyspraxia is more prevalent in adults with ASD than in controls. In the general population, dyspraxia is associated with higher autistic traits and lower empathy, which could suggest that motor coordination skills are important in empathy and effective social interaction[8]. Identifying motor problems in individuals with ASD might be of great importance in care planning and the effect of interventions.



The current study has several limitations. Test takers were not blinded to group membership. We think it is difficult to prevent raters from knowing whether a participant is in the ASD or control group. In future study, one could keep the raters blind to study hypothesis. In this study however, inter rater agreement was high (96%) and raters were trained by a professional (JK) in the field of motor disorder in psychiatric populations. Second, we used rating scales, which are not typically developed for the use in pediatric populations. However, we used an age and IQ matched control group, and understanding of the instructions and collaboration were excellent with all participants. Third, we had a relatively small sample size and therefore a reduced chance of detecting true effects. It is also possible that false positive results occur. Looking at other studies in this field, number of participants range, with exception by the study of Green, et al (2009)[70] from 11 to 51. Still, future research should focus on larger groups. Fourth, data distribution forced us to use Mann-Whitney tests in the rating scale analysis, with all of its shortcomings. We could not control for age and IQ, factors that are known to influence motor performance. Nevertheless, we used an age and IQ matched control groups. Another important shortcoming could be that the method and analysis used in the instrumental measurement are not specific enough to capture impairments in movement in ASD. Using time series analysis in future research could give us more information.

Despite the shortcomings, this study has important methodological advantages. Participants with ASD were carefully diagnosed; ADI and ADOS, the 'gold standard' for diagnosing ASD, were used in the procedure. None of the participants were on antipsychotic or antiepileptic drugs, thus our results cannot be explained by medication effects. As mentioned before; ASD, PD and psychotic disorders share similarities in phenotypes, but also seem distinct entities with important differences in for example age of onset. Although our pilot study creates valuable insights, it also raises many new questions. Future research should therefore focus on the differences between (older) individuals with ASD, Parkinson's disease and psychotic disorders on instrumental and observational measurements of movement disorder. Additional indexes may then be used in the analysis such as approximate entropy, sample entropy and signal-to-noise ratio[71-73].

## Conclusion

The results of this pilot study should only be interpreted within the context of its limitations. In this study, individuals with ASD show significantly more hypokinetic behavior compared to healthy controls, which may not be strictly dopaminergic in origin, but may rather reflect a weak central coherence of neuronal networks related to the motor system in which developmental changes are present. However, many questions remain. Our data encourage explanation of motor disturbance in ASD by future research.

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**Author contributions** MALMK conceived of the study, participated in its design and coordination, performed the measurement, performed the statistical analysis and drafted the manuscript; AW participated in the interpretation of the data, performed statistical analysis and drafted the manuscript; JPK participated in the design and coordination of the study and helped to draft the manuscript; DET participated in the interpretation of the data and helped to draft the manuscript; PVH participated in the interpretation of the data and helped to draft the manuscript; WGS conceived of the study, participated in its design and coordination, participated in the interpretation of the data and helped to draft the manuscript. All authors read and approved the final manuscript.

## Compliance with ethical standards

**Conflicts of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinski declaration and its later amendments or comparable ethical standards.

## References


1. Damme TV, Simons J, Sabbe B, van West D. Motor abilities of children and adolescents with a psychiatric condition: A systematic literature review. *World J Psychiatry* 2015;5(3):315-329.
2. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-5 (5th ed.)*. Washington DC: American Psychiatric Publishing; 2013.
3. Clearfield MW. Learning to walk changes infants' social interactions. *Infant Behav Dev* Feb 2011;34(1):15-25.
4. MacDonald M, Lord C, Ulrich DA. The relationship of motor skills and social communicative skills in school-aged children with autism spectrum disorder. *Adapt Phys Activ Q* Jul 2013;30(3):271-282.
5. Pusponegoro HD, Efar P, Soedjatmiko, Soebadi A, Firmansyah A, Chen HJ, Hung KL. Gross Motor Profile and Its Association with Socialization Skills in Children with Autism Spectrum Disorders. *Pediatr Neonatol* Dec 2016;57(6):501-507.
6. Mody M, Shui AM, Nowinski LA, Golas SB, Ferrone C, O'Rourke JA, McDougle CJ. Communication Deficits and the Motor System: Exploring Patterns of Associations in Autism Spectrum Disorder (ASD). *J Autism Dev Disord* 2017/01/01 2017;47(1):155-162.
7. Hilton CL, Zhang Y, Whilte MR, Klohr CL, Constantino J. Motor impairment in sibling pairs concordant and discordant for autism spectrum disorders. *Autism* 2012;16.
8. Cassidy S, Hannant P, Tavassoli T, Allison C, Smith P, Baron-Cohen S. Dyspraxia and autistic traits in adults with and without autism spectrum conditions. *Mol Autism* 2016;7:48.
9. Brand S, Jossen S, Holsboer-Trachsler E, Pühse U, Gerber M. Impact of aerobic exercise on sleep and motor skills in children with autism spectrum disorders–a pilot study. *Neuropsychiatr Dis Treat* 2015;11:1911-1920.
10. Srinivasan SM, Eigsti IM, Gifford T, Bhat AN. The effects of embodied rhythm and robotic interventions on the spontaneous and responsive verbal communication skills of children with Autism Spectrum Disorder (ASD): A further outcome of a pilot randomized controlled trial. *Res Autism Spectr Disord* Jul 2016;27:73-87.
11. Woo CC, Leon M. Environmental enrichment as an effective treatment for autism: a randomized controlled trial. *Behav Neurosci* Aug 2013;127(4):487-497.
12. Obeso JA, Rodriguez-Oroz MC, Stamelou M, Bhatia KP, Burn DJ. The expanding universe of disorders of the basal ganglia. *The Lancet* 2014/8/15/ 2014;384(9942):523-531.
13. Staal WG, Langen M, van Dijk S, Mensen VT, Durston S. DRD3 gene and striatum in autism spectrum disorder. *The British Journal of Psychiatry* 2015;206:431-432.
14. Damasio AR, Maurer RG. A neurological model for childhood autism. *Arch Neurol* Dec 1978;35(12):777-786.
15. Vilensky JA, Damasio AR, Maurer RG. Gait disturbances in patients with autistic behavior: a preliminary study. *Arch Neurol* Oct 1981;38(10):646-649.
16. Hollander E, Wang AT, Braun A, Marsh L. Neurological considerations: autism and Parkinson's disease. *Psychiatry research* Nov 30 2009;170(1):43-51.
17. Ball N, Teo W-P, Chandra S, Chapman J. Parkinson's Disease and the Environment. *Front Neurol* 2019-March-19 2019;10.

18. Ozonoff S, Iosif AM. Changing conceptualizations of regression: What prospective studies reveal about the onset of autism spectrum disorder. *Neuroscience and biobehavioral reviews* May 2019;100:296-304.
19. Cacabelos R. Parkinson's Disease: From Pathogenesis to Pharmacogenomics. *Int J Mol Sci* Mar 4 2017;18(3).
20. Nguyen M, Roth A, Kyzar EJ, Poudel MK, Wong K, Stewart AM, Kalueff AV. Decoding the contribution of dopaminergic genes and pathways to autism spectrum disorder (ASD). *Neurochem Int* 2014;66:15-26.
21. Staal WG. Autism, DRD3 and repetitive and stereotyped behavior, an overview of the current knowledge. *European Neuropsychopharmacology* 2015;25(9):1421-1426.
22. DeLong MR, Wichmann T. Circuits and circuit disorders of the basal ganglia. *Arch Neurol* 2007;64(1):20-24.
23. Gasso P, Mas S, Bernardo M, Alvarez S, Parellada E, Lafuente A. A common variant in DRD3 gene is associated with risperidone-induced extrapyramidal symptoms. *Pharmacogenomics J* 2009;9(6):404-410.
24. van Harten PN, Tenback DE. Letter to the Editor: Movement disorders should be a criterion for schizophrenia in DSM-V. *Psychol Med* 2009;39(10):1754-1756.
25. Burbach JP, van der Zwaag B. Contact in the genetics of autism and schizophrenia. *Trends Neurosci* Feb 2009;32(2):69-72.
26. Stone WS, Iguchi L. Do Apparent Overlaps between Schizophrenia and Autistic Spectrum Disorders Reflect Superficial Similarities or Etiological Commonalities? *N Am J Med Sci (Boston)* Jul 25 2011;4(3):124-133.
27. Koning JP, Tenback DE, van Os J, Aleman A, Kahn RS, van Harten PN. Dyskinesia and parkinsonism in antipsychotic-naive patients with schizophrenia, first-degree relatives and healthy controls: a meta-analysis. *Schizophr Bull* 2010;36(4):723-731.
28. Koning JP. Movement disorders in patients with schizophrenia and their siblings; symptoms, side effects and mechanical measurements. *Utrecht: Psychiatry* 2011.
29. Mittal VA, Daley M, Shiode MF, Bearden CE, O'Neill J, Cannon TD. Striatal volumes and dyskinetic movements in youth at high-risk for psychosis. *Schizophr Res* 2010;123(1):68-70.
30. Mittal VA, Orr JM, Turner JA, Pelletier AL, Dean DJ, Lunsford-Avery J, Gupta T. Striatal abnormalities and spontaneous dyskinesias in non-clinical psychosis. *Schizophr Res* 2013;151(1-3):141-147.
31. Caligiuri MP, Lohr JB. Fine force instability: a quantitative measure of neuroleptic-induced dyskinesia in the hand. *J Neuropsychiatr* 1990;2:395-398.
32. Lohr JB, Caligiuri MP. Quantitative instrumental measurement of tardive dyskinesia: a review. *Neuropsychopharmacology* 1992;6(4):231-239.
33. Ozonoff S. Reliability and validity of the Wisconsin Card Sorting Test in studies of autism. *Neuropsychology* 1995;9(4):491-500.
34. Wechsler D. WAIS-III Nederlandstalige bewerking. Technische handleiding. Lisse: Harcourt Test Publishers; 2005.
35. Wechsler D. Nederlandse bewerking: Kort, W., Schittekatte, M., Dekker, P. H., Verhaeghe, P., Compaan, E. L., Bosmans, M., et al. (2005). Wechsler Intelligence Scale for Children Derde Editie NL: Handleiding en Verantwoording. London: Harcourt Test Publishers; 2005.
36. Lord C, Rutter M, Couteur A. Nederlandse bewerking: Jonge, M. V. de, & Bildt, A. de (2007). Autism Diagnostic Interview-Revised: a revised version of a diagnostic inter-

view for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord* 1994;24.
37. Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, DiLavore PC. Nederlandse bewerking: Bildt, A. de, & Jonge, M. V. de (2008). The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord* 2000;30.
38. Guy W. Abnormal involuntary movement scale (AIMS). *ECDEU assessment manual for psychopharmacology* 1976.
39. Martínez-Martín P, Gil-Nagel A, Morlán Gracia L, Balseiro Gomez J, Martínez-Sarriés J, Bermejo F, Group tCM. Unified Parkinson disease rating scale characteristics and structure. *Movement Disorders* 1994;9:76-83.
40. Glazer WM. Review of incidence studies of tardive dyskinesia associated with typical antipsychotics. *J Clin Psychiatry* 2000;61:15-20.
41. Dean CE, Russel JM, Kuskowski MA, Caligiuri MP, Nugent SM. Clinical rating scales and instruments. How do they compare in assessing abnormal involuntary movements? *Journal of clinical psychopharmacology* 2004;24:298-304.
42. Stein RB, Oguztoreli MN. Tremor and other oscillations in neuromuscular systems. *Biological cybernetics* 1976;22(3):147-157.
43. Caligiuri MP, Lohr JB, Ruck RK. Scaling of movement velocity: A measure of neuromotor retardation in individuals with psychopathology. *Psychophysiology* 1998;35(4):431-437.
44. Caligiuri MP, Teulings HL, Filoteo JV, Song D, Lohr JB. Quantitative measurement of handwriting in the assessment of drug-induced parkinsonism. *Human movement science* Oct 2006;25(4-5):510-522.
45. Starkstein S, Gellar S, Parlier M, Payne L, Piven J. High rates of parkinsonism in adults with autism. *Journal of neurodevelopmental disorders* 2015;7(1):29.
46. Shin H-W, Chung SJ. Drug-induced parkinsonism. *Journal of clinical neurology* 2012;8(1):15-21.
47. Koning JP, Kahn R, Tenback DE, van Schelven LJ, van Harten PN. Movement disorders in nonpsychotic siblings of patients with nonaffective psychosis. *Psychiatry Res* 2011;188(1):133-137.
48. Müller R-A, Shih P, Keehn B, Deyoe JR, Leyden KM, Shukla DK. Underconnected, but How? A Survey of Functional Connectivity MRI Studies in Autism Spectrum Disorders. *Cereb Cortex* 2011;21(10):2233-2243.
49. Fournier KA, Hass CJ, Naik SK, Lodha N, Cauraugh JH. Motor Coordination in Autism Spectrum Disorders: A Synthesis and Meta-Analysis. *J Autism Dev Disord* 2010;40(10):1227-1240.
50. Gowen E, Hamilton A. Motor abilities in autism: a review using a computational context. *J Autism Dev Disord* 2013;43:323-344.
51. Rane P, Cochran D, Hodge SM, Haselgrove C, Kennedy D, Frazier JA. Connectivity in Autism: A review of MRI connectivity studies. *Harv Rev Psychiatry* Jul-Aug 2015;23(4):223-244.
52. O'Reilly C, Lewis JD, Elsabbagh M. Is functional brain connectivity atypical in autism? A systematic review of EEG and MEG studies. *PLoS One* 2017;12(5):e0175870.
53. Hahamy A, Behrmann M, Malach R. The idiosyncratic brain: distortion of spontaneous connectivity patterns in autism spectrum disorder. *Nat Neurosci* 2015;18.

54. Heinsfeld AS, Franco AR, Craddock RC, Buchweitz A, Meneguzzi F. Identification of autism spectrum disorder using deep learning and the ABIDE dataset. *NeuroImage: Clinical* 2018;17:16-23.
55. Monk CS, Peltier SJ, Wiggins JL, Weng S-J, Carrasco M, Risi S, Lord C. Abnormalities of intrinsic functional connectivity in autism spectrum disorders. *Neuroimage* 2009;47(2):764-772.
56. Weng SJ, Wiggins JL, Peltier SJ, Carrasco M, Risi S, Lord C. Alterations of resting state functional connectivity in the default network in adolescents with autism spectrum disorders. *Brain Res* 2010;1313.
57. Di Martino A, Kelly C, Grzadzinski R, et al. Aberrant striatal functional connectivity in children with autism. *Biological psychiatry* May 1 2011;69(9):847-856.
58. Woodward ND, Giraldo-Chica M, Rogers B, Cascio CJ. Thalamocortial dysconnectivity in autism spectrum disorder: an analysis of the autism brain imaging data exchange. *Biological Pyschiatry: Cognitive Neuroscience and Neuroimaging* 2017;2(1):76-84.
59. Nebel MB, Joel SE, Muschelli J, Barber AD, Caffo BS, Pekar JJ, Mostofsky SH. Disruption of functional organization within the primary motor cortex in children with autism. *Hum Brain Mapp* 2014;35(2):567-580.
60. Mostofsky SH, Burgess MP, Gidley Larson JC. Increased motor cortex white matter volume predicts motor impairment in autism. *Brain* 2007;130(8):2117-2122.
61. Mostofsky SH, Powell SK, Simmonds DJ, Goldberg MC, Caffo B, Pekar JJ. Decreased connectivity and cerebellar activity in autism during motor task performance. *Brain* 2009;132.
62. Floris DL, Barber AD, Nebel MB, et al. Atypical lateralization of motor circuit functional connectivity in children with autism is associated with motor deficits. *Molecular Autism* 2016;7(1):35.
63. Uddin LQ, Supekar K, Lynch CJ, Khouzam A, Phillips J, Feinstein C, Ryali S, Menon V. Salience Network–Based Classification and Prediction of Symptom Severity in Children With Autism. *JAMA psychiatry* 2013;70(8):869-879.
64. Nomi JS, Uddin LQ. Developmental changes in large-scale network connectivity in autism. *NeuroImage: Clinical* 2015;7:732-741.
65. Maximo JO, Cadena EJ, Kana RK. The Implications of Brain Connectivity in the Neuropsychology of Autism. *Neuropsychol Rev* March 01 2014;24(1):16-31.
66. Baradaran N, Tan SN, Liu A, Ashoori A, Palmer SJ, Wang ZJ, Oishi MM, McKeown MJ. Parkinson's disease rigidity: relation to brain connectivity and motor performance. *Front Neurol* 2013;4:67.
67. Kostrubiec V, Huys R, Jas B, Kruck J. Age-dependent relationship between socio-adaptability and motor coordination in high functioning children with autism spectrum disorder. *J Autism Dev Disord* 2018;48:209-224.
68. Marko MK, Crocetti D, Hulst T, Donchin O, Shadmehr R, Mostofsky SH. Behavioural and neural basis of anomalous motor learning in children with autism. *Brain* 2015;138(3):784-797.
69. Koolen S, Vissers CTW, Egger JI, Verhoeven L. How stimulus and task complexity affect monitoring in high-functioning adults with autism spectrum disorder. *J Autism Dev Disord* 2014;44:2499-2513.
70. Green D, Charman T, Pickles A, Chandler S, Loucas T, Simonoff E. Impairment in movement skills of children with autistic spectrum disorders. *Dev Med Child Neurol* 2009;51.

71. Chow JW, Stokic DS. Variability, frequency composition, and temporal regularity of submaximal isometric elbow flexion force in subacute stroke. *Exp Brain Res* 2016;234:3145-3155.
72. Deutsch KM, Newell KM. Changes in the structure of children's isometric force variability with practice. *J Exp Child Psychol* 2004;88(4):319-333.
73. Slifkin AB, Newell KM. Noise, information transmission, and force variability. *J Exp Psychol Hum Percept Perform* 1999;25(3):837.

# Appendix: details of the procedure and apparatus

## Mechanical instruments for measuring force variability and velocity scaling

- ***Measurement of dyskinesia and resting tremor using Force Variability (FV)***

Dyskinesia can be assessed mechanically by measuring FV, as indicated by the subject's attempt to exert constant pressure on a load cell (see Figure 1) and measuring the variations in the force applied over time[1-4] (see Figure 4).

*Procedure*

Participants are instructed to exert constant target pressure, first by pushing a button with the index finger of their hand to measure hand dyskinesia[5] The button and spatula are connected to a load cell attached to a monitor showing a real-time graph indicating target and actual force applied (Figures 1 and 2). The strength required to achieve the target height on the graph is set to an equivalent of 3 Newton for the index finger[4, 5]. Participants perform each exercise 3 times for a duration of 20 seconds each, separated by 5-second rest periods. The first trial is used to accustom the patient to the test. Mean data of the two subsequent measurements are used for analysis. For dyskinesia, only force variation measured in the 0 to 3 Hz frequency range is used as this reflects dyskinesia best[6] and is unaffected by resting tremor (which is measured at the 4 to 6 Hz frequency band)[7]. This technique has been validated for finger dyskinesia[1-4, 8, 9]

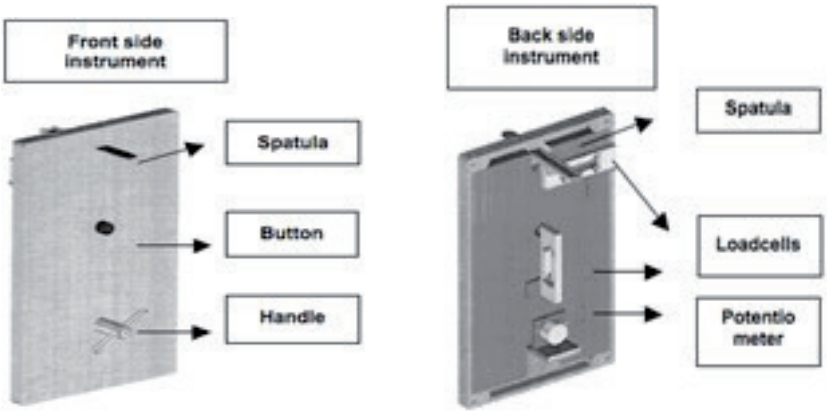


**Fig 1.** Mechanical instrument for measuring force variability and velocity scaling

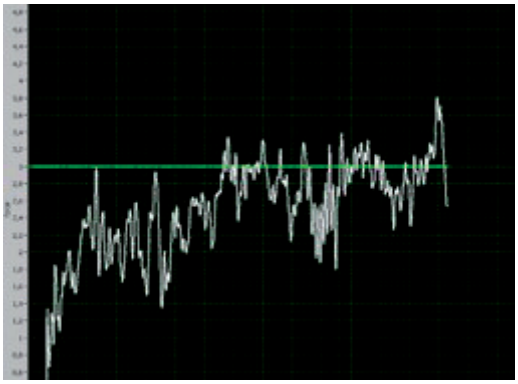

**Figure 2.** Test for force variability, as seen on the computer screen. Example subject's force variability when trying to match the target height of 3N. *N* Newton

## Technical specifications Force Variability measurement

### Force measurement

#### Force measurement finger

| | |
|---|---|
| Button | plastic, directly connected to the loadcell |
| Load cell | load sensor for 3 kg nominal |
| Intended power | 3.0 N (approx. 300 grams) |
| Pressure point height | approx. 25 cm above table top |
| Force measurement direction | vertical, downward |

#### Force measurement general

| | |
|---|---|
| Measuring range | > 2 times intended force |
| Overload capability | safe up to 1.5x nominal power of the sensor |
| Deviation | <0.4 mm at nominal force of the sensor |
| Inaccuracy | according to specs sensor: <0.3% at the intended force |
| Analog filtering | 1st order Low Pass, -3dB at 200 Hz |
| Sampling | 12 bit, 2.5 kHz |
| Digital filtering | Low Pass, -10% at 10 Hz, -3 dB at 18 Hz |
| Software | MS Windows, MatLAb |
| Hardware Laptop | Dell Inspiron 1525, |
| Processor | Intel Pentium duo core T2370 |
| LCD display | 15.4" widescreen with a 1280 × 800 resolution |

- ***Measurement of bradykinesia using Velocity Scaling (VS)***

Bradykinesia can be mechanically quantified by measuring the ability to adjust movement velocity to changing distances[10, 11]. For example, normal individuals, when moving from one fixed target to another, perform different movements in roughly equal time. Thus, moving from one object to another 20 cm away takes approximately the same time as moving to an object 40 cm away when instructed to move as quickly as possible. To do this, the average velocity of the arm movement must increase to compensate for the longer target distance. Participants with bradykinesia (e.g. with Parkinson's' disease or drug-induced parkinsonism) are less able to scale their movement velocity and require more time as distances increase (Figures 3 and 4)[10, 12, 13].



***Procedure***

Participants are instructed to flex a handle (Figure 1) with their wrist as fast but as accurately as possible in order to move a flexible cursor presented on the computer screen to a target cursor located at 25 degrees and 45 degrees from the midline of the wrist flexion (Figure 3)[10]. The handle is connected to a potentiometer (Figure 1) attached to monitor showing in real-time the target and flexible cursor (Figure 3). Participants perform 32 movement measurements consisting of 16 measurements for each of the two randomly presented target locations, for each hand, for a total of 64 movements [10]. VS scores are expressed as degrees per second per degree (deg/s/deg). The VS measure is a valid and reliable measure of antipsychotic-induced bradykinesia [10, 11].

## Technical specifications Velocity Scaling

| | |
|---|---|
| **Measuring range** | measured with a potentiometer with a range of> = 18 degrees. The range is limited by working end stops. |
| **Inaccuracy** | angle between end stops (120 degrees) within +/- 1% degree Position measurement potentiometer within +/- 2 degrees (according to specs potentiometer). |
| **Handle Plate** | with rubber handle, dimensions approx. 90 x 45 $mm^2$. |
| **Rest position handle** | vertical (rest = middle between end stops). This position is not visible or tangibly indicated on the mechanical arrangement. |
| **Direction axis of rotation** | horizontal, approximately straight away from the person. Turns to the left (viewed counter-clockwise from the test subject) are measured as positive. |
| **Handle rotary** | Friction smooth running, mounted |
| **Potentiometer** | Rotary |
| **Data acquisition instrument** | Hardware: National Instruments (NI) USB-6008 |
| **Sampling frequency**: | 12-Bit, 10 kS/s |
| **Movements** | self-paced |

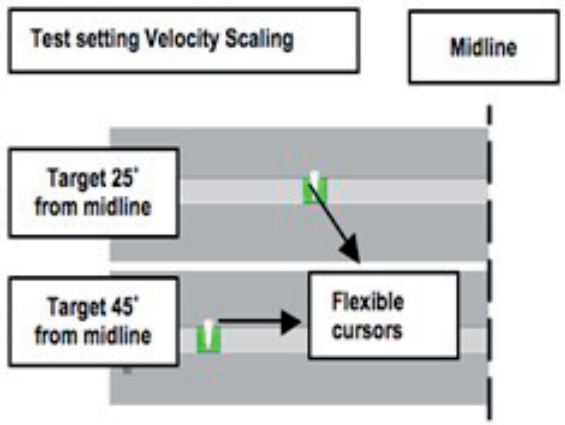


**Fig 3.** Test for velocity scaling

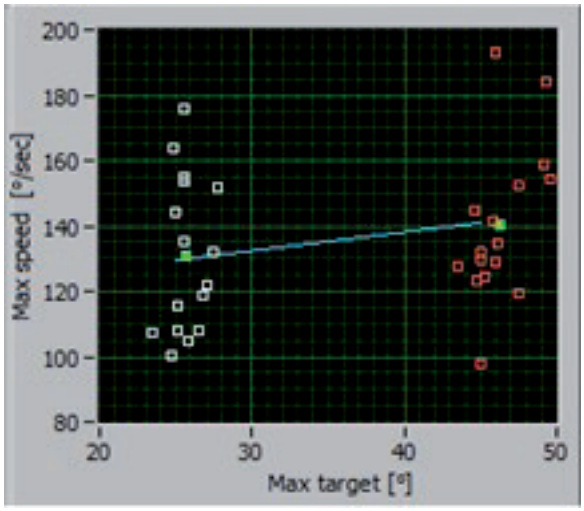


**Figure 4.** *Example of subject with bradykinesia (unable to increase peak velocity when distance increases)*
Y-axis: maximum speed (peak velocity) of flexing wrist
X-axis: targeted distance located at 25 degrees and 45 degrees from the midline of the wrist flexion

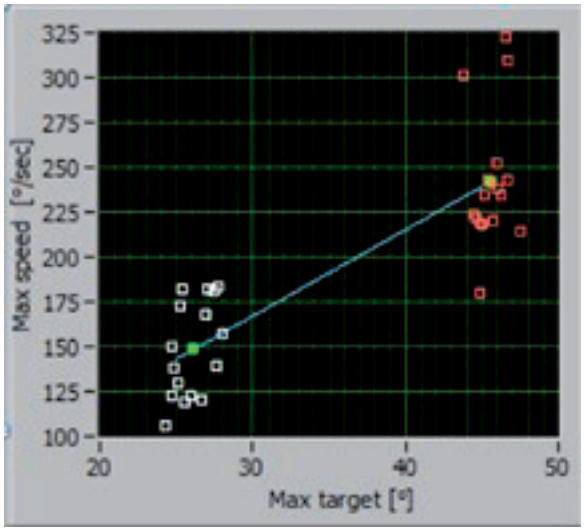


**Figure 5.** *Example of subject without bradykinesia (able to increase peak velocity when distance increases)*
Y-axis: maximum speed (peak velocity) of flexing wrist
X-axis: targeted distance located at 25 degrees and 45 degrees from the midline of the wrist flexion

## References


1. Caligiuri MP, Lohr JB. Fine force instability: a quantitative measure of neuroleptic-induced dyskinesia in the hand. *J Neuropsychiatr* 1990;2:395-398.
2. Caligiuri MP, Lohr JB. A disturbance in the control of muscle force in neuroleptic-naive schizophrenic patients. *Biological psychiatry* Jan 15 1994;35(2):104-111.
3. Cortese L, Caligiuri MP, Malla AK, Manchanda R, Takhar J, Haricharan R. Relationship of neuromotor disturbances to psychosis symptoms in first-episode neuroleptic-naive schizophrenia patients. *Schizophr Res* 2005;75(1):65-75.
4. Dean CE, Russel JM, Kuskowski MA, Caligiuri MP, Nugent SM. Clinical rating scales and instruments. How do they compare in assessing abnormal involuntary movements? *Journal of clinical psychopharmacology* 2004;24:298-304.
5. Koning JP, Kahn R, Tenback DE, van Schelven LJ, van Harten PN. Movement disorders in nonpsychotic siblings of patients with nonaffective psychosis. *Psychiatry Res* 2011;188(1):133-137.
6. Lohr JB, Caligiuri MP. Quantitative instrumental measurement of tardive dyskinesia: a review. *Neuropsychopharmacology* 1992;6(4):231-239.
7. Stein RB, Oguztoreli MN. Tremor and other oscillations in neuromuscular systems. *Biological cybernetics* 1976;22(3):147-157.
8. Caligiuri MP, Lohr JB, Rotrosen J, Adler L, Lavori P, Edson R, Tracy K. Reliability of an instrumental assessment of tardive dyskinesia: results from VA Cooperative Study #394. *Psychopharmacology* Jul 1997;132(1):61-66.
9. Caligiuri MP, Lohr JB, Vaughan RM, McAdams L. Fluctuation of tardive dyskinesia. *Biol Psychiatry* 1995/09/01/ 1995;38(5):336-339.
10. Caligiuri MP, Lohr JB, Ruck RK. Scaling of movement velocity: A measure of neuromotor retardation in individuals with psychopathology. *Psychophysiology* 1998;35(4):431-437.
11. Caligiuri MP, Teulings HL, Filoteo JV, Song D, Lohr JB. Quantitative measurement of handwriting in the assessment of drug-induced parkinsonism. *Human movement science* Oct 2006;25(4-5):510-522.
12. Benecke R. Clinical features and laboratory findings for differentiating parkinsonian syndromes. *Journal of neurology* Oct 2002;249 Suppl 3:Iii/6-14.
13. Berardelli A, Dick JP, Rothwell JC, Day BL, Marsden CD. Scaling of the size of the first agonist EMG burst during rapid wrist movements in patients with Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry* Nov 1986;49(11):1273-1279.

# Part II.

## Movement disorders as side effect of antipsychotic medication

# 4

# Chapter 4.

## Acute movement disorders associated with the use of second-generation antipsychotics in borderline personality disorder; a meta-analysis

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Antipsychotic drugs are used off-label in about one third[1] of the patients with borderline personality disorder (BPD) for specific symptom domains[2] and the number of prescriptions seem to be increasing[3]. However, side effects have been given only limited attention. In the present study a meta-analysis was carried out on acute movement disorders in BPD patients receiving a second generation antipsychotic drug.



Movement disorders are well-known side effects of antipsychotics and, although more profound in first generation antipsychotics, they have also been associated with the use of second generation antipsychotics[4, 5]. Susceptibility for antipsychotic-related movement disorders may not be the same for different psychiatric disorders[6], thus results from studies in patients with schizophrenia cannot be generalized to other disorders including BPD.

Although most of the placebo controlled randomized controlled trials (PC-RCT's) in BPD published in the past decade measured movement disorders in contrast to earlier research, power in these studies might have been too low to detect significant differences in movement disorders. Therefore a meta-analysis on the occurrence of movement disorders in BPD patients treated with an antipsychotic was conducted. Because most of the PC-RCT's had a duration of twelve weeks or shorter only the prevalence of acute movement disorders was investigated. For meta-analytic purpose PC-RCT's were included that studied the effects of antipsychotics in patients with a diagnosis of BPD according to the Diagnostic and Statistical Manual of Mental Disorders, DSM III, DSM III-R or DSM IV, and that had measured movement disorders using validated structured rating scales.

The presence of parkinsonism and akathisia were defined by the following criteria: Parkinsonism: a total mean score of at least 0.3 on the Simpson Angus Scale (SAS). Akathisia: a score of 1 or greater on both the objective and subjective symptoms on the Barnes Akathisia Rating Scale (BARS) or a score of 1 or greater on item 6 of the *Udvalg for Kliniske Undersøgelser (*UKU).

EMBASE, PUBMED and clinicaltrials.gov were searched for relevant literature. In addition we searched for cross references. Our search revealed 14 PC-RCT's on efficacy of antipsychotic medication in BPD published between 1980 and August 2013. In 7 of these studies, movement disorders were assessed with structured rating scales but no data about movement disorders were reported. Therefore, authors were asked for this information.

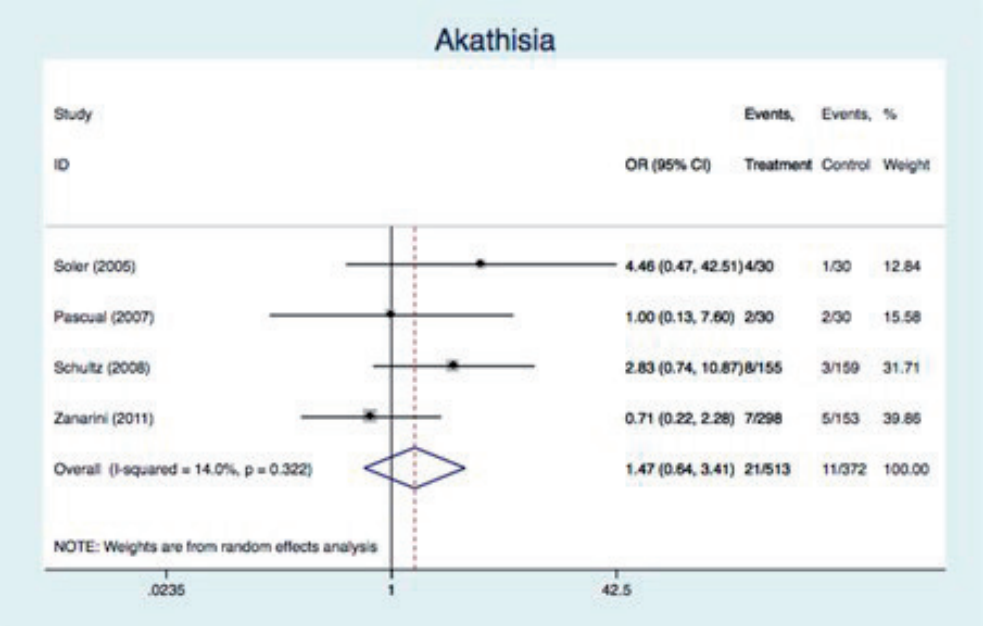
We received data from three olanzapine studies[7-9] and one ziprasidone study[10]. In the olanzapine study by Soler et al. (2005; N= 30/30), the mean dose was 8.8 mg (sd 3.8) and the SAS and BARS were used to measure movement disorders. The olanzapine study by Zanarini et al. (2011) examined two treatment groups, one receiving a daily dose of 2.5 mg (N=150), and the other 5-10 mg, mean 6.7 (sd not retrievable; N=148), and the SAS, BARS and Abnormal Involuntary Movement Scale (AIMS), measuring dyskinesia, were used as rating scales for movement disorders. These same scales were used in the olanzapine study by Schulz et al. (2008; N= 155/159) in which the mean dose was 7.1mg (sd 5.1). In the ziprasidone study (N= 30/30) the mean dose was 84.1 (sd 54.8) and the modified UKU was used for the assessment of movement disorders. Two of the olanzapine studies[7, 8] had used a slightly different criterion for the presence of akathisia then we did (they used a score of 2 or greater on item 4, global score, as cut off point). Effects were pooled using a random effects model as described by DerSimonian & Laird[11], with the estimate of heterogeneity being taken from the Mantel-Haenszel model to calculate odds ratios using STATA 12. Heterogeneity was quantified using the I-squared measure[12]. Our analyses showed odds ratios that were elevated in the medication groups; 1.57 (95% CI 0.66 – 3.77) for parkinsonism, and 1.47 (95% CI 0.64 – 3.41) for akathisia. Odds ratios did not reach statistical significance (figure 1.)

## DISCUSSION

This first meta-analysis regarding the risks on antipsychotic-related movement disorders in BPD shows that the risk on acute parkinsonism and akathisia for patients on low dosages of olanzapine is not significantly increased compared to placebo. Therefore, the use of low dosages of olanzapine seems to be relatively safe with regard to acute movement disorders.

In psychotic patients who develop antipsychotic-related parkinsonism and/or akathisia, this emerges for 90% within days till 12 weeks[13]. Therefore the length of studies in our meta-analyses should have been sufficient for determining the rates of these acute movement disorders. Also, the power of our analyses should have been adequate to detect a clinically relevant effect.

The most plausible explanation for our findings lies in the drugs and dosages used in the studies in our meta-analyses. Parkinsonism and akathisia are more likely to occur with higher dosages of antipsychotic drugs. For parkinsonism, this can be explained by the level of striatal dopamine D2 receptor occupancy



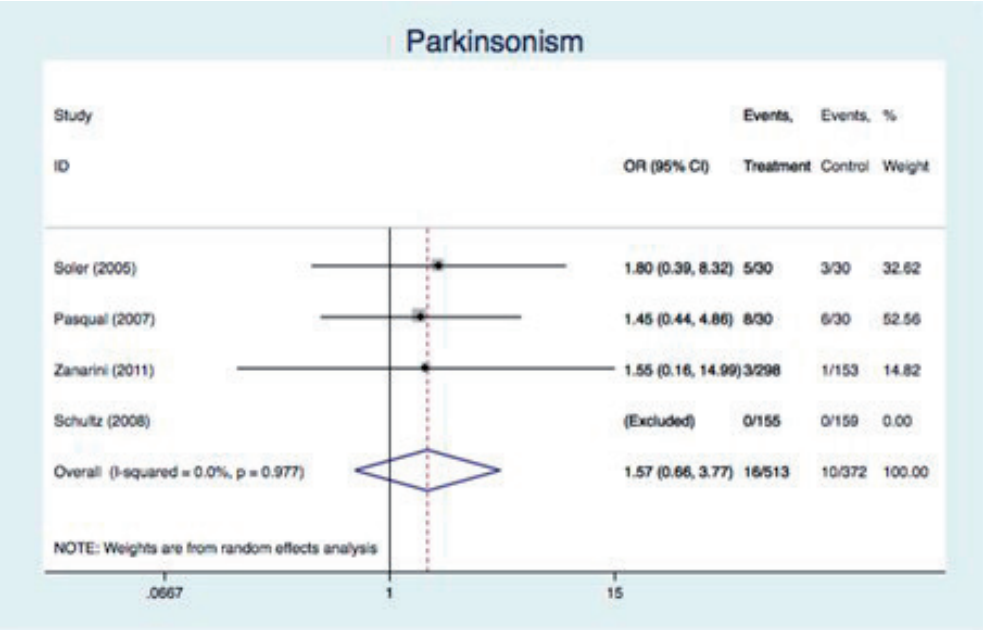




**Figure 1.** Odds ratios for medication versus control groups for parkinsonism and akathisia

as parkinsonism emerges at occupancies of 78%[14]. Low doses of olanzapine, in the range of 5 – 10 mg usually do not induce striatal D2 occupancy percentages above this threshold[15]. Yet, the neurobiology of akathisia is not well known, and various hypotheses including different neurotransmitter systems have been proposed[4]. The association of akathisia with dopamine blocking drugs however still points to some role of dopaminergic transmission in its pathophysiology and the relation between akathisia and dosage is well established.

Besides the low dosages used, the fact that most of the data in our meta-analyses were on olanzapine was probably another major reason for our findings. Olanzapine has been found to have some of the lowest risks of acute movement disorders among the second generation antipsychotics[5] which can partly be explained by its anticholinergic properties[16]. As a consequence of the differences between second generation antipsychotics with regard to risk of movement disorders[4, 5], our results can not be generalised beyond olanzapine.

Although per definition, the length of the studies was too short to develop tardive movement disorders, three of them did assess symptoms of tardive dyskinesia[7, 8, 10]. Using the same analysis as described above we did not find a significant difference between the medication and control groups. This is probably due to the short duration of the studies as tardive movement disorders normally develop after months or even years of antipsychotic treatment. While this meta-analysis shows a low risk on acute movement disorders, it is important to emphasize that olanzapine is related to weight gain and metabolic syndrome. This should be weighed in the choice of the antipsychotic in BPD.

A limitation of our study is that we could retrieve data from only four studies on two drugs which is limited for a meta-analysis. However, a substantial number of events could be analyzed. Another limitation is that only PC-RCT's were included, which has the obvious advantage with regard to the internal validity of the results, but may limit generalizability to the patients treated in daily practice. Patients in PC-RCT's are a highly selected group that may differ in relevant parameters from ordinary patients regarding susceptibility for movement disorders. One may think of factors like substance abuse, intermittent use of medication, polypharmacy and comorbid conditions.

Nevertheless, we tentatively conclude that the use of low dose olanzapine in BPD might be safe with regard to acute movement disorders. Long-term studies are needed to evaluate the occurrence of tardive movement disorders in BPD.

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## AUTHOR DISCLOSURE INFORMATION

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For our meta-analysis, data of the articles of Schulz et al (Br J Psychiatry. 2008;193:485Y492) and Zanarini et al (J Clin Psychiatry. 2011;72:1353Y13562) were received directly from Eli Lilly.

## Literature


1. Baker-Glenn E, Steels M, Evans C. Use of psychotropic medication among psychiatric out-patients with personality disorder. *The Psychiatrist* March 1, 2010 2010;34(3):83-86.
2. Ingenhoven TJM, Duivenvoorden HJ. Differential Effectiveness of Antipsychotics in Borderline Personality Disorder: Meta-Analyses of Placebo-Controlled, Randomized Clinical Trials on Symptomatic Outcome Domains. *J Clin Psychopharmacol* 2011;31(4):489-496.
3. Pascual JC, Martin-Blanco A, Soler J, Ferrer A, Tiana T, Alvarez E, Perez V. A naturalistic study of changes in pharmacological prescription for borderline personality disorder in clinical practice: from APA to NICE guidelines. *Int Clin Psychopharmacol* 2010;25(6):349-355.
4. Kane JM, Fleischhacker WW, Hansen L, Perlis R, Pikalov A, Assuncao-Talbott S. Akathisia: an updated review focusing on second-generation antipsychotics. *J Clin Psychiatry* 2009;70(5):627-633.
5. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Kissling W, Davis JM, Leucht S. Second-Generation Antipsychotic Drugs and Extrapyramidal Side Effects: A Systematic Review and Meta-analysis of Head-to-Head Comparisons. *Schizophr Bull* January 1, 2012 2010;38(1):167-177.
6. Gao K, Kemp DE, Ganocy SJ, Gajwani P, Xia G, Calabrese JR. Antipsychotic-induced extrapyramidal side effects in bipolar disorder and schizophrenia. A systematic Review. *J Clin Psychopharmacol* 2008;28(2):203-209.
7. Schulz S, Zanarini MC, Bateman A, et al. Olanzapine for the treatment of borderline personality disorder: Variable dose 12-week randomised double-blind placebo-controlled study. *British Journal of Psychiatry* Dec 2008;193(6):485-492.
8. Zanarini MC, Schulz SC, Holland CD, et al. A dose comparison of olanzapine for the treatment of borderline personality disorder: a 12-week randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2011;72(10):1353-1362.
9. Soler J, Pascual JC, Campins J, Barrachina J, Puigdemont D, Alvarez E, Perez V. Double-Blind, Placebo-Controlled Study of Dialectical Behavior Therapy Plus Olanzapine for Borderline Personality Disorder. *The American journal of psychiatry* Jun 2005;162(6):1221-1224.
10. Pascual JC, Soler J, Puigdemont D, Pérez-Egea R, Tiana T, Alvarez E, Pérez V. Ziprasidone in the treatment of borderline personality disorder: a double blind, placebo controlled, randomized study. *J Clin Psychiatry* 2008;69(4):603-608.
11. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-188.
12. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-560.
13. Van Harten PN, Wilffert B. Movement disorders. In: Loonen AJM, Hovens JE, eds. *Functional psychopharmacology*. Utrecht: de Tijdstroom; 2012:393-405.
14. Kapur S, Zipursky RB, Jones C, Remington G, Houle S. Relationship between dopamine D2 occupancy, clinical respons, and side effects: a double-blind PET study of first episode schizophrenia. *American Journal of Psychiatry* 2000;157(4):514-520.

15. Frankle WG, Gil R, Hackett E, et al. Occupancy of dopamine D2; receptors by the atypical antipsychotic drugs risperidone and olanzapine: theoretical implications. *Psychopharmacology (Berl)* 2004;175(4):473-480.
16. Chew ML, Mulsant BH, Pollock BG, et al. A model of anticholinergic activity of atypical antipsychotic medications. *Schizophrenia Research* 2006;88(1-3):63-72.

# 5

# Chapter 5.

## The effect on relapse rate and psychiatric symptomatology: Switching a combination of first- and second-generation antipsychotic polypharmacy to antipsychotic monotherapy in long-term inpatients with schizophrenia and related disorders. A pragmatic randomized open-label trial (SwAP trial)

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## ABSTRACT

### Background

There is little evidence to support the use of antipsychotic polypharmacy, and there are concerns about safety and side effects. Nonetheless, it is commonly used in the treatment of long-term inpatients with schizophrenia. This study investigated the effects of switching from a combination of first- and second-generation antipsychotics (FGA and SGA) to monotherapy (FGA or SGA) on relapse rates and psychiatric symptomatology.

### Methods

Institutionalized patients with chronic psychotic disorders using a combination of SGA and FGA (n=136) participated in a randomized open-label trial. The SWITCH group discontinued either FGA or SGA, the STAY group continued combination treatment. Relapse and psychotic symptoms were measured at baseline and during follow up at 3, 6 and 9 months. Psychiatric symptomatology was measured using the Brief Psychiatric Rating Scale (BPRS). Relapse was defined as (i) an increase in BPRS score of at least 2 points on any item, or (ii) an increase of at least 4 points in total BPRS score and an adjustment of antipsychotics.

### Results

A logistic regression model, corrected for sex, showed that the probability of relapse was significantly lower in the SWITCH group: 0.29 (95% CI 0.13–0.62). The protective effect of switching to monotherapy was probably attributable to patients continuing clozapine as monotherapy. For patients who did not experience a relapse nor dropped out, BPRS total scores decreased significantly more in the SWITCH ($p = 0.0001$).

### Conclusion

Switching from a combination of FGA and SGA to monotherapy in long-term inpatients does not increase the relapse rate and may even reduce it.



### Keywords:

Schizophrenia, antipsychotics, polypharmacy, relapse, switching

# 1. Introduction

Antipsychotic medication plays a central role in the pharmacotherapy of schizophrenia. In the long-term treatment of inpatients with schizophrenia, a combination of antipsychotics is commonly prescribed. Indeed, several studies have shown that the prevalence of antipsychotic polypharmacy in the treatment of schizophrenia ranges from 23% to 60% worldwide [1-3]. This polypharmacy often involves a combination of first and second-generation antipsychotics (FGA and SGA) [4].



However, results on the efficacy of this combined use are inconsistent [5-8]. Even more problematically, a combination of FGA and SGA appears to induce more side effects than monotherapy [9-12]. Thus, most treatment guidelines discourage the use of a combination of antipsychotics for the treatment of schizophrenia [13, 14].

Several studies have compared continued antipsychotic polypharmacy with switching from polypharmacy to monotherapy [15-20]. One of these studies showed that switching from polypharmacy to monotherapy was successful in 69% of outpatients with decreased metabolic parameters without leading to increased hospitalization [15]. In another study, switching to monotherapy in outpatients with schizophrenia resulted in improvements in attention, skills of daily living and working skills [17]. A meta-analysis of six RCTs found more all-cause discontinuation in patients who switched to monotherapy compared to patient who stayed of polypharmacy. Nonetheless, no differences were found in relapse, psychopathology, efficacy or side effects. However, the authors concluded that the quality of existing evidence was low [21]. Moreover, only two small RCTs included inpatients [16, 18], and only one included inpatients exclusively [16]. None of the aforementioned studies investigated the switch from a combination of an FGA and an SGA to either FGA or SGA specifically.

In the present study we therefore investigated the effect of switching from antipsychotic polypharmacy (two or more antipsychotics including FGA and SGA) to monotherapy (either FGA or SGA) on the relapse rate and psychiatric symptomatology of institutionalized patients with chronic psychotic disorders who were being treated with antipsychotic polypharmacy. Our study takes the form of a pragmatic randomized controlled trial, allowing us to closely mimic clinical practice and reach a sensitive patient population[22] .

# 2. Methods

## 2.1 Study design and study participants

A nine-month randomized pragmatic open-label trial was conducted to study the effect of switching from antipsychotic polypharmacy to monotherapy in institutionalized patients with chronic psychotic disorders who were using two or more antipsychotics consisting of a combination of FGA and SGA. The primary outcome measure was relapse rate and a secondary outcome measure was psychiatric symptomatology. Patients were randomized to a STAY group where the current polypharmacy was continued, or a SWTICH group, where the antipsychotic polypharmacy was switched to monotherapy.

The study was conducted from 2010 to 2017. Participants were recruited at two psychiatric hospitals in the Netherlands: five long-stay wards at GGz Centraal and three at GGZ Altrecht. In the Netherlands, the mental healthcare and health insurance system is organized in such a way that, for a patient to receive care at these long-stay wards, patients have to be continually admitted for at least a year and may not be eligible for sheltered living because of their level of functioning. For the recruitment ,the study design was presented to the clinical staff, the patients and their families. Then the eligible patients were asked by their own psychiatrists whether they would be interested in participating. Patients were asked to participate and interviewed in person by the researchers with their families present and written informed consent was obtained. Before the trial, the DSM-IV diagnosis of schizophrenia or another psychotic disorder was obtained by interviewing the patients and reviewing their medical records. The study and recruitment procedures were approved by the Dutch Medical Ethical Committee for mental health care institutions. The study was registered with the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT), number 2009-013708-30.

## 2.2 Inclusion and exclusion criteria

The inclusion criteria were: (i) a diagnosis of schizophrenia or another psychotic disorder, (ii) age between 18-65 years old, (iii) the original medication had to be a combination of two or more antipsychotics consisting of FGA and SGA, (iv) patients had to understand the nature of the study and give their written informed consent. Patients were excluded if they were psychiatrically or physically unable to participate, for example due to acute psychosis, suicidal ideation, mental retardation, aggression or physical health issues such as renal failure, cancer or pregnancy.

## 2.3 Randomization and procedure for tapering antipsychotics

Patients were randomized (see supplementary materials p1) to a STAY group or a SWITCH group. In the SWITCH group, the treatment regimen consisted of gradually reducing either FGA or SGA medication during a 90-day tapering-off period, after which monotherapy was continued. When three antipsychotics were used, two of the original antipsychotics were tapered-off. The protocol required that tapering was within 3 months, plus or minus two weeks. Only one patient took longer to taper the medication. Each patient's psychiatrist decided whether to switch to either FGA or SGA monotherapy. Protocols advise to tailor dosage and choice of specific antipsychotic to the case of individual patients [23]. This is especially important in the case of vulnerable groups, like in the current study. The tapering-off period was followed by six months of follow-up. The first (3-month) follow-up was conducted immediately after the tapering period. Symptoms were assessed at baseline (before tapering-off) and at three, six, and nine months, counted from the baseline visit. During the whole course of the study, medication was administered by trained nursing staff. Patients always took their medication under supervision, thus enhancing treatment adherence.



## 2.4 Measurements and relapse

During each visit, psychiatric symptomatology was assessed with the 24-item Brief Psychiatric Rating Scale with a 1-7 scale for each item (BPRS) [24, 25]. We used the subscales as defined by Dingemans et al. [26] based on a validated Dutch translation [27].

Relapse was defined as (i) an absolute increase in BPRS score of at least 2 points on any item, or (ii) an absolute increase of at least 4 points in the total BPRS score [28-30]. Such a change in BPRS score was defined as a relapse only if the patient required a change in antipsychotic medication. If a relapse was ascertained, a final visit (the discontinuation visit) was carried out, and these patients were excluded from the study.

To detect a relapse, the nursing staff were instructed to watch for signs of deterioration of psychotic symptoms in participants. If deterioration was observed, the nursing staff notified the treating psychiatrist, who then assessed the patient. In case of a possible relapse, the researchers performed a psychiatric interview with the patient to assess whether the study criteria of relapse were fulfilled.

## 2.5 Rater training

Two raters with clinical experience conducted the interviews with the participants. One rater was a clinical psychologist, the other a resident in training for

psychiatrist (MS), who became a psychiatrist during the study. These raters were trained by a psychiatrist-epidemiologist (DT) specializing in patients with severe mental illness. Raters were not blinded. However, the same patients were interviewed by the same raters at every follow-up. This reduces the influence of possible rater bias on the results, as it would have been constant rather than variable.

## 2.6 Data analysis

Analyses were carried out in SPSS 25 and R version 3.6.1. To determine the influence of group (SWITCH or STAY) on relapse rate corrected for other possible predictors, we used a logistic regression model. All variables of interest – group, sex, age, BPRS total score at baseline and the interactions of group and sex, group and age, and sex and age –were hierarchically entered into the model. The contribution of each next variable was assessed by comparing the -2 log likelihood of the new model against the previous one. Analyses of model diagnostics are described in the supplementary materials.

For the analyses of differences between the two groups regarding change in psychotic symptoms over time for the patients who did not experience a relapse, assumptions for parametric testing were not met. Therefore, the R package nparLD was used [31], which was specifically designed for non-parametric analysis of repeated measures data in factorial designs. The between-subjects factor was group (SWITCH or STAY), and the within-subjects factor was the BPRS total score at the four time points (baseline, after tapering-off, follow-up 1 and follow-up 2). After the omnibus test, post-hoc tests were used to compare each follow-up measurement against baseline. For all tests, the ANOVA-type statistic (ATS) is reported.

## 2.7 Handling of missing BPRS items

Using multiple imputation in SPSS, values of missing items in BPRSs were estimated based on all available BPRS items. This procedure was carried out five times. After imputation, BPRSs for which a maximum of 20% (four) items were missing were used for analyses [32], and BPRSs with more than four missing items were excluded.

The analysis of the group difference in psychotic symptom progression during the four visits for patients who did not relapse, was carried out on each imputed dataset. Here we have reported the difference with the median p-value. Post-hoc tests, tests for the subscales of the BPRS and graphs were based on the same

imputed dataset. Details of missing values and BPRSs and results of the imputation are given in the supplementary materials.

## 3. Results

### 3.1 Descriptive results

A total of 136 patients were included, of which 66 were randomized to the SWITCH group and 70 to the STAY group (Fig. 1). Nine patients dropped out of the study (SWITCH: n=5, 7.6%)



STAY: n=4, 5.7%). Reasons for drop out in the SWITCH group were moving to another facility (n=1), death from heart-lung disease (n=1), and requests from patients and caregivers to stop participation (n=3). In the STAY group reasons for dropping out were requests to stop from the patient (n=1) and from both patients and caregivers (n=3).

Demographic and clinical characteristics of both groups are summarized in Table 1. For antipsychotics, defined daily dose (DDD) was calculated using the website of the WHO Collaborating Centre for Drug Statistics Methodology (https://www.whocc.no/atc_ddd_index/) [33].

In the total sample, 55 unique combinations of antipsychotics were used at baseline. The most frequently used combinations were oral flupentixol and clozapine (SWITCH: n=12, STAY: n=12), followed by oral flupentixol and olanzapine (SWITCH: n=4, STAY: n=5), oral haloperidol and clozapine (SWITCH: n=5, STAY: n=4), and LAI zuclopenthixol and clozapine (SWITCH: n=4, STAY: n=4). All other combinations were used by fewer than seven patients. See supplementary Table 1 for all combinations of antipsychotics prescribed at baseline.

The vast majority of patients in the SWITCH group (n=57, 89.1%) stopped taking FGA while the remainder (n=7, 10.9%) stopped taking the SGA. Data were missing for two patients. Of the of the patients in the SWITCH group who used clozapine (n=44, 67.7 %), only 1 (1.5%) discontinued clozapine. Of the 25 patients in the SWITCH group who used a LAI antipsychotic, 18 (75%) discontinued the LAI, 6 (25%) stayed on a LAI and one patient had died before the discontinuation period had started. All patients in the SWITCH group except one stayed on either an SGA or a LAI FGA.

**Table 1.** Demographic and clinical patient characteristics at baseline

| | SWITCH (n = 66) | STAY (n = 70) | p-value[a] |
|---|---|---|---|
| Age, mean (SD) | 52.4 (12.7) | 54.9 (11.3) | 0.650 |
| Male sex, n (%) | 38 (57.6) | (43) 61.4 | 0.647 |
| Education, n (%) | | | 0.365 |
| No education | 5 (7.7) | 5 (8.8) | |
| Elementary school | 10 (15.4) | 11 (19.3) | |
| Lower secondary/vocational education | 38 (58.5) | 31 (54.4) | |
| Higher secondary education | 6 (9.2) | 9 (15.8) | |
| Higher vocational education/ University | 6 (9.2) | 1 (1.8) | |
| Marital status, n (%) | | | 0.301 |
| Never married | 59 (92.2) | 55 (85.9) | |
| Married/living with spouse | 0 | 1 (1.6) | |
| Divorced | 4 (6.3) | 8 (12.5) | |
| Widowed | 1 (1.6) | 0 | |
| Ethnicity % | | | 0.506 |
| White | 49 (77.8) | 55 (83.3) | |
| Other | 14 (22.2) | 11 (16.7) | |
| Diagnosis % | | | 0.923 |
| Schizophrenia | 56 (86.2) | 60 (88.2) | |
| Schizoaffective disorder | 6 (9.2) | 5 (7.5) | |
| Schizophreniform disorder | 3 (4.6) | 3 (4.4) | |
| BPRS total score at baseline, mean (SD) | 50.7 (14.8) | 47.5 (11.0) | 0.165 |
| BPRS average item score positive subscale, mean (SD) | 2.6 (0.9) | 2.5 (0.8) | 0.280 |
| BPRS average item score depressive subscale, mean (SD | 2.1 (0.7) | 2.1 (0.6) | 0.844 |
| BPRS average item score negative subscale, mean (SD) | 1.8 (0.7) | 1.7 (0.8) | 0.391 |
| BPRS average item score manic subscale, mean (SD) | 2.0 (1.0) | 1.8 (0.7) | 0.228 |
| Total duration of treatment at GGz Centraal, years, mean (SD)[b] | 17.9 (10.9) | 22.1 (6.9) | 0.021 |
| Antipsychotic medication | | | |
| Total DDD antipsychotic, mean (SD) | 3.16 (2.10) | 2.62 (1.41) | 0.080[c] |
| DDD FGA, mean (SD) | 1.86 (1.98) | 1.29 (0.96) | 0.040[c] |
| DDD SGA, mean (SD) | 1.28 (0.64) | 1.34 (0.78) | 0.658 |
| FGA and Clozapine, % | 44 (66.7) | 39 (55.7) | 0.191 |
| LAI FGA and SGA[d] | 25 (37.9) | 21 (30.0) | 0.332 |

**Table 1.** Continued

| | SWITCH (n = 66) | STAY (n = 70) | p-value[a] |
|---|---|---|---|
| Use of three antipsychotics, % | 15 (22.7) | 10 (14.3) | 0.204 |
| Concomitant pharmacotherapy | | | |
| Antidepressants, % | 17 (26.8) | 25 (33.7) | 0.209 |
| Lithium, % | 5 (7.6) | 4 (5.7) | 0.739 |
| Mood stabilizers, % | 14 (21.2) | 12 (17.1) | 0.546 |
| Benzodiazepines, % | 27 (40.9) | 43 (61.4) | 0.017 |
| Biperiden, % | 25 (37.9) | 30 (42.9) | 0.554 |

SWITCH: first generation antipsychotic or second-generation antipsychotic was discontinued; STAY: stay on combination treatment with first generation antipsychotic and second-generation antipsychotic; BPRS: Brief Psychiatric Rating Scale; DDD = Defined Daily Dose; FGA = First Generation Antipsychotic.
Number of participants with missing data: Education: SWITCH: n = 1; STAY: n = 13; Marital status: SWITCH: n = 2; STAY: n = 6; Ethnicity: SWITCH: n = 3; STAY: n = 4 Diagnosis: SWITCH: n = 1; STAY: n = 2. BPRS total score and subscales: SWITCH: n = 4; STAY: n = 4; Total DDD antipsychotic: SWITCH: n = 2, STAY: n = 1; DDD FGA: SWITCH: n=2; STAY: n=1.
[a] Difference in age, BPRS total scores, average item scores per BPRS subscale, total DDD antipsychotic, DDD FGA and DDD SGA were tested using an independent samples *t-test*. For differences in sex, ethnicity, the use of an FGA and clozapine, LAI FGA and SGA, more than 2 antipsychotics, antidepressants, mood stabilizers, and benzodiazepines, chi-square tests were used. As the assumptions of the chi-square test did not hold for differences in education, marital status, diagnosis, and the use of lithium, Fisher's exact tests were carried out.
[b] Total years of treatment could only be retrieved for patients from GGz Centraal and not from GGz Altrecht.
[c] The differences in total DDD AP and DDD FGA were mainly driven by one patient in the SWITCH group who used a very high dose of long acting injectable (LAI) fluphenazine.
[d] When the study was conducted, only FGA were available as LAI at the wards where participants were treated.



## 3.2 Relapse

Of the 136 patients that participated, 55 (40.4%) experienced a relapse. Figure 2 shows the BPRS total scores for continue and discontinue visits. There were fewer relapses in the SWITCH group (n=18, 27.3%) than in the STAY group (n=37, 52.0%). Most of the relapses (n=41, 74.5% of the total number of relapses) occurred in the first three months of the study (Fig. 1.)

Group and sex made a significant contribution to the logistic regression model whereas the other variables did not. Group and sex were therefore kept in the final model (Table 2). Being treated in the SWITCH group had a protective effect with an odds ratio (OR) of 0.29 (95% CI 0.13–0.62) compared to being treated in the STAY group. Female sex was associated with a greater risk of relapse with an OR of 3.03 (95% CI 1.40–6.56) compared to male sex. Because of the high percentage of patients using clozapine and the fact that in the SWITCH group all

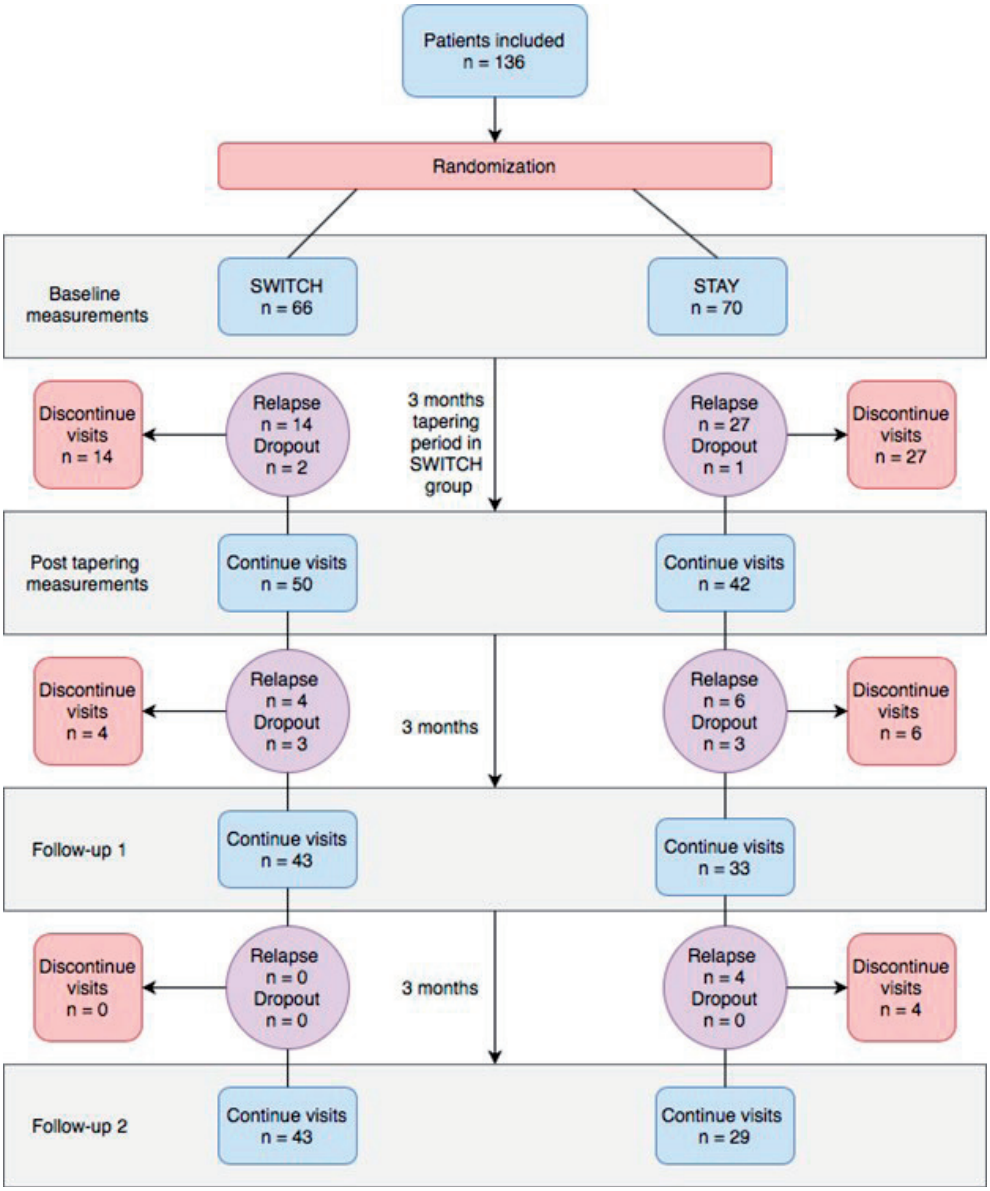


*Figure 1.* Flow of patients into SWITCH and STAY conditions during the study. SWITCH: first- or second-generation antipsychotic was discontinued; STAY: stay on combination treatment with first- and second-generation antipsychotic; Discontinue visit: final visit when a patient experienced a relapse, after which the patient stopped participating in the study.

patients except one who used clozapine at baseline continued to use clozapine as monotherapy, post hoc tests were carried out to examine the effect of clozapine use on relapse. Clozapine use at baseline and the interaction of clozapine and group were added to the logistic regression model as described above. The resulting model (Table 3.) showed a significant interaction between group and use of clozapine. Sensitivity analyses using the same logistic regression model corrected for sex were performed in clozapine users and non-clozapine users separately. The results showed that clozapine users in the SWITCH group had a significantly lower probability of relapse than clozapine users in the STAY group (OR=0.12, 95% CI 0.04-0.38). There was no significant effect of group in the non-clozapine users (OR=0.81, 95% CI 0.25-2.70). Details of the models are given in the supplementary materials (Supplementary Tables 2 and 3).



**Table 2.** Logistic regression model of the effect of group and sex on relapse
n=127

| | B (SE) | Wald x2 | OR (95% CI) | p-value |
|---|---|---|---|---|
| Constant | -0.19 (0.29) | 0.40 | | 0.526 |
| SWITCH group | -1.26 (0.40) | 10.05 | 0.29 (0.13 - 0.62) | 0.002 |
| Female sex | 1.11 (0.40) | 7.88 | 3.03 (1.40 - 6.56) | 0.005 |

OR = Odds ratio $R^2$ = 0.10 (Hosmer-Lemeshow), 0.13 (Cox-Snell), 0.17 (Nagelkerke). Model $x^2$ (2) = 17.53, $p$=0.000

**Table 3.** Logistic regression model of the effect of group, sex, use of clozapine and group*clozapine interaction on relapse
n=1[2]6a

| | B (SE) | Wald x2 | OR (95% CI) | p-value |
|---|---|---|---|---|
| Constant | -0.42 (0.44) | 0.92 | | 0.339 |
| SWITCH group | -0.21 (0.61) | 0.11 | 0.81 (0.25 – 2.70) | 0.737 |
| Female sex | 1.26 (0.42) | 8.89 | 3.52 (1.54 – 8.04) | 0.003 |
| Use of clozapine | 0.32 (0.53) | 0.37 | 1.38 (0.49 – 3.91) | 0.543 |
| Group*clozapine | -1.94 (0.84) | 5.35 | 0.14 (0.028 – 0.744) | 0.021 |

OR = Odds ratio $R^2$ = 0.15 (Hosmer-Lemeshow), 0.19 (Cox-Snell), 0.25 (Nagelkerke). Model $x^2$ (4) = 26.30, $p$=0.000

[a]One patient who was prescribed clozapine in the SWITCH group and discontinued clozapine was excluded from the analysis

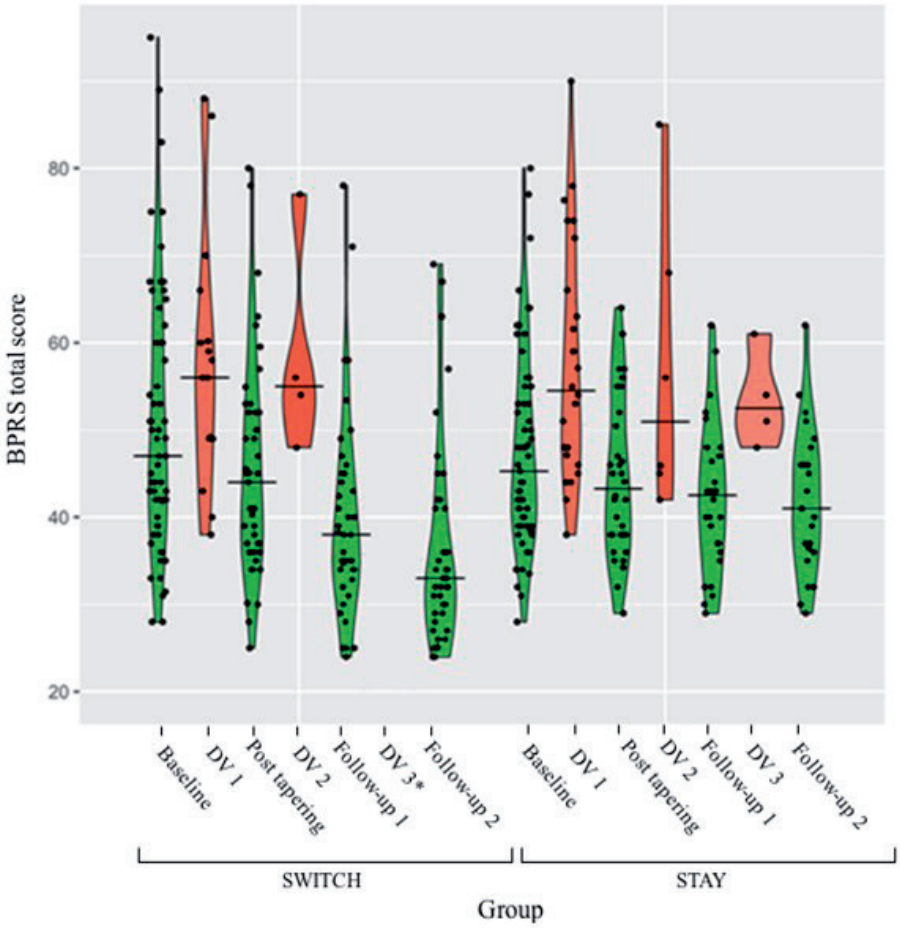


**Fig. 2**. BPRS total scores and medians for Continue and Discontinue Visits. : Median SWITCH: first generation antipsychotic or second-generation antipsychotic was discontinued; STAY: stay on combination treatment with first generation antipsychotic and second-generation antipsychotic; BPRS: Brief Psychiatric Rating Scale; DV 1: Discontinue visits for patients experiencing a relapse between Baseline and the Post tapering measurement; DV 2: Discontinue visits for patients experiencing a relapse between the Post tapering measurement and Follow-up 1. DV 3: Discontinue visits for patients experiencing a relapse between Follow-up 1 and Follow-up 2. *There were no relapses and therefore no discontinue visits between follow-up 1 and 2 in the SWITCH group

## 3.3 Descriptive results for patients who did not experience a relapse and completed the study

Of the 136 patients who were randomized, 72 (52.9%, SWITCH n=43, STAY n=29) stayed in the study until the final measurement (follow-up 2). These patients did not relapse and did not drop out of the study. Table 4 shows the psychotropic

medication of these patients at follow-up 2. In the SWITCH group, the discontinuation of one or two antipsychotics was accompanied by a reduction in total DDD antipsychotics for most patients (n=38, 92.7%) while there was an increase in total DDD for a small minority (n=3, 7.3%; data were missing for 2 patients).

**Table 4**. Use of psychotropic medication at follow-up 2 (9 months after baseline) for patients who did not relapse nor drop out during the study period

| | SWITCH (n = 43) | STAY (n = 29) |
|---|---|---|
| Total DDD antipsychotic, mean (SD) | 1.26 (0.67) | 3.20 (1.48) |
| FGA and clozapine, n (%) | 0 | 16 (55.2) |
| FGA only, n (%) | 1 (2.3) | 0 |
| SGA only,* n (%) | 42 (97.7) | 0 |
| Clozapine only, n (%) | 33 (76.7) | 0 |
| Use of three antipsychotics, n (%) | 0 | 6 (20.7) |
| Concomitant pharmacotherapy | | |
| Antidepressants, n (%) | 12 (27.9) | 10 (34.5) |
| Lithium, n (%) | 3 (7.0) | 2 (6.9) |
| Mood stabilizers, n (%) | 13 (30.2) | 6 (20.7) |
| Benzodiazepines, n (%) | 17 (39.5) | 17 (58.6) |
| Biperiden, n (%) | 9 (20.9) | 9 (31.0) |

DDD: defined daily dose; FGA: first generation antipsychotic; SGA: second generation antipsychotic
*One patient (2.3 %) in the SWITCH group used 2 SGA's at follow-up 2.



### 3.4 Course of psychotic symptoms

For patients who did not relapse and did not drop out of the study, the differences in psychotic symptom progression as measured by the BPRS over the four time points between the SWITCH and STAY group were tested. Fig. 3 shows the BPRS total scores of both groups over time. The omnibus test for all four time points showed no significant main effect for group (ATS=2.26, $p$=0.1329). The effects for time (ATS=59.67, $p$<0.0001) and the interaction between group and time (ATS, $p$ = 0.0001) were highly significant.

Post-hoc testing for the interaction showed no significant effect when comparing the post tapering measurement against baseline (ATS=0.25, $p$=0.618). However, follow-up 1 and follow-up 2 both differed significantly from baseline when no correction for multiple testing was used (ATS=5.45, $p$=0.020 and ATS=16.75, $p$<0.001, respectively). After applying a Bonferroni correction, alpha became 0.017, and only follow-up 2 compared to baseline remained significant. As shown in Figure 3, the decrease in BPRS total score between baseline and follow-up 1

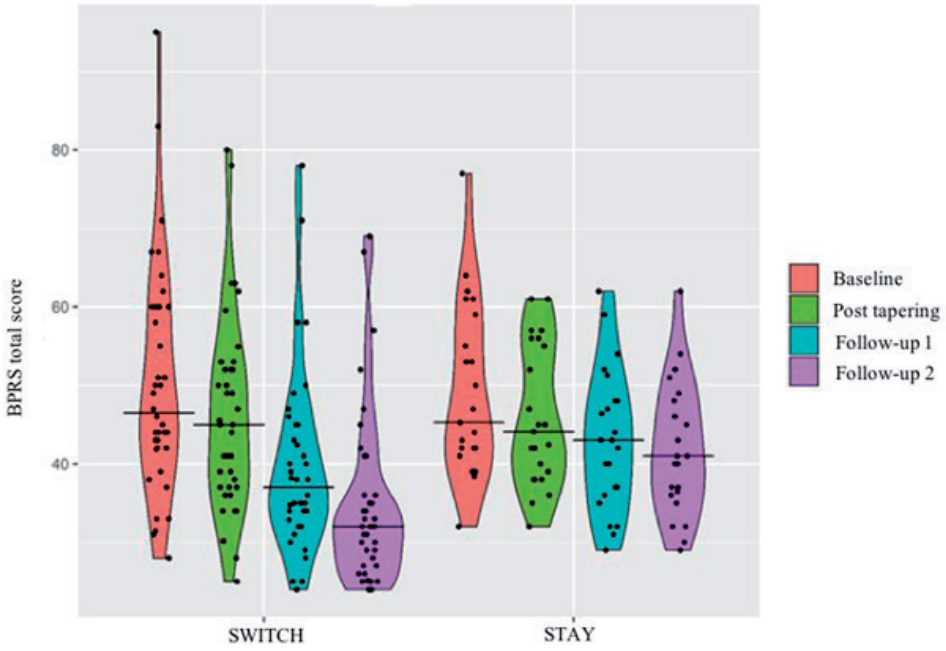


**Fig 3**. BPRS total scores and medians for patients who completed the study. -: Median; SWITCH: cessation group. First generation antipsychotic or second generation antipsychotic was discontinued; STAY: stay on combined treatment with first generation antipsychotic and second generation antipsychotic; BPRS: Brief Psychiatric Rating Scale

and between baseline and follow-up 2 was greater in the SWTICH group than in the STAY group. In the SWITCH group, the mean BPRS total score decreased with 15.2 points from baseline (50.2) till follow-up 2 (35.0), while in the STAY group the decrease was 7.2 points (49.1 at baseline and 41.8 at follow-up 2).

In exploratory analyses both the omnibus and post-hoc tests as described above were carried out on four subscales of the BPRS separately. Results are described in the supplementary materials.

## 4. Discussion

This is the first RCT in which the effect of switching from a combination of FGA and SGA polypharmacy to antipsychotic monotherapy in institutionalized patients with schizophrenia on relapse and psychotic symptoms has been investigated. Switching to antipsychotic monotherapy had a protective effect on the probability of relapse (OR 0.29, 95% CI 0.13–0.62). Switching to clozapine

monotherapy decreased the probability of relapse compared with staying on clozapine plus an FGA (OR=0.12, 95% CI 0.04-0.38). There was no significant effect on relapse for switching to a non-clozapine monotherapy compared with staying on non-clozapine SGA plus FGA (OR=0.81, 95% CI 0.25-2.70). This suggest that the effect was due to the patients in the SWITCH group who continued clozapine as monotherapy. For patients who did not relapse nor drop out and stayed in the study until the final measurement, we observed a greater reduction in psychotic symptomatology in the SWITCH group than in the STAY group between baseline and both follow-ups. In both groups, more relapses occurred in the first three months than later in the study, and females had a much greater risk of relapse than males.



The current study was designed as a pragmatic RCT with the aims of studying the effect of switching to monotherapy in clinical practice. Patients were randomized to switch to antipsychotic monotherapy or to remain on antipsychotic polypharmacy and a time frame for tapering in the switch group was protocolled. In order to stay close to actual clinical practice, an open design was chosen and treatment decisions, i.e. which antipsychotic(s) to discontinue, whether to change dose, or to change comedication other than antipsychotics, were left to the treating psychiatrist. Also, the clinical judgement of the psychiatrist that a change in antipsychotic medication because of worsening of symptoms was needed, was required to meet the criteria for relapse. While these choices reduce internal validity, generalizability to normal clinical practice in long stay-wards is optimized.

The study was carried out at long-stay wards of two institutions for specialized mental health care in the Netherlands. The Dutch mental health and health insurance system are organized in such a way that only patients who have been admitted continually for at least a year, can be treated at the respective wards. In practice these are patients with severe symptoms which is reflected in duration of treatment and BPRS scores in our sample.

Interestingly, although psychiatrists were free to choose which antipsychotic to taper in the SWITCH group, the FGA's were tapered for almost 90% of the patients. For six out of seven patients who continued an FGA, this comprised a LAI formulation. Furthermore, the majority of patients in the study was prescribed clozapine and, all but one of these patients continued clozapine as monotherapy. Thus, in the SWITCH group, all patients, except one, were switched to either an SGA (mostly clozapine) or a LAI FGA, which is important for the interpretation of the current results.

To our knowledge, no other RCTs investigating the switch from a combination of FGA and SGA to either FGA or SGA have been published. In most earlier RCTs investigating the switch from antipsychotic polypharmacy to monotherapy, all antipsychotic agents were allowed [17-19, 34] and one study investigated the switch from a combination of clozapine and olanzapine to clozapine monotherapy[16]. Those earlier RCTs did not have relapse defined as an outcome measure. However, all-cause discontinuation was reported [16-19, 34]. A recent meta-analysis found more all-cause discontinuation in switch compared to stay patients [21]. Nonetheless, in all included studies the majority of patients in the switch groups could be transitioned to monotherapy. In addition, no group differences in discontinuation due to lack of efficacy or side effects were found. With respect to severity of psychopathology no differences were found either. More specifically, four out of five RCTs found no or hardly any differences in symptom trajectories between the two groups [15, 17, 18]. In contrast, Constantine and colleagues reported an increase in symptoms over time in the switch compared to the stay group for patients on two non-clozapine oral antipsychotics. However, participants who remained on clozapine or a long acting injectable (LAI) antipsychotic did not experience an increase in symptom severity[20].

Besides type of antipsychotic agents used, other main differences with the RCTs mentioned above are the inclusion of inpatients only in the current study (except [16]) and the use of three antipsychotics at baseline by a substantial minority of patients.

Our study is the first RCT to report a lower probability of relapse for patients who switch from a combination of FGA and clozapine to clozapine monotherapy. Clozapine was not used in two of the five earlier RCTs on switching antipsychotic polypharmacy to monotherapy [15, 17]. In two other studies, part of the patients [18] and all patients [16] received clozapine, and continued to use it as monotherapy. Borlido and colleagues did not report results for patients who switched to clozapine monotherapy separately. Repo-Tiihonen et al. found no significant differences in symptom severity between inpatients switching from the combination of olanzapine and clozapine to clozapine monotherapy compared with continuation of combined use. Important differences between their study and the current one, are the use of two SGA's as antipsychotic polypharmacy and the smaller sample size (n=15) in the study by Repo-Tiihonen. Furthermore, the studies by Borlido et al. and Repo-Tiihonen et al. had a duration of 12 weeks including the tapering period, whereas in the present study, the beneficial effects of monotherapy on psychotic symptoms were present at three months follow-up (three months after the second antipsychotic was tapered off) and became even

more pronounced at the follow-up at 6 months. The current results are in line with the findings from a nationwide register-based study in Finland in which clozapine monotherapy was more effective in the prevention of rehospitalization in patients with schizophrenia than clozapine combined with oral FGA [8]. Of note, the most effective was a combination of clozapine and aripiprazole.

Clozapine is one of the most effective antipsychotics currently available [21, 35], and the only agent that is recommended for treatment-refractory schizophrenia [36]. Some evidence suggests that clozapine may also ameliorate dopamine supersensitivity psychosis [37]. It could be that the addition of an FGA, with high affinity to the D2 receptor, disturbs the loose binding of clozapine to this receptor, decreasing its efficacy. Thus, in chronic patients who are prescribed a combination of clozapine and FGA, switching to clozapine monotherapy may enhance efficacy.



An interesting finding from our study was that in both the SWITCH group and the STAY group, most relapses occurred in the first three months, while other studies reported relapses during the entire switching process [38, 39]. We hypothesize that the early relapses in both the SWITCH and STAY groups may be explained by a subgroup of patients with a very high vulnerability for relapse. Those patients may have had a higher probability of relapse in general and thus for relapse in the first three months as well. As a consequence of the study design by which patients who relapsed discontinued the study, the somewhat less vulnerable patients had a higher chance of remaining in the study beyond the first three months, a process analogue to the epidemiological concept of the survival effect [40].

An unexpected finding was a higher relapse risk in females compared to males. Relapses are generally more common among men than women [41], probably due to hormonal differences. Estrogens play a protective role in women with schizophrenia, due to the downregulating effect of estrogens on dopamine receptors [42]. Indeed, the efficacy of antipsychotics has been shown to decline among women in menopause [43]. Therefore, an explanation for this higher relapse in females in the current study could be that most female patients (82%) were 50 years or older, suggesting that many of them were already in the postmenopausal phase.

### 4.1 Limitations and strengths

Firstly, the open-label design may have led to an observer expectancy effect. However, based on the literature, the observers actually expected the patients in the SWITCH group to exhibit a higher relapse rate than those in the STAY group. Secondly, this study only included patients in the chronic phase of a psychotic

disorder. This means our results should not be generalized to patients with acute psychotic disorders. Thirdly, only patients who were prescribed a combination of FGA's and SGA's were included. Subgroups of patients using clozapine and non-clozapine antipsychotics were large enough for sensitivity analyses. Consequently, results were based on relatively homogeneous treatment groups, which makes them easier to interpret. However, results should not be generalized to antipsychotic polypharmacy consisting of either SGA or FGA. Finally, because of the open label design and the freedom for treating psychiatrists in treatment choices, the study has strong ecological validity [44].

## 5. Conclusion

In long-term inpatients with schizophrenia, antipsychotic polypharmacy including FGA and SGA can be safely switched to either SGA or LAI FGA monotherapy with respect to the risk of relapse. For patients who are prescribed clozapine in combination with FGA, switching to clozapine monotherapy is superior in relapse prevention.

### Role of funding source

The funder has played no role in the research.

### Declaration of competing interest

The authors declare no potential conflicts of interest.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2022.03.008.

## REFERENCES


1. Broekema WJ, de Groot IW, van Harten PN. Simultaneous prescribing of atypical antipsychotics, conventional antipsychotics and anticholinergics-a European study. *Pharmacy world & science : PWS* Jun 2007;29(3):126-130.
2. Fontanella CA, Hiance-Steelesmith DL, Guirgis H, Campo JV. Trends in and predictors of long-term antipsychotic polypharmacy use among Ohio Medicaid patients with schizophrenia, 2008–2014. *Psychiatr Serv* 2018;69(9):1015-1020.
3. Ganguly R, Kotzan JA, Miller LS, Kennedy K, Martin BC. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998-2000. *The Journal of clinical psychiatry* Oct 2004;65(10):1377-1388.
4. Correll CU, Gallego JA. Antipsychotic polypharmacy: a comprehensive evaluation of relevant correlates of a long-standing clinical practice. *The Psychiatric clinics of North America* Sep 2012;35(3):661-681.
5. Correll CU, Rummel-Kluge C, Corves C, Kane JM, Leucht S. Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. *Schizophrenia bulletin* Mar 2009;35(2):443-457.
6. Katona L, Czobor P, Bitter I. Real-world effectiveness of antipsychotic monotherapy vs. polypharmacy in schizophrenia: to switch or to combine? A nationwide study in Hungary. *Schizophrenia research* Jan 2014;152(1):246-254.
7. Galling B, Roldan A, Hagi K, et al. Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis. *World psychiatry : official journal of the World Psychiatric Association (WPA)* Feb 2017;16(1):77-89.
8. Tiihonen J, Taipale H, Mehtälä J, Vattulainen P, Correll CU, Tanskanen A. Association of Antipsychotic Polypharmacy vs Monotherapy With Psychiatric Rehospitalization Among Adults With Schizophrenia. *JAMA psychiatry* May 1 2019;76(5):499-507.
9. van Harten PN, Hoek HW, Matroos GE, van Os J. Incidence of tardive dyskinesia and tardive dystonia in African Caribbean Patients on long-term antipsychotic treatment: the Curaçao Extrapyramidal Syndromes Study V. *The Journal of clinical psychiatry* 2006;67:1920-1927.
10. De Hert M, Detraux J, Van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol* 2012;8(2):114-126.
11. Tenback DE, Pijl B, Smeets H, Van Os J, van Harten PN. All-cause mortality and medication risk factors in schizophrenia. *J Clin Psychopharmacol* 2012;32(1):31-35.
12. Tenback DE, van Harten PN, Slooff CJ, Belger MA, van Os J. Effects of antipsychotic treatment on tardive dyskinesia: a 6-month evaluation of patients from the European Schizophrenia Outpatient Health Outcomes (SOHO) Study. *The Journal of clinical psychiatry* Sep 2005;66(9):1130-1133.
13. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Schizophrenia, second ed. Arlington, VA, USA: American Psychiatric Association. 2014.
14. NICE National institute for Health and Care Excellence, Schizophrenia Clinical guideline.

15. Essock SM, Schooler NR, Stroup TS, McEvoy JP, Rojas I, Jackson C, Covell NH. Effectiveness of switching from antipsychotic polypharmacy to monotherapy. *The American journal of psychiatry* Jul 2011;168(7):702-708.
16. Repo-Tiihonen E, Hallikainen T, Kivistö P, Tiihonen J. Antipsychotic Polypharmacy in Clozapine Resistant Schizophrenia: A Randomized Controlled Trial of Tapering Antipsychotic Co-treatment. *Mental illness* Jul 26 2012;4(1):e1.
17. Hori H, Yoshimura R, Katsuki A, Sugita AI, Atake K, Nakamura J. Switching to antipsychotic monotherapy can improve attention and processing speed, and social activity in chronic schizophrenia patients. *Journal of psychiatric research* Dec 2013;47(12):1843-1848.
18. Borlido C, Remington G, Graff-Guerrero A, Arenovich T, Hazra M, Wong A, Daskalakis ZJ, Mamo DC. Switching from 2 to 1 antipsychotics in schizophrenia: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2016;77(1):e14-e20.
19. Constantine RJ, Andel R, McPherson M, Tandon R. The risks and benefits of switching patients with schizophrenia or schizoaffective disorder from two to one antipsychotic medication: A randomized controlled trial. *Schizophr Res* 2015;166(1):194-200.
20. Constantine RJ, Andel R, McPherson M, Tandon R. Is the risk of antipsychotic polypharmacy discontinuation dependent on the agents used? *Psychiatry Res* 2018/05/01/ 2018;263:238-244.
21. Matsui K, Tokumasu T, Takekita Y, et al. Switching to antipsychotic monotherapy vs. staying on antipsychotic polypharmacy in schizophrenia: A systematic review and meta-analysis. *Schizophr Res* 2019;209:50-57.
22. Chalkidou K, Tunis S, Whicher D, Fowler R, Zwarenstein M. The role for pragmatic randomized controlled trials (pRCTs) in comparative effectiveness research. *Clin Trials* Aug 2012;9(4):436-446.
23. Tandon R, Belmaker R, Gattaz WF, et al. World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. *Schizophr Res* 2008;100(1-3):20-38.
24. Andersen J, Larsen JK, Schultz V, et al. The Brief Psychiatric Rating Scale. Dimension of schizophrenia--reliability and construct validity. *Psychopathology* 1989;22(2-3):168-176.
25. Dazzi F, Shafer A, Lauriola M. Meta-analysis of the Brief Psychiatric Rating Scale - Expanded (BPRS-E) structure and arguments for a new version. *Journal of psychiatric research* Oct 2016;81:140-151.
26. Dingemans PM, Linszen DH, Lenior ME, Smeets RM. Component structure of the expanded Brief Psychiatric Rating Scale (BPRS-E). *Psychopharmacology* Dec 1995;122(3):263-267.
27. Hafkenscheid A. De Brief Psychiatric Rating Scale. *Psychopraxis* 2005;7(5):169-174.
28. Olivares JM, Sermon J, Hemels M, Schreiner A. Definitions and drivers of relapse in patients with schizophrenia: a systematic literature review. *Ann Gen Psychiatry* 2013;12(1):1-11.
29. Gaertner I, Gaertner HJ, Vonthein R, Dietz KJJocp. Therapeutic drug monitoring of clozapine in relapse prevention: a five-year prospective study. 2001;21(3):305-310.
30. Xiang Y-Q, Zhang Z-J, Weng Y-Z, Zhai Y-M, Li W-B, Cai Z-J, Tan Q-R, Wang C-Y. Serum concentrations of clozapine and norclozapine in the prediction of relapse of patients with schizophrenia. *Schizophr Res* 2006;83(2-3):201-210.

31. Noguchi K, Gel YR, Brunner E, Konietschke F. nparLD: An R Software Package for the Nonparametric Analysis of Longitudinal Data in Factorial Experiments. 2012;50(12).
32. Foa EB, Huppert JD, Leiberg S, Langner R, Kichic R, Hajcak G, Salkovskis PM. The Obsessive-Compulsive Inventory: Development and validation of a short version. *Psychological Assessment* 2002;14(4):485-496.
33. WHO CCfDSM. Available from: http://www.whocc.no/atcddd/.
34. Essock SM, Schooler NR, Stroup TS, McEvoy JP, Rojas I, Jackson CJ, Covell NH. Effectiveness of Switching From Antipsychotic Polypharmacy to Monotherapy. *Am J Psychiatry* 2011;168(7):702-708.
35. Takeuchi H, Lee J, Fervaha G, Foussias G, Agid O, Remington G. Switching to Clozapine Using Immediate Versus Gradual Antipsychotic Discontinuation: A Pilot, Double-Blind, Randomized Controlled Trial. *J Clin Psychiatry* 2017;78(2):223-228.
36. Siskind D, McCartney L, Goldschlager R, Kisely S. Clozapine v. first-and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. *BJPsych* 2016;209(5):385-392.
37. Nakata Y, Kanahara N, Kimura H, Watanabe H, Iyo M. Efficacy of clozapine on dopamine supersensitivity psychosis in schizophrenia. *Int Clin Psychopharmacol* 2017;32(3):169-173.
38. Ganguli R. Rationale and strategies for switching antipsychotics. *Am J Health Syst Pharm* 2002;59(suppl_8):S22-S26.
39. Lin H-C, Chong M-Y, Lee Y, Yeh W-C, Lin P-Y. Switching of antipsychotics to aripiprazole in the treatment of schizophrenia. *Chang Gung Med J* 2009;32(4):409-416.
40. Arrighi HM, Hertz-Picciotto I. The evolving concept of the healthy worker survivor effect. *Epidemiology* Mar 1994;5(2):189-196.
41. Kazadi N, Moosa M, Jeenah F. Factors associated with relapse in schizophrenia. *S Afr J Psychiatr* 2008;14(2):52-62.
42. Häfner H. From onset and prodromal stage to a life-long course of schizophrenia and its symptom dimensions: how sex, age, and other risk factors influence incidence and course of illness. *Psychiatry* 2019:9804836.
43. González-Rodríguez A, Catalán R, Penadés R, Cortés VR, Torra M, Seeman MV, Bernardo M. Antipsychotic response worsens with postmenopausal duration in women with schizophrenia. *J Clin Psychopharmacol* 2016;36(6):580-587.
44. March JS, Silva SG, Compton S, Shapiro M, Califf R, Krishnan R. The case for practical clinical trials in psychiatry. *Am J Psychiatry* 2005;162(5):836-846.

# Supplementary materials

## Determination of the sample size

For determination of the sample size, relapse percentages from a study in which maintenance treatment with antipsychotics was compared to gradual discontinuation were used [1]. (At the time the study was designed, no RCT's comparing switch to antipsychotic monotherapy versus stay on polypharmacy were published yet). For a logistic regression with two groups, alpha 0.05, beta 0.80, relapse percentages of 20% versus 44% and drop out of 20%, 79 patients per group were needed. However, drop out turned out to be much lower (5 patients in the SWTICH and 4 patients in the STAY group) and therefore 66 and 70 patients in SWITCH and STAY groups, respectively, were sufficient to demonstrate a significant difference under the above mentioned conditions.

## Randomization

For randomization to either SWITCH or STAY group, SPSS 18 was used. Using the random number function RV.Uniform which returns a random number from a uniform distribution between a chosen minimum and maximum value, combined with the truncate function Trunc1 which rounds any decimal to zero, and setting the limits between zero and two, randomly ordered zero's and ones were generated. The following syntax was used: COMPUTE Group=TRUNC(RV. UNIFORM(0,2)).

## Concealment of allocation

The randomization file was created by a research assistant (RE) and was kept by AW. Patients were included by MS and a research assistant ND, who, after a patient gave informed consent, contacted AW. AW assigned the patient to the next line in the randomization file and told MS/ND in which group the patient would participate. AW worked as a research coordinator and did not know any of the patients.

## Model diagnostics

For the logistic regression models, the following diagnostics were investigated: standardized residuals, analogues of Cook's distances, standardized DFBetas, and leverage statistics. Testing for multicollinearity was carried out by fitting a linear model on the data and obtaining VIF and tolerance statistics.

## Missing BPRS items

Four hundred twenty four BPRS's were administered, which comprises 97% of all BPRSs due. Of these administered BPRSs, 62 (15%) had missing values on one

Supplementary Table 1. Combinations of antipsychotics used in the sample

| **Combinations of 2 antipsychotics** | **SWITCH (n = 66)**<br>**n** | **STAY (n = 70)**<br>**n** |
|---|---|---|
| Fluphenazine LAI, clozapine | 4 | 0 |
| Fluphenazine LAI, olanzapine | 1 | 1 |
| Haloperidol oral, clozapine | 5 | 4 |
| Haloperidol oral, olanzapine | 0 | 1 |
| Haloperidol oral, quetiapine | 0 | 2 |
| Haloperidol oral, risperidone | 1 | 0 |
| Haloperidol LAI, clozapine | 2 | 2 |
| Haloperidol LAI, olanzapine | 0 | 1 |
| Pipamperon, clozapine | 0 | 2 |
| Pipamperon, sulpiride | 0 | 1 |
| Broomperidol LAI, olanzapine | 1 | 0 |
| Flupentixol oral, clozapine | 12 | 12 |
| Flupentixol oral, olanzapine | 4 | 5 |
| Flupentixol oral, quetiapine | 2 | 3 |
| Flupentixol oral, sulpiride | 0 | 1 |
| Flupentixol oral, aripiprazole | 1 | 0 |
| Flupentixol LAI, clozapine | 2 | 3 |
| Flupentixol LAI, olanzapine | 1 | 3 |
| Flupentixol LAI, risperidone | 1 | 0 |
| Zuclopentixol oral, clozapine | 1 | 3 |
| Zuclopentixol oral, olanzapine | 0 | 1 |
| Zuclopentixol LAI, clozapine | 4 | 4 |
| Zuclopentixol LAI, olanzapine | 2 | 0 |
| Zuclopentixol LAI, quetiapine | 1 | 1 |
| Zuclopentixol LAI, risperidone | 0 | 1 |
| Zuclopentixol LAI, aripiprazole | 0 | 1 |
| Pimozide, clozapine | 3 | 3 |
| Pimozide, olanzapine | 0 | 1 |
| Pimozide, aripiprazole | 0 | 1 |
| Penfloridol, clozapine | 1 | 1 |
| Penfloridol, olanzapine | 1 | 1 |
| Penfloridol, quetiapine | 1 | 1 |
| | | |
| **Combinations of 3 antipsychotics** | | |
| Fluphenazine LAI, pipamperon, clozapine | 1 | 0 |
| Fluphenazine LAI, olanzapine, quetiapine | 1 | 0 |
| Haloperidol oral, pipamperon, clozapine | 0 | 1 |

Supplementary Table 1. Continued

| Combinations of 2 antipsychotics | SWITCH (n = 66) n | STAY (n = 70) n |
|---|---|---|
| Haloperidol oral, pipamperon olanzapine | 1 | 0 |
| Haloperidol LAI, flupentixol LAI, quetiapine | 1 | 0 |
| Haloperidol LAI, penfloridol, aripiprazole | 0 | 1 |
| Haloperidol LAI, pipamperon, clozapine | 1 | 0 |
| Haloperidol LAI, clozapine, risperidon | 0 | 1 |
| Haloperidol LAI, clozapine, aripiprazole | 1 | 0 |
| Pipamperon, flupentixol oral, olanzapine | 0 | 2 |
| Pipamperon, flupentixol LAI, sertindol | 0 | 1 |
| Pipamperon, zuclopentixol oral, clozapine | 2 | 0 |
| Pipamperon, zuclopentixol LAI, olanzapine | 0 | 1 |
| Pipamperon, pimozide, aripiprazol | 1 | 0 |
| Pipamperon, clozapine, aripiprazol | 0 | 1 |
| Broomperidol LAI, zuclopentixol oral, olanzapine | 1 | 0 |
| Flupentixol oral clozapine, sulpiride | 1 | 0 |
| Flupentixol oral, clozapine, aripiprazole | 0 | 1 |
| Flupentixol LAI, clozapine, sulpride | 1 | 0 |
| Flupentixol LAI, clozapine, risperidon | 0 | 1 |
| Zuclopentixol oral clozapine, aripiprazole | 1 | 0 |
| Penfloridol, clozapine, risperidon | 1 | 0 |
| Penfloridol, olanzapine, aripiprazole | 1 | 0 |

LAI: long acting injectable

or more items. Another 11 that should have been administered were completely missing due patients who missed one or more visits or refusing parts of the measurements including the BPRS. Of the BPRSs with missing items, 43 BPRS total scores and their respective subscale scores could be calculated after imputation of missing items. For patients who did not experience a relapse and did not drop out, the analyses of the progression of psychotic symptoms required BPRS total scores at all four time points per patient. Due to imputation, 19 patients with missing values could be included in these analyses.

## Model fit Logistic regression model of the effect of group and sex on relapse

The standardized residuals showed that the model fitted reasonably well. Only 4.7% of the values were greater than the absolute value of 1.96 and there were no values greater than the absolute value of 2.58. There were no datapoints that

exerted undue influence on the model. All analogues of Cook's distances and standardized DFBetas were smaller than the absolute value of 1 and there were no leverage values greater than two times the average leverage. As there were no VIF values greater than 10 or tolerance values smaller than 0.1, there was no multicollinearity between the predictors.

## Model fit Logistic regression model of the effect of group, sex, use of clozapine and group*clozapine interaction on relapse

There were two cases (1.6%) with a standardized residual above the absolute value of 2.58. All other values were smaller than the absolute value of 1.96. All analogues of Cook's distances and DFBetas were smaller than the absolute value of 1. There were no leverage values greater than two times the average leverage. There was evidence for multicollinearity between use of clozapine and the interaction term group*clozapine (use of clozapine: tolerance=0.092, VIF=10.83; group*use of clozapine: tolerance=0.086, VIF=11.64). The tolerance values for group and sex were greater than 0.1 and the corresponding VIF values were less than 10.



**Supplementary Table 2.** Logistic regression model of the effect of group for clozapine users corrected for sex
n=77

| | B (SE) | Wald x2 | OR (95% CI) | p-value |
|---|---|---|---|---|
| Constant | -0.10 (0.38) | 0.069 | | 0.793 |
| SWITCH group | -2.14 (0.60) | 12.92 | 0.12 (0.37 – 0.38) | 0.000 |
| Female sex | 1.25 (0.59) | 4.48 | 3.49 (1.10 – 11.12) | 0.034 |

OR=Odds ratio $R^2$=0.22 (Hosmer-Lemeshow), 0.21 (Cox-Snell), 0.29 (Nagelkerke). Model $x^2$ (2) = 18.14, $p$=0.000

**Supplementary Table 3.** Logistic regression model of the effect of group for non-clozapine users corrected for sex
n=49

| | B (SE) | Wald x2 | OR (95% CI) | p-value |
|---|---|---|---|---|
| Constant | -0.43 (0.49) | 0.76 | | 0.383 |
| SWITCH group | -0.21 (0.61) | 0.11 | 0.81 (0.46 – 2.70) | 0.737 |
| Female sex | 1.26 (0.60) | 4.41 | 3.54 (1.09 – 11.52) | 0.036 |

OR=Odds ratio $R^2$=0.07 (Hosmer-Lemeshow), 0.09 (Cox-Snell), 0.12 (Nagelkerke). Model $x^2$ (2) = 4.76, $p$=0.093

### Model fit Logistic regression model of the effect of group for clozapine users corrected for sex

Two cases (2.6%) had standardized residuals above the absolute value of 2.58. Those were to men in the SWITCH group using clozapine who had a relapse. All other standardized residuals were smaller than the absolute value of 1.96. There were no datapoints that exerted undue influence on the model. All analogues of Cook's distances and standardized DFBetas were smaller than the absolute value of 1 and there were no leverage values greater than two times the average leverage. There was no multicollinearity between the predictors, there were no VIF values greater than 10 or tolerance values smaller than 0.1.

### Model fit Logistic regression model of the effect of group for non-clozapine users corrected for sex

All standardized residuals were smaller than the absolute value of 1.96. There were no datapoints that exerted undue influence on the model. All analogues of Cook's distances and standardized DFBetas were smaller than the absolute value of 1 and there were no leverage values greater than two times the average leverage. There was no multicollinearity between the predictors, there were no VIF values greater than 10 or tolerance values smaller than 0.1.

### Exploratory analysis of BPRS subscales

Exploratory analyses were carried out on the four BPRS subscales (positive, depressive, negative, and mania) to explore on which symptom domains the course of psychotic symptoms differed between SWITCH and STAY groups. Supplementary table 1. shows ANOVA type statistics and uncorrected significance values for omnibus and, if applicable, post hoc tests, for the interaction between group (SWITCH versus STAY) and average item level BPRS subscale scores at all four time points. As these were exploratory analyses, we choose not to correct for multiple testing.

Omnibus tests were significant for positive, depressive, and negative subscales but not for the mania subscale. All three subscales with a significant omnibus test showed a similar pattern with no significant difference between the post-tapering versus baseline measurement and increasing significance over fu versus baseline and fu 2 versus baseline, where the latter was highly significant for all three subscales.

Supplementary table 2. Omnibus and post hoc test for differences in the course of psychotic symptoms measured by BPRS subscales between SWITCH and STAY groups for patients who completed the study

| BPRS subscale | Omnibus test ATS *(p-value)* | Post tapering – baseline ATS *(p-value)* | FU 1 – baseline ATS *(p-value)* | FU 2 – baseline ATS *(p-value)* |
|---|---|---|---|---|
| Positive | 5.64 (0.002) | 0.02 (0.895) | 2.31 (0.128) | 11.92 (<0.001) |
| Depressive | 12.24 (<0.001) | 0.40 (0.530) | 6.07 (0.014) | 19.19 (<0.001) |
| Negative | 6.07 (0.001) | 3.32 (0.07) | 10.46 (0.001) | 12.36 (<0.001) |
| Mania | 1.79 (0.160) | - | - | - |

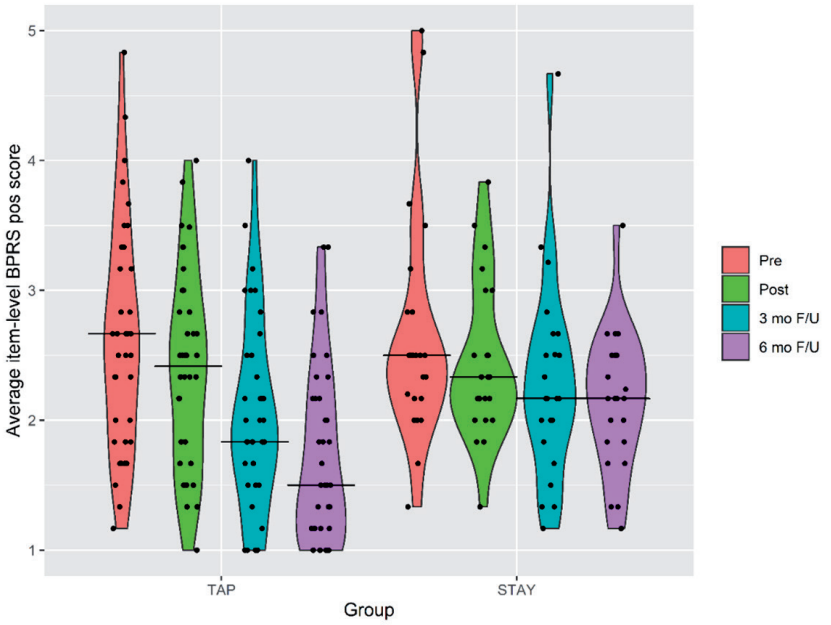
BPRS: Brief Psychiatric Rating Scale; ATS: ANOVA type statistic; FU 1: follow-up 1; FU 2: follow-up 2.



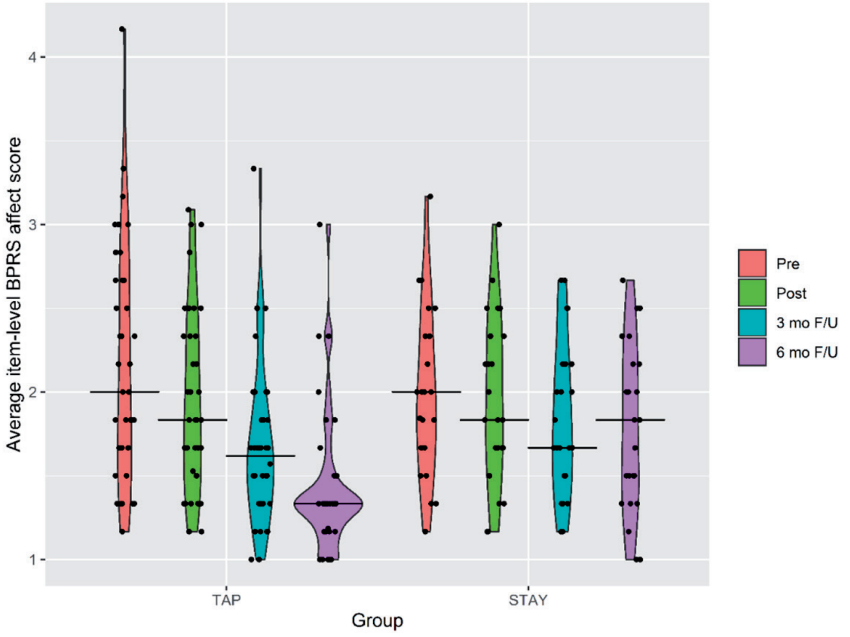
Supplementary figures 1-4 illustrate the results. The median of the positive subscale (supplementary figure 1.) shows a decrease over the first three measurements for both groups, but keeps decreasing until follow-up 2 in the SWITCH group, whereas in the STAY group the decrease has stopped and the median is stable between fu 1 and fu 2.

For the depressive subscale (supplementary figure 2.), the median decreases over the first three measurements in both groups but while the decrease continues until measurement four in the SWITCH group, an increase from measurement three to four is seen in the STAY group. The median for negative symptoms (supplementary figure 3.) decrease over the first three measurements in the SWITCH group and stays the same in measurement four, while in the STAY group medians on all four time points are equal. For the mania subscale (supplementary figure 4.) there is a decrease between baseline and the post-tapering measurement in both groups, after which the decrease continues in the SWITCH group but stays on a similar level in the STAY group. However, as the omnibus test was not significant, post hoc tests were not conducted and differences are not regarded statistically significant.

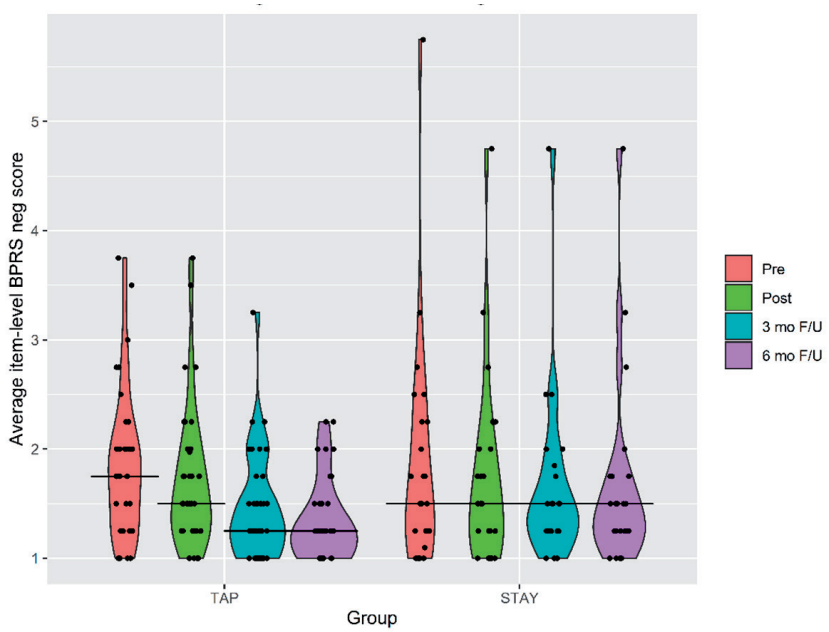
1. Wunderink L, Nienhuis FJ, Sytema S, Slooff CJ, Knegtering R, Wiersma D. Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. The Journal of clinical psychiatry. 2007; 68(5): 654-61.



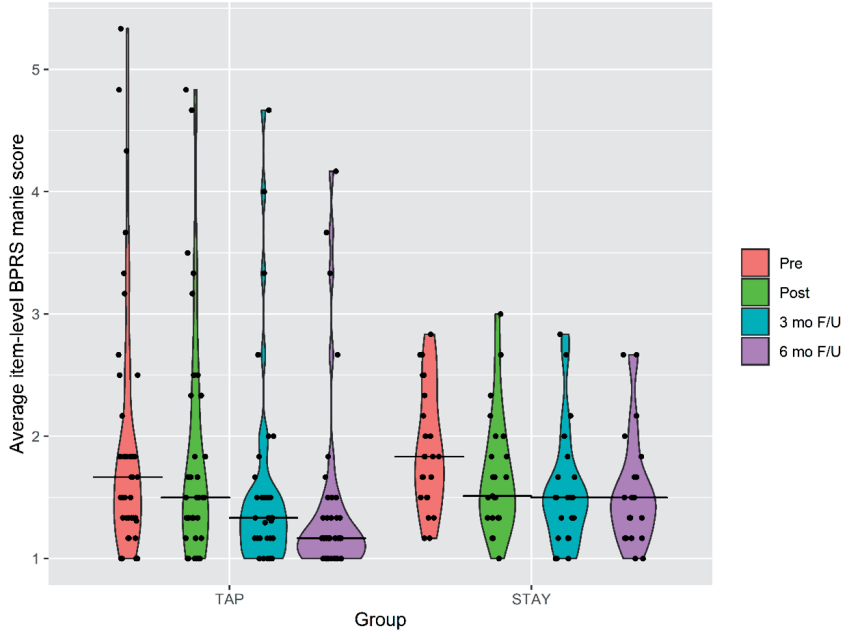

Suppl Fig. 1. Average item-level BPRS pos score




Suppl Fig 2. Average item-level BPRS depressive score




Suppl Fig 3. Average item-level BPRS negative score




Suppl Fig 4. Average item-level BPRS mania score

# Part III.

## Movement disorders as risk factor for mortality

6

# Chapter 6.

## Movement disorders and mortality in severely mentally ill patients: the Curacao Extrapyramidal Syndromes Study XIV

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## Abstract

### Background and Hypothesis

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 difference. Research suggests an association between tardive dyskinesia (TD) and mortality; however, results are inconclusive. In addition, studies investigating associations between parkinsonism or akathisia and mortality are rare. We hypothesized that TD would be a risk factor for mortality in patients with SMI.

### Study Design

We studied a cohort of 157 patients diagnosed predominantly with schizophrenia on the former Netherlands Antilles. TD, parkinsonism, and akathisia were assessed with rating scales on eight occasions over a period of 18 years. Twenty-four years after baseline, survival status and if applicable date of death were determined. Associations between movement disorders and survival were analyzed using Cox regression. Sex, age, antipsychotics, antidepressants and benzodiazepines at each measurement occasion were tested as covariates.

### Study Results

Parkinsonism was a significant risk factor with an HR of 1.02 per point on the motor subscale of the Unified Parkinson's Disease Rating Scale (range 0 – 56). TD and akathisia were not significantly associated with mortality.

### Conclusions

Parkinsonism may be an important risk factor for mortality in SMI patients. This finding calls for more follow-up and intervention studies to confirm this finding and to explore whether treatment or prevention of parkinsonism can reduce excess mortality.



### Key words

Tardive dyskinesia, parkinsonism, akathisia, schizophrenia, survival, life expectancy

## Introduction

Patients with severe mental illness (SMI) are at an increased risk of early death in comparison with the general population[1, 2]. In schizophrenia and bipolar disorder, diagnoses that are highly prevalent in SMI populations, standardized mortality rates of 2 – 4.6 have been found[3-5], leading to a substantial reduced life expectancy of 9 – 25 years[3, 6-8].

Besides major lifestyle related problems such as smoking, little physical activity, an 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 can be induced by antipsychotics, but also reflect a fundamental aspect of neurodevelopmental pathophysiology involving the sensitization of dopaminergic nigrostriatal circuits[14].

Several authors studied a possible link between TD and mortality. Some found higher mortality rates in SMI patients with TD than in those without TD[11, 12, 15-17] but others reported negative findings[18-21]. There is a paucity of research on parkinsonism and akathisia and MD combined[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 from the Curacao Extrapyramidal Syndromes Study in which we assessed the association between MD and mortality. The Curacao Extrapyramidal Syndromes Study comprises a 24-year follow-up study in which patients with SMI treated at the only psychiatric hospital on the island of Curacao (former Netherlands Antilles) were repeatedly assessed for the presence and severity of MD since 1992[22-26]. In the present study, we investigate if TD, parkinsonism, and akathisia are associated with mortality in a sample of 157 mainly African Caribbean patients.

## Methods

### Setting and patients

The present study is part of the Curacao Extrapyramidal Syndromes Study[22, 23]. Patients from the Klinika Capriles (formerly Dr. D. R. Capriles clinic), the only psychiatric hospital of the former Netherlands Antilles (nowadays Curacao), were

assessed 8 times over the course of an 18-year period including assessments 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, and 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[22].

## Measurements

Patients were assessed in 1992, 1993, 1994, 1996, 1997, 1998, 2001, and 2009 for TD, parkinsonism, akathisia, and medication use. 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)[27] and case definition was based on Schooler and Kane criteria for probable TD[28]. The motor examination part of the Unified Parkinson's Disease Rating Scale (UPDRS)[29] 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[22]. Akathisia was rated with the Barnes Akathisia Rating Scale (BARS)[30] and a patient was considered a case when a score of 2 or higher on item 4 was given. Cases, i.e. patients who could be diagnosed with a movement disorder, were used here for illustrative purposes only (table 2). For the Cox analysis, data about movement disorders were used in a continuous manner.

At baseline and at each follow-up assessment, a trained physician collected current medication use. At baseline, age, sex, DSM III-R diagnosis (schizophrenia or other, where schizophrenia included codes 295.1, 295.2, 295.3, 295.4, 295.6, 296.7 and 295.9), cocaine use, type of treatment (inpatient or day care), age at first admission, duration of illness, total years of admission, duration of last admission and lifetime intake of anticholinergics were extracted from patients' files.

Seven years after the final assessment (follow-up seven), on April first, 2016, all-cause mortality was obtained using the patient's charts and the mortality register of Curacao. For the deceased patients, date of death was recorded.

### Data analysis

The association between MD and mortality was analyzed using a Cox regression with measurement occasion (baseline and 7 follow-ups) (microlevel) clustered in subjects (macrolevel), with the (i) STCOX routine of the STATA 13 statistical program (StataCorp. 2009); and (ii) SHARED(ID) procedure for shared frailty, where the random component enters the hazard multiplicatively. Fitting the Cox model with the time-varying covariates was performed with STSPLIT, AT(FAILURES) procedure. 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 PHTEST procedure.



The total score of the AIMS, the motor part of the UPDRS and the score of item 4 of the BARS at each assessment were included as 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)[31] of antipsychotics, benzodiazepines, and antidepressants. Age and sex were included as time-independent variables. Variables with a p-value greater than 0.2 in a univariate analysis were dropped. 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), a linear-quadratic term remained in the final model as suggested by Cleves (2010)[32].

## 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. Twenty-six patients could not be analyzed due to missing data. Therefore, data of 157 patients were used for the analysis.

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

**Table 1. Sample characteristics at baseline**

| Characteristics | n= 157 |
|---|---|
| Age, mean (SD) | 48.8 (15.6 |
| Males, n (%) | 115 (73.2) |
| Ethnicity, n (%) | |
| African-Caribbean | 109 (74.7) |
| Mixed | 29 (19.9) |
| Caucasian | 6 (4.1) |
| Other | 2 (1.4) |
| Primary diagnosis schizophrenia, n (%) | 130 (82.8) |
| Cocaine use, n (%) | 30 (19.1) |
| Type of treatment, n (%) | |
| Inpatient treatment | 143 (91.1) |
| Day care treatment | 14 (8.9) |
| Age at first admission, mean (SD) | 26.2 (10.1) |
| Duration of illness in years, mean (SD) | 23.6 (14.3) |
| Total years of admission, mean (SD) | 16.8 (14.4) |
| Duration of last admission in years, mean (SD) | 12.8 (13.8) |
| Lifetime intake of anticholinergics (g benztropine equivalents), mean (SD) | 23.6 (23.2) |

Number of cases with missing data; Ethnicity: n = 11; : Age at first admission: n = 10; Duration of Illness: n=10; Total years of admission: n=11; Duration of last admission in years: n=11; Lifetime intake of anticholinergics: n=42.

In Table 2, age, medication use, prevalence and severity of MD at each assessment and the numbers of patients that died in each consecutive time interval are presented. Of the 157 included in the Cox regression 84 patients (54%) died during follow-up. Mean age of death was 67.4 years (SD 15.6, range 24 – 94).

## Movement disorders

MD prevalence fluctuated over time (Table 2). Across all eight measurements, TD cases were the most prevalent ranging between 37.6 % and 61.5 %. The prevalence of parkinsonism and akathisia ranged from 27.4%–40.0% and 1.3%–12.8%, respectively.

**Table 2: Time varying sample characteristics**

| Measurement<br>Year<br>Number of patients alive | Baseline<br>1992-1993<br>n = 157 | FU 1<br>1993<br>n = 151 | FU 2<br>1994<br>n = 143 | FU 3<br>1996<br>n = 136 | FU 4<br>1997<br>n = 133 | FU 5<br>1998<br>n = 131 | FU 6<br>2001<br>n = 122 | FU 7<br>2009<br>n = 96 |
|---|---|---|---|---|---|---|---|---|
| Number of patients that died in subsequent time interval (n) | 6 | 8 | 7 | 3 | 2 | 9 | 26 | 23 |
| Mean age (SD)* | 48.8 (15.6) | 53.0 (14.7) | 50.4 (13.9) | 53.8 (13.2) | 53.0 (12.7) | 54.5 (12.7) | 55.5 (13.0) | 61.4 (10.7) |
| Medication | | | | | | | | |
| Antipsychotics | | | | | | | | |
| FGA only, n (%) | 146 (93.0) | 93 (84.5) | 104 (89.7) | 79 (86.8) | 74 (83.1) | 67 (79.8) | 72 (67.9) | 38 (48.1) |
| SGA only, n (%) | 0 | 8 (7.3) | 7 (6.0) | 9 (9.9) | 12 (13.5) | 10 (11.9) | 15 (14.2) | 14 (17.7) |
| Combination FGA and SGA n (%) | 0 | 0 | 0 | 0 | 0 | 1 (1.2) | 13 (12.3) | 21 (26.6) |
| No antipsychotic, n (%) | 11 (7.0) | 9 (8.2) | 5 (4.3) | 3 (3.3) | 3 (3.4) | 6 (7.1) | 6 (5.7) | 6 (7.6) |
| DDD antipsychotics**, mean (SD) | 1.8 (1.4) | 1.9 (1.5) | 2.0 (1.3) | 2.0 (1.6) | 2.1 (1.5) | 2.4 (1.7) | 2.1 (1.6) | 2.4 (1.4) |
| Antidepressants, n (%)** | 9 (5.7) | 9 (8.1) | 9 (7.8) | 10 (11.0) | 7 (7.9) | 3 (3.6) | 10 (9.4) | 4 (5.0) |
| 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 (%) | 29 (18.5) | 23 (20.1) | 34 (29.3) | 31 (34.0) | 31 (34.8) | 35 (41.7) | 52 (49.1) | 41 (51.3) |
| DDD benzodiazepines**, mean (SD) | 1.4 (1.0) | 1.2 (0.9) | 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 (%) | 59 (37.6) | 59 (53.6) | 72 (61.5) | 56 (61.5) | 49 (53.3) | 43 (51.2) | 63 (59.4) | 41 (51.9) |
| Mean score cases AIMS (SD) | 7.5 (3.4) | 7.8 (2.7) | 9.6 (4.3) | 9.6 (4.0) | 9.3 (3.8) | 9.2 (3.8) | 9.9 (4.3) | 8.6 (3.2) |
| Parkinsonism, cases (%) | 56 (35.7) | 44 (40.0) | 37 (31.6) | 30 (33.0) | 26 (28.3) | 23 (27.4) | 37 (34.9) | 24 (30.4) |
| Mean score cases motor part UPDRS (SD) | 18.6 (10.1) | 18.5 (12.2) | 17.9 (11.2) | 22.4 (9.4) | 21.0 (10.2) | 22.7 (12.1) | 19.1 (12.3) | 15.5 (12.1) |
| Akathisia, cases (%) | 16 (10.2) | 9 (8.2) | 15 (12.8) | 7 (7.7) | 2 (2.2) | 5 (6.0) | 5 (4.7) | 1 (1.3) |
| Mean score cases item 4 BARS | 2.6 (0.8) | 2.7 (0.7) | 2.8 (0.6) | 2.6 (0.8) | 2.5 (0.7) | 2.6 (0.5) | 2.8 (0.8) | 3.0 |

FU: follow-up; FGA: first generations antipsychotic; SGA: second generation antipsychotic; DDD: Defined Daily Dose; AIMS: Abnormal Involuntary Movement Scale; UPDRS: Unified Parkinson Disease Rating Scale; BARS: Barnes Akathisia Rating Scale; AP: antipsychotics; AD: antidepressants; MD: movement disorders; TD: tardive dyskinesia

* In case of missing data about age and MD, no measurement had taken place at the respective FU.

Number of patients alive with missing data: FU1: all variables: n=41; FU2: age and MD n=26, medication: n=27; FU3: all variables: n=45; FU4: age and MD: n=41, medication: n=44; FU5: all variables: n=47; FU6: all variables: n=16; FU7: age: n=18, AP: n=18, AD: n=17; benzodiazepines: n=17; TD: n=18, parkinsonism: n=18, akathisia: n=19.

**Means and SDs in DDD for the patients who used the respective medications are given.

## Psychotropic medication

Up until 1992 only FGA were available in Curacao, which is reflected in the percentages of patients using FGA and SGA between 1992 and 2009 (Table 2). At baseline in 1992/1993, FGA were used by 93.0% of the sample while the remaining 7.0% did not take antipsychotic medication. Most patients continued to use an FGA, either alone or in combination with an SGA, which was the case for 74.7 % of the patients in 2009. Use of SGA, starting from 0% in 1992/1993, increased to 44.3% in 2009, either alone or in combination with a FGA. The percentage of patients taking no antipsychotics varied between 3.3% and 8.2%. Antidepressants were used by 3.6 % - 11.0% of the patients. The use of benzodiazepines gradually increased from 18.5% at baseline to 51.3% at follow-up 7 in 2009.

## Cox regression

Table 3 shows the results for the possible predictors of mortality from univariate analyses. Age, sex, parkinsonism, antipsychotic type and DDD antipsychotics were significant predictors and were included in a multivariate model. TD, akathisia, DDD benzodiazepines, DDD antidepressants, were not significant as univariate predictors and were therefore not included. Extra-linearity was tested for parkinsonism, age, and DDD antipsychotics and significance was found for the latter two variables. Linear-quadratic terms for age and DDD antipsychotics were therefore added to the final model (Cleves 2008). Interactions of age and time, and age and parkinsonism were tested of which only the former was significant

**Table 3. Univariate tests for possible predictors of mortality**

| Variable | Hazard Ratio | 95% Confidence interval | P value |
|---|---|---|---|
| Age | 1.058 | 1.038 – 1.078 | 0.000* |
| Tardive dyskinesia | 1.024 | 0.981 – 1.069 | 0.276 |
| Parkinsonism | 1.029 | 1.014 - 1.045 | 0.000* |
| Akathisia | 0.764 | 0.475 – 1.23 | 0.267 |
| DDD antipsychotics | 0.727 | 0.600 – 0.879 | 0.001* |
| DDD antidepressants | 1.239 | 0.596 – 2.58 | 0.566 |
| DDD benzodiazepines | 0.813 | 0.594 – 1.117 | 0.203 |
| | $X^2$ | **df** | |
| Sex | 5.62 | 1 | 0.018* |
| Type of antipsychotic[a] | 7.83 | 3 | 0.050* |

DDD: Defined Daily Dose

[a]Type of antipsychotic was one of the following categories: no antipsychotic; first generation antipsychotic(s) (FGA) only; second generation antipsychotic(s)(SGA) only; a combination of FGA and SGA

* $p < 0.2$

and thus included in the final model. Hazard ratios (HR) and significance for the variables in the final multivariate model are presented in Table 4. Parkinsonism was positively associated with mortality (HR =1.020, 95% CI 1.001–1.038, $p$ = 0.034). Age showed significance as a linear squared predictor (HR =1.002, 95% CI 1.0004–1.0032, $p$ = 0.015). DDD antipsychotic displayed a significant linear (HR =0.972, 95% CI 0.692 – 0.997 $p$ = 0.047) and a trend as a linear-squared relation (HR =1.154, 95% CI 0.993–1.340, $p$ = 0.061). The survival function adjusted for parkinsonism, age, and DDD antipsychotics is shown in Figure 1. Separate survival functions adjusted for parkinsonism, age and DDD antipsychotics are given in the Supplementary materials.

**Table 4. Final Cox proportional hazards model**

| Variable | Hazard Ratio | 95% Confidence interval | P value |
|---|---|---|---|
| Female sex | 1.267 | 0.742 - 2.163 | 0.385 |
| Age | 0.995 | 0.937 – 1.056 | 0.863 |
| Age*time | 1.001 | 0.995 – 1.007 | 0.765 |
| Age linear-squared | 1.002 | 1.0004 - 1.0032 | 0.015* |
| Age linear-squared*time | 1.000 | 0.99975 - 1.0003 | 0.117 |
| Parkinsonism | 1.020 | 1.001 - 1.038 | 0.034* |
| DDD antipsychotics | 0.792 | 0.629 – 0.997 | 0.047* |
| DDD antipsychotics linear-squared | 1.154 | 0.993 - 1.340 | 0.061 |
| No antipsychotic** | 0.965 | 0.318 - 2.933 | 0.951 |
| FGA only** | 0.984 | 0.442 - 2.192 | 0.970 |
| Both FGA and SGA** | 1.021 | 0.254 - 4.104 | 0.976 |

DDD: Defined Daily Dose; FGA: first generation antipsychotics; SGA: second generation antipsychotics
* $p < 0.05$
** Reference category: SGA only

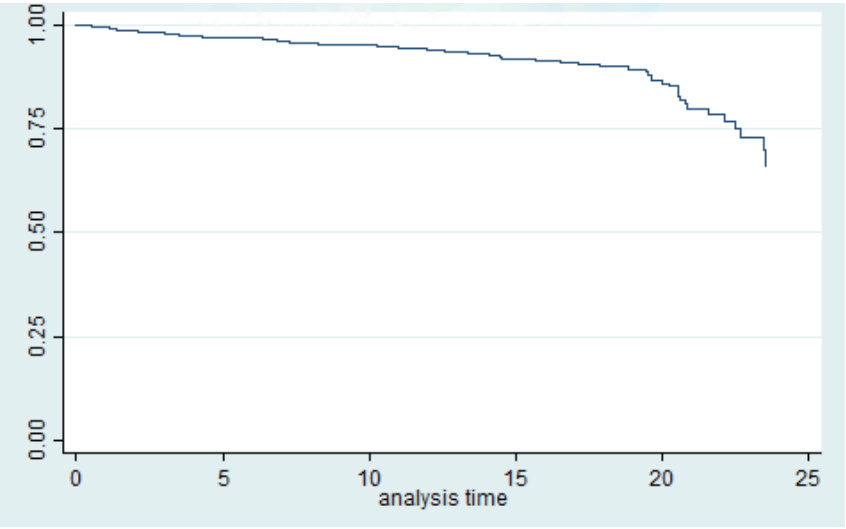


**Figure 1. Survival function adjusted for parkinsonism, age, and DDD antipsychotics**

## Discussion

Our findings indicate that parkinsonism is a significant risk factor for mortality in patients with SMI whereas TD and akathisia are not.

For parkinsonism, one point increase on the motor examination subscale of the UPDRS was associated with a HR of 1.02. The motor part of the UPDRS consists of 14 items which can be scored 0-4 leading to a range of possible scores of 0 – 56. In our sample, the SD for cases with parkinsonism was close to 10 points and an increase of 10 points would lead to an increase in the HR of mortality of 21%.

Previous studies on the association between MD and mortality in SMI focused on TD[2-10] while only two studies also included parkinsonism [19, 29]. Modestin and colleagues[19] reported a higher mortality rate in patients with parkinsonism than in those without, when studying 200 psychiatric patients treated with antipsychotic medication after 9 years follow-up. However, after adjustment only age remained as a significant risk factor. Important differences with our study are that the study by Modestin and colleagues (i) assessed MD only at baseline and (ii) had a follow up of 9 years in contrast with the 24 years of follow-up in the current study. Given the fluctuating nature of MD, assessing MD only at one time might not give enough information to draw conclusions[33]. Measuring MD at multiple time points, as we did in the current study, is probably a more valid design to address this research question. A retrospective study by Schoepf and

colleagues (2014)[34] examined deaths in schizophrenia patients in general hospitals in relation to mental and physical comorbidity. Their results showed an odds ratio of 5.0 for the association between the presence of parkinsonism and hospital mortality, which can be considered a very strong effect. Parkinsonism though, was not measured with formal rating scales which may have diminished the precision of the effect estimate.

Outside the field of psychiatry, two studies reported an association between parkinsonism and mortality in people aged 65 years and over[30, 31]. Firstly, in a community sample the presence of parkinsonism was associated with a twofold increase in the risk of death[30] and gait disturbance in particular heightened the risk. Secondly, in a mixed sample of patients with Alzheimer's disease and subjects without dementia, parkinsonism was a risk factor for mortality in both subgroups. Interestingly, the latter study focused on spontaneous parkinsonism as subjects receiving parkinsonism-inducing medication were excluded which suggest that, along with drug-induced parkinsonism, spontaneous parkinsonism may also be a risk factor. Similarly, in Parkinson's Disease, severity of motor symptoms, especially postural imbalance and gait disturbance have been found to be associated with mortality[35, 36].



Considering all these findings of parkinsonism as a risk factor for mortality in different populations with different underlying causes for parkinsonian symptoms, it can be hypothesized that parkinsonism is an independent predictor of all-cause mortality.

It is not directly clear how parkinsonism increases mortality risk, but parkinsonism is related to several other factors associated with mortality such as a higher rate of fall incidents and dysphagia which can lead to asphyxia and pneumonia[37]. Also it could be hypothesized that the relationship is indirect and, in patients with SMI, might be (partly) based on the association between both spontaneous[38, 39] and drug-induced[40] parkinsonism with cognitive impairments. Indeed, cognitive deficits may be related to unhealthy lifestyle or less awareness of physical problems and/or access to physical healthcare. Another explanation may be the that parkinsonism reduces physical activity and increases sedentary behavior[41], which in turn increase the mortality rate.

Given the high prevalence of parkinsonism in SMI patients and several studies suggesting that parkinsonism may lead to shorter survival, it is important to explore this relationship in more depth, e.g., would reducing parkinsonism also increase survival?

TD was not significantly associated with risk of death in the present study. Previous studies have reported inconsistent results. Four of eleven studies reported an association between TD and mortality[12, 15-17], two reported a trend[42, 43], and five no association[18-21, 43]. 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 included studies suffered from methodological problems, such as fewer than five years follow-up[3, 4, 6, 8] and no control for known confounders such as antipsychotic dose[15-17, 19, 42]. In 2009, three additional studies on the association between TD and mortality were published using the more sophisticated Cox and logistic regression analyses, which are better suited to this type of data than the Chi-square test[12, 20, 21]: (i) Dean and Thuras (2009)[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 (2009)[21] did not find an association; and (iii) Chong et al (2009) 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[44, 45] which may, therefore, be a confounding factor in the association between TD and survival. Despite this association, none of the studies up to now including the present study, controlled for psychiatric symptom severity which poses a limitation to the findings.

Akathisia did not show a significant association with all-cause mortality which is consistent with the single previous study[21].

We observed a significant effect for DDD antipsychotics as a linear association and a trend for a linear-quadratic effect, which combined reflects a partially U-shaped curve.

Well known metabolic side effects of predominantly second generation antipsychotics, and in turn their association with adverse health outcomes like type 2 diabetes and cardiovascular disease has let to many studies addressing the question how (cumulative) exposure to antipsychotics affects mortality[46]. A robust finding reported by recently published large register-based cohort studies and one systematic review and meta-analysis is that any use is associated with a lower risk compared to no use in schizophrenia[7, 46-49]. One cohort study (n=21,492),

using nation-wide registers in Sweden, investigated cumulative antipsychotic exposure expressed in DDD and mortality. The relation in chronic patients showed a U-shaped curve in which patients who did not use an antipsychotic had the highest risk, followed by the high dose (>1.5 DDD/day), low dose (<0.5 DDD/day) and moderate dose(0.5-1.5 DDD/day) categories. The shape of the curve we found seems somewhat similar. Nonetheless, above mentioned studies with large numbers of patients, are better powered to give a precise estimate of the relationship.

An important strength of the study is that it was conducted on the former Netherlands Antilles, which, because they are islands, comprise a well-defined catchment area. Along with the fact that the Klinika Capriles is the only psychiatric hospital on the former Netherlands Antilles, and that almost all of the eligible patients agreed to participate (99%), selection bias is relatively small. On the other hand, at the former Netherlands Antilles, stigma on mental disorders is somewhat stronger than in most western countries and patients with mental illness are to a greater extent taken care of by family members. Thus, patients admitted to the Klinika Capriles consisted generally of those with the most severe psychiatric illnesses which is reflected in our sample. Our results can therefore be generalized to populations with severe psychiatric disorders receiving antipsychotic treatment and might not apply to populations with milder illnesses. A further strength arising from the fact that the Klinika Capriles was the only psychiatric facility on the islands is that our data is close to covering the complete treatment history of the participants. Another major strength of the current study is the use of multiple measurements of MD as time varying covariates. This is especially important given the fluctuating nature of MD in SMI patients[33]. Moreover, the follow-up period of 24 years of the current study is the longest up to now.



Some important factors known to influence mortality were not measured, including access to and adequate use of physical healthcare and metabolic parameters. Indeed one would have to include these variables if the aims were to build a prediction model for mortality. Our aim, however, was to estimate the association of MD and mortality and because the variables mentioned above are not directly related to MD we think that omitting these variables does not bias our results. In contrast, other factors, i.e. symptom severity[44], cognitive functioning[38-40, 50], physical activity[41], use of alcohol, illicit drug use[51] and smoking[52] have been found to be related to both MD and mortality and the lack of information on those variables puts a limitation to the present findings.

Nevertheless, given the effect size we found for the association between parkinsonism and mortality, combined with other reports of this association, we think evidence points towards parkinsonism as a risk factor. This could be confirmed in large well controlled studies with multiple measurements over time with regard to MD, use of psychotropic medication, symptom severity, cognitive functioning, physical activity, smoking, use of alcohol, and illicit drug use. Such studies may give more insight how these variables are interrelated and influence mortality.

## Conclusion

In conclusion, parkinsonism was a significant risk factor for mortality in a cohort of patients with SMI. An increase of 10 points (equals one SD) increased the HR of mortality with 21%. TD and akathisia did not show an association with mortality. To study the complex interplay between MD and mortality more well controlled follow-up studies are needed. With the knowledge that antipsychotics differ in their potency to induce parkinsonism, an intervention study is of great clinical importance to find out whether treatment or prevention of parkinsonism can reduce mortality.

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## References

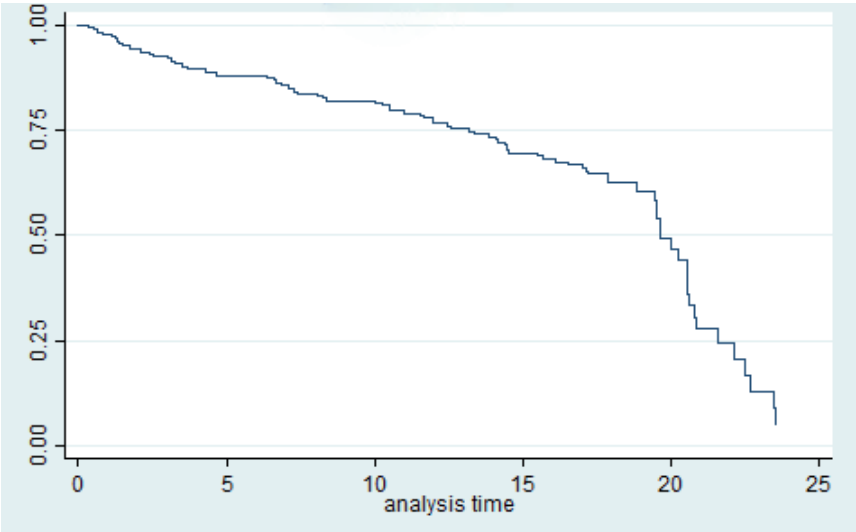

1. Langan Martin J, McClean G, Park J, Martin DJ, Connolly M, Mercer SW, Smith DJ. Impact of socioeconomic deprivation on rate and cause of death in severe mental illness. *BMC Psychiatry* 2014;14.
2. Chang C-K, Hayes RD, Broadbent M, Fernandes AC, Lee W, Hotopf M, Stewert R. All-cause mortality among people with serious mental illness (SMI), substance use disorders, and depressive disorders in southeast London: a cohort study. *BMC Psychiatry* 2010;10(77).
3. Laursen TM. Life expectancy among persons with schizophrenia or bipolar affective disorder. *Schizophr Res* 2011;131(1-3):101-104.
4. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? *Archives of General Psychiatry* 2007;64(10):1123-1131.
5. Lomholt LH, Andersen DV, Sejrsgaard-Jacobsen C, et al. Mortality rate trends in patients diagnosed with schizophrenia or bipolar disorder: a nationwide study with 20 years of follow-up. *International Journal of Bipolar Disorders* 2019/03/01 2019;7(1):6.
6. Crump C, Winkleby MA, Sundquist K, Sundquist J. Comorbidities and Mortality in Persons With Schizophrenia: A Swedish National Cohort Study. *Am J Psychiatry* 2013;170(3):324-333.
7. Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, Haukka J. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *The Lancet* 2009/8/28/ 2009;374(9690):620-627.
8. Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and mortality in bipolar disorder: A swedish national cohort study. *JAMA psychiatry* 2013;70(9):931-939.
9. Heald A, Pendlebury J, Anderson S, Narayan V, Guy M, Gibson M, Haddad P, Livingston M. Lifestyle factors and the metabolic syndrome in Schizophrenia: a cross-sectional study. *Annals of General Psychiatry* 2017;16(1):12.
10. De Hert M, Correll CU, Bobes J, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World psychiatry : official journal of the World Psychiatric Association (WPA)* 2011;10:52-77.
11. Ballesteros J, Gonzáles-Pinto A, Bulbena A. Tardive dyskinesia associated with higher mortality in psychiatric patients: results of a meta-analysis of seven independent studies. *J Clin Psychopharmacol* 2000;20(2):188-194.
12. Chong S-A, Tay JAM, Subramaniam M, Pek E, Machin D. Mortality Rates Among Patients With Schizophrenia and Tardive Dyskinesia. *J Clin Psychopharmacol* 2009;29(1):5-8.
13. Bakker PR, de Groot IW, van Os J, van Harten PN. Long-Stay Psychiatric Patients: A Prospective Study Revealing Persistent Antipsychotic-Induced Movement Disorder. *PLoS One* 2011;6(10):e25588.
14. Tenback DE. An epidemiological approach to elucidate dopaminergic mechanisms in tardive dyskinesia in schizophrenia. *University Press Maastricht* 2006.
15. Mehta D, Mallya A, Volavka J. Mortality of patients with tardive dyskinesia. *Am J Psychiatry* 1978;135(3):371-372.

16. McClelland HA, Dutta D, Metcalfe A, Kerr TA. Mortality and facial dyskinesia. *British Journal of Psychiatry* 1986;148:310-316.
17. Yagi G, Takamiya M, Kanba S, Kamijima K. Mortality Rate of Schizophrenic Patients with Tardive Dyskinesia during 10 Years: A Controlled Study. *The Keio Journal of Medicine* 1989;38(1):70-72.
18. Kucharski LT, Smith JW, Dunn DD. Mortality and tardive dyskinesia. *Am J Psychiatry* 1979;136(9):1228.
19. Yassa R, Mohelsky H, Dimitry R, Schwartz G. Mortality rate in tardive dyskinesia. *Am J Psychiatry* 1984;141(8):1018-1019.
20. Dean CE, Thuras PD. Mortality and tardive dyskinesia: long-term study using the US National Death Index. *The British Journal of Psychiatry* 2009-04-01 00:00:00 2009;194(4):360-364.
21. Modestin J, Vogt Wehrli M, Stephan PL, Agarwalla P. Relationship between Neuroleptic Extrapyramidal Syndromes and Patients' All-Cause Mortality. *Pharmacopsychiatry* 2009;42(02):57-60.
22. van Harten PN, Matroos GE, Hoek HW, Kahn RS. The prevalence of tardive dystonia, tardive dyskinesia, parkinsonism and akathisia. The Curaçao Extrapyramidal Syndromes Study: I. *Schizophr Res* 1996;19(195-203).
23. van Harten PN, Hoek HW, Matroos GE, Koeter M, Kahn RS. The inter-relationships of tardive dyskinesia, parkinsonism, akathisia and tardive dystonia: the Curaçao Extrapyramidal Syndromes Study II. *Schizophr Res* 1997;26(2-3):235-242.
24. van Harten PN, Hoek HW, Matroos GE, van Os J. Incidence of tardive dyskinesia and tardive dystonia in African Caribbean Patients on long-term antipsychotic treatment: the Curaçao Extrapyramidal Syndromes Study V. *The Journal of clinical psychiatry* 2006;67:1920-1927.
25. van Harten PN, Hoek HW, Matroos GE, van Os J. Evidence that lithium protects against tardive dyskinesia: The Curaçao Extrapyramidal Syndromes study VI. *European Neuropsychopharmacology* 2008;18(2):152-155.
26. Van Harten PN. The Curaçao Extrapyramidal Syndromes Study, an 18 yrs prospective study of inpatients with severe mental Illness. *Neuropsychopharmacology* 2012;136.
27. Lane RD, Glazer WM, Hansen TE, Berman WH, Kramer SI. Assessment of tardive dyskinesia using the Abnormal Involuntary Movement Scale. *The Journal of nervous and mental disease* 1985;173(6):353-357.
28. Schooler NR, Kane JM. Research diagnosis for tardive dyskinesia. *Arch Gen Psychiatry* 1982;39:486-487.
29. Martínez-Martín P, Gil-Nagel A, Morlán Gracia L, Balseiro Gomez J, Martínez-Sarriés J, Bermejo F, Group tCM. Unified Parkinson disease rating scale characteristics and structure. *Movement Disorders* 1994;9:76-83.
30. Barnes TRE. A rating scale for drug-induced akathisia. *British Journal of Psychiatry* 1989;154:672-676.
31. World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index [website], cited 2013 June.
32. Cleves M, Gould W, Gutierrez RG, Marchenko YV. *An introduction to survival analysis using Stata.* Third ed. Texas: A Stata Press Publication. StataCorp LP; 2010.
33. Modestin J, Wehrli MV, Stephan PL, Agarwalla P. Evolution of neuroleptic-induced extrapyramidal syndromes under long-term neuroleptic treatment. *Schizophr Res* 2008;100(1-3):97-107.

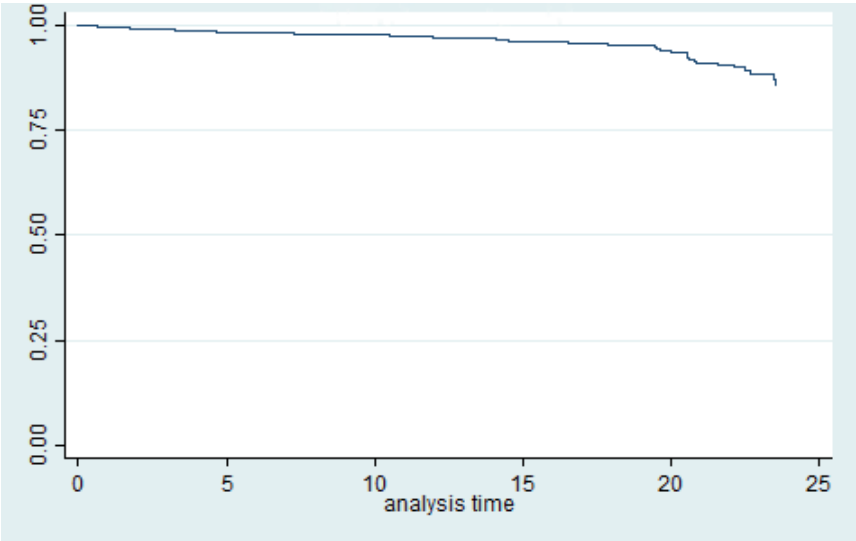
34. Schoepf D, Uppal H, Potluri R, Heun R. Physical comorbidity and its relevance on mortality in schizophrenia: a naturalistic 12-year follow-up in general hospital admissions. *Eur Arch Psychiatry Clin Neurosci* 2014;264(1):3-28.
35. Santos-García D, Suárez-Castro E, Ernandez J, et al. Predictors of Mortality in Nondemented Patients With Parkinson Disease: Motor Symptoms Versus Nonmotor Symptoms. *J Geriatr Psychiatry Neurol* 2018;31(1):19-26.
36. Forsaa EB, Larsen JP, Wentzel-Larsen T, Alves G. What predicts mortality in Parkinson disease? *A prospective population-based long-term study* 2010;75(14):1270-1276.
37. Kulkarni DP, Kamath VD, Stewart JT. Swallowing Disorders in Schizophrenia. *Dysphagia* Aug 2017;32(4):467-471.
38. Cuesta MJ, Sánchez-Torres AM, García de Jalón E, Campos MS, Ibáñez B, Moreno-Izco L, Peralta V. Spontaneous Parkinsonism Is Associated With Cognitive Impairment in Antipsychotic-Naive Patients With First-Episode Psychosis: A 6-Month Follow-up Study. *Schizophr Bull* September 1, 2014 2014;40(5):1164-1173.
39. Molina JL, González Alemán G, Florenzano N, et al. Prediction of Neurocognitive Deficits by Parkinsonian Motor Impairment in Schizophrenia: A Study in Neuroleptic-Naïve Subjects, Unaffected First-Degree Relatives and Healthy Controls From an Indigenous Population. *Schizophr Bull* 2016;42(6):1486-1495.
40. Potvin S, Aubin G, Stip E. Antipsychotic-induced parkinsonism is associated with working memory deficits in schizophrenia-spectrum disorders. *Eur Arch Psychiatry Clin Neurosci* 2015;265(2):147-154.
41. Pieters LE, Deenik J, Tenback DE, van Oort J, van Harten PN. Exploring the Relationship Between Movement Disorders and Physical Activity in Patients With Schizophrenia: An Actigraphy Study. *Schizophrenia bulletin* Jul 8 2021;47(4):906-914.
42. Youssef HA, Waddington JL. Morbidity and mortality in tardive dyskinesia: associations in chronic schizophrenia. *Acta Psychiatr Scand* 1987;75(1):74-77.
43. Inada T, Koshiishi M, Ohnishi K, Yagi G. The Life Expectancy of Schizophrenic Patients with Tardive Dyskinesia. *Human Psychopharmacology: Clinical & Experimental* 1992;7(4):249-254.
44. Tenback DE, van Harten PN, Slooff CJ, van Os J. Worsening of psychosis in schizophrenia is longitudinally associated with tardive dyskinesia in the European Schizophrenia Outpatient Health Outcomes study. *Compr Psychiatry* 2007/10// 2007;48(5):436-440.
45. Murray RM, Van Os J. Predictors of outcome in schizophrenia. *Journal of clinical psychopharmacology* Apr 1998;18(2 Suppl 1):2s-4s.
46. Vermeulen J, van Rooijen G, Doedens P, Numminen E, van Tricht M, de Haan L. Antipsychotic medication and long-term mortality risk in patients with schizophrenia; a systematic review and meta-analysis. *Psychological medicine* Oct 2017;47(13):2217-2228.
47. Torniainen M, Mittendorfer-Rutz E, Tanskanen A, Björkenstam C, Suvisaari J, Alexanderson K, Tiihonen J. Antipsychotic Treatment and Mortality in Schizophrenia. *Schizophr Bull* 2014;41(3):656-663.
48. Taipale H, Tanskanen A, Mehtälä J, Vattulainen P, Correll CU, Tiihonen J. 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). *World psychiatry : official journal of the World Psychiatric Association (WPA)* 2020;19(1):61-68.

49. Tiihonen J, Mittendorfer-Rutz E, Torniainen M, Alexanderson K, Tanskanen A. Mortality and Cumulative Exposure to Antipsychotics, Antidepressants, and Benzodiazepines in Patients With Schizophrenia: An Observational Follow-Up Study. *Am J Psychiatry* 2016;173(6):600-606.
50. Aichele S, Cekic S, Rabbitt P, Ghisletta P. Cognition-Mortality Associations Are More Pronounced When Estimated Jointly in Longitudinal and Time-to-Event Models. *Front Psychol* 2021-August-06 2021;12(3277).
51. Deik A, Saunders-Pullman R, San Luciano M. Substance Abuse and Movement Disorders: Complex Interactions and Comorbidities. *Current Drug Abuse Reviews //* 2012;5(3):243-253.
52. Decina P, Caracci G, Sandik R, Berman W, Mukherjee S, Scapicchio P. Cigarette smoking and neuroleptic-induced parkinsonism. *Biological psychiatry* Sep 15 1990;28(6):502-508.

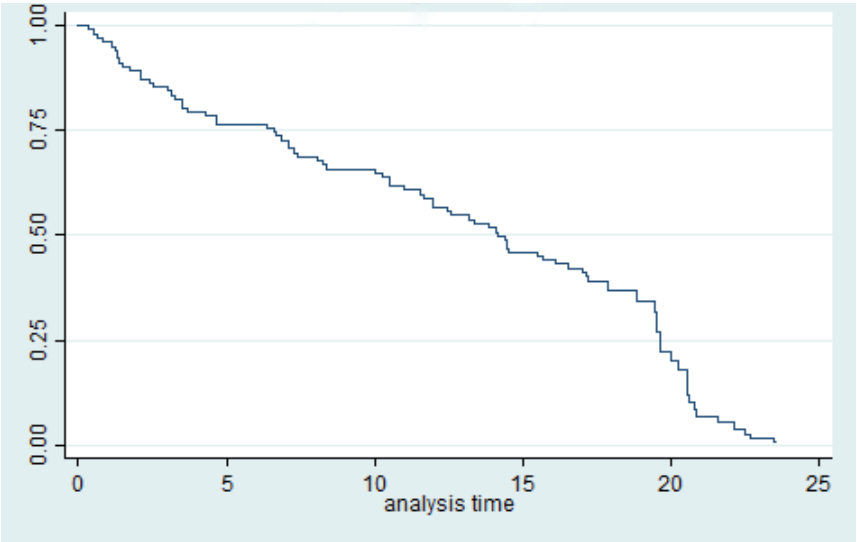
## Supplementary materials




**Suppl. Figure 1. Survival function adjusted for parkinsonism**




**Suppl. Figure 2. Survival function adjusted for age**




**Suppl. Figure 3. Survival function adjusted for Defined Daily Dose (DDD) antipsychotics**

# 7

# Chapter 7

General discussion

Movement abnormalities (Mas) occur frequently in psychiatric disorders[1-4]. Although a broad range of MAs are recognized, in this thesis we focus on three movement disorders (MDs): (tardive) dyskinesia, parkinsonism and akathisia. We studied MDs in individuals with auditory verbal hallucinations (AVH) in the absence of a psychiatric disorder, autism spectrum disorder (ASD), borderline personality disorder (BPD), and psychotic disorders. Robust evidence shows that MDs can be both a symptom of psychiatric disorders and a side effect of antipsychotic medication[1, 3, 5-14]. In treated patients, MDs are likely drug-emergent effects in some cases, and may represent disease-based MDs modified by the antipsychotic medication in others[15]. In addition, research has demonstrated that MDs have prognostic value for clinical and functional outcomes in psychotic disorders[16, 17], and that tardive dyskinesia may be a risk factor for higher mortality[18, 19]. Therefore, we have approached MDs from these three perspectives: in Part I, we examined MDs as symptom; in Part II, we studied MDs in patients using antipsychotic medication; and in Part III, we investigated if MDs may be a risk factor for mortality.



## Part I. Movement disorders as symptom

We have investigated two MDs as symptom: dyskinesia in individuals experiencing AVH in the absence of a diagnosable psychiatric disorder[20], and dyskinesia and parkinsonism in children and adolescents with autism spectrum disorders (ASD)[21]. Innovative in both studies was the use of a mechanical instrument to measure dyskinesia. In the ASD group tremor and bradykinesia were also measured mechanically. In the study on ASD, MDs were assessed with traditional rating scales as well, enabling comparison between the results from the two ways of measurement.

### Subclinical dyskinesia in healthy individuals with auditory verbal hallucinations

For the study on dyskinesia in subjects with AVH in the absence of a diagnosable psychiatric disorder, data was used from a larger project investigating various aspects of AVH including phenomenology, risk factors, and neurobiology[22]. Dyskinesia was measured in a subset of the included participants[20].

We found a positive correlation between schizotypy and dyskinesia in the combined sample of healthy individuals with and without AVH. In addition, we demonstrated that dyskinesia was present in a higher proportion of the participants with AVH than the control group. Our results provided further support for the continuum view of psychosis and underscored the earlier conclusion of Sommer

and colleagues[22] that AVH in this population are part of a general heightened expression of the psychosis phenotype.

For clinical practice, the most relevant findings in the context of the continuum paradigm probably pertain to the predictive validity of subclinical psychotic symptoms and subclinical MDs for the development of psychotic disorders. Accurate identification of subjects at the highest risk of psychosis enables early targeted interventions to delay or prevent psychosis, decrease psychotic symptoms, improve functional outcomes and potentially reduce long term disability[23-26]. A considerable amount of research in this context has been dedicated to subjects aged between 14 and 35-years seeking help for mental health complaints presenting with subclinical psychotic symptoms. Rates for transition to psychosis in individuals classified as 'Clinical High Risk' (CHR) or 'Ultra-High Risk' (UHR) are around 25% over three years[25, 26]. In contrast to CHR/UHR populations, the individuals from the study on AVH were not help seeking at the time of inclusion and they were carefully screened for the absence of psychiatric disorders. Also, the mean age of healthy subjects with AVH was 44 (SD 13) and the majority of them had already passed the peak age for psychosis incidence (15-35) at the time of inclusion[22]. Thus, these subjects come from a different population than CHR/UHR samples. Daalman and colleagues examined transition to psychosis and need for mental health care over time in the individuals with AVH in a follow-up study five years after the baseline measurements[27]. Results showed that 6% of the participants with AVH had developed psychosis versus none of the control participants which was significant at trend level, and higher than the general incidence rates of psychosis. Additionally, a significantly higher proportion of 39% of the individuals with AVH had developed a need for mental healthcare compared to 12% of the control group. Depression in remission and distress due to AVH were significant risk factors for the development of psychopathology in the participants with AVH. The authors proposed that prediction of psychosis and psychopathology might be enhanced by the inclusion of biomarkers such as decreased language lateralization, cortical thickness, or aberrant connectivity. Returning to the findings of the present study, a substantial minority of 24% of the individuals with AVH displayed instrumentally measured dyskinesia. Given the prognostic value of MAs for poor functional and symptomatic outcome in psychotic disorders in general[16, 17], and of dyskinesia in CHR/UHR subjects in particular[17, 28], we suggest that instrumentally measured dyskinesia in subjects with AVH may also be a prognostic marker for a heightened risk of developing psychosis or need for mental health care in individuals with AVH. Future studies into this topic are warranted.

## Discrepancies between results from rating scales and mechanical measurements in autism spectrum disorder

In the study on MDs in children and adolescents with ASD, dyskinesia and parkinsonism were measured both with traditional rating scales and with a mechanical instrument. Using rating scales, we observed a significantly higher occurrence of bradykinesia in children and adolescents with ASD in comparison to typically developing control groups. Furthermore, in the adolescent group, participants with ASD displayed a trend-level higher prevalence of dyskinesia than the control participants. Surprisingly, the instrumental measurements of bradykinesia and dyskinesia did not demonstrate any difference between the ASD and control groups. Possible explanations for our findings pertaining to the underlying neurobiology and the effect of social interaction on performance in ASD have been extensively discussed in chapter 3. Here we will discuss the sensitivity and validity of low frequency (range 0-3 Hz) force variability (L-FV) as a measure for dyskinesia, and velocity scaling (VS) for bradykinesia in comparison with rating scales in more detail. As there were no differences in resting tremor on either measurement method, and the prevalence was very low, the current data are less suitable for a further discussion of sensitivity and concurrent validity of both measurement methods regarding tremor.



In chapter 3, we used non-parametric analyses based on mean rank order to test for possible differences between ASD and control groups. Most earlier studies used a different approach, in which movement disorders were dichotomized (present/not present) using cut-off points derived from the distribution of scores from patient and/or control groups, such as the 95th percentile score of healthy control particpants[20, 29-32]. Thus, in order to be able to better compare our results with those of previous research, here we have also dichotomized the instrumental data based on the 95$^{th}$ percentile score of the control groups (unpublished data). Table 1. shows the numbers and percentages of cases for both the rating scales and instrumental measurements.

*Dyskinesia*

For dyskinesia, there were few cases on any measurement method, but slightly more based on the AIMS than on the instrumental data (table 1.) The difference can largely be explained by the AIMS assessing dyskinesia also in other body parts than the hands. When only taking item 5 of the AIMS (dyskinesia of the upper extremities: arms, wrists, hands, fingers) into account, numbers of cases were: children: ASD: n=3 (13.6%); controls: n= 1 (4.5%); adolescents: ASD: n=2 (9.1%), controls: n=0 (0%). In contrast to the current findings, studies in the psychosis spectrum have generally reported more cases defined with L-FV than

Table 1. Cases of movement disorders defined with rating scales and instrumental measurements

| | Children (age 6-12) | | | | Adolescents (age 13-25)* | | | |
|---|---|---|---|---|---|---|---|---|
| | ASD (n=22) | | Controls (n=22) | | ASD (n=23) | | Controls (n=27) | |
| | RS | IM | RS | IM | RS | IM | RS | IM |
| Dyskinesia, n (%) | 4 (18.2) | 2 (9.1) | 1 (4.5) | 0 (0) | 4 (17.4) | 2 (9.1) | 0 (0) | 1 (4.0) |
| Bradykinesia, n (%) | 11 (50) | 2 (9.1) | 1 (4.5) | 1 (4.5) | 15 (65.4) | 0 (0) | 2 (7.7) | 1 (4.0) |

RS: rating scales; IM: instrumental measurements
Case definitions: Dyskinesia: RS: a score of ≥2 on any item of the AIMS. IM: Children: score >18.99; Adolescents: score >8.29. Bradykinesia RS: a score of ≥2 on any of the following items of the UPDRS part III: 18, 19, 23-31. IM: Children: score <1.52, Adolescents: score<1.46.
*Participants with missing values: Adolescents, instrumental measurements: ASD: n=1; Controls, instrumental measurements: n=1.

with rating scales using widely accepted case definitions[29-32]. Furthermore, to our knowledge, findings on L-FV in the psychosis spectrum have been in line with hypotheses including the presence of subclinical dyskinesia in populations at the healthier end of the spectrum[20, 31, 33].

We found a correlation of .17 (p=0.132) between upper extremity dyskinesia on the AIMS and L-FV in the ASD group and .42 (p=0.002) in the control group. In both groups, the range of scores on the AIMS item 5 was limited; 0-3 in the ASD group and 0-2 in the control group. Furthermore, the distribution was right skewed with 80% of the participants in the ASD group and 84% of the control group scoring a 0. Despite these statistical limitations, the correlation in the control group was strong and highly significant. It is therefore all the more puzzling that there was no significant correlation in the ASD group. Earlier results on the concurrent validity of L-FV with (hand) dyskinesia from rating scales have been mixed. Caligiuri et al. (1990)[29] reported a Spearman correlation of 0.73 (p<0.01) between total low frequency spectral power and AIMS item 5 in 17 patients with TD. However, in a study in antipsychotic-naïve patients with first episode psychosis, no association was found between the Extrapyramidal Signs Rating Scale-Dyskinesia and L-FV[30]. Similarly, in patients who were prescribed antipsychotic medication no agreement was found between cases defined with the AIMS and L-FV (kappa 0.15)[32, 34]. In both studies, the authors explained their findings by pointing out that the instrument measures only hand dyskinesia. Correlations or agreements between the rating scale items measuring hand dyskinesia with the instrumental measurements were not reported.

***Bradykinesia***

The difference in percentages of cases between those defined by the UPDRS and VS in the ASD groups are striking (table 1.) As discussed above in relation to dyskinesia, bradykinesia is also assessed in multiple body parts with rating scales, whereas the mechanical instrument only measures bradykinesia in the arms/hands. Indeed, part of the differences between numbers of cases defined with the UPDRS versus the mechanical measurements are explained by UPDRS defined cases with bradykinesia manifesting in other body parts than the hands. However, still when only taking bradykinesia in the hands into account, the UPDRS showed a higher sensitivity compared to VS in ASD (number of cases: children: ASD: n=5 (22.7%), controls: n=1 (4.5%); adolescents: ASD: n=9 (40.9%), controls: n=2 (7.4%)).

Caligiuri et al (1998) reported a sensitivity of VS similar to clinical observation using a cut-off point of two SD's below the mean of the control group. In another study, using the same instrument and task, velocity instead of VS was used[32]. Results showed that velocity was not more sensitive than the Simpson Angus Scale (SAS). However, in two other studies, VS displayed a higher sensitivity compared with the SAS and UPDRS respectively[30, 35].



Inspecting the concurrent validity, we observed no significant correlations between VS and the summed items of the UPDRS measuring hand bradykinesia (Pearson's r: ASD group: 0.06 ($p$= 0.362); control group: -0.07 ($p$=0.331)). Findings on concordance with rating scales and clinical observation from the group of Caligiuri have been inconclusive. In one study, they reported that of 15 subjects with clinical ratings of at least mild bradykinesia, 9 (60%) exhibited abnormal VS. Of 18 patients without clinical bradykinesia, 6 (33%) patients were cases based on VS[36]. The authors reported a high sensitivity (84%) and perfect specificity (100%) when discriminating patients with Parkinson's Disease from healthy controls. Furthermore, in antipsychotic-naïve patients with first episode psychosis, significant agreement between VS and the SAS was found [32]. In the study where velocity was used to measure bradykinesia, a significant inverse correlation between VS and the SAS was reported for the left hand but not for the right hand[32].

***Concluding remarks***

Regarding 'sensitivity' in the sense of the number of cases that can be identified using either way of measurement, one should keep in mind that, besides the type of measurement used, results also depend highly on the cut-off points chosen. This is illustrated by Dean and colleagues, showing that prevalence of dyskinesia varied from 62% based on IM of the right hand, to 26% with an AIMS score of ≥2

in two body areas. AIMS total score ≥4, IM of the left hand, Dyskinesia Identification Scale Condensed User Version ≥5 and AIMS ≥3 in any body area, respectively, yielded percentages somewhere between these limits. Of note, whereas the IM of the right hand was the most sensitive measure, AIMS total score ≥4 was next and was more sensitive than IM of the left hand.

Thus, although several authors have concluded that L-FV and VS are valid and more sensitive than observational rating scales, we suggest a more nuanced view. These IMs are superior with regard to reliability and may be more sensitive in detecting abnormalities in the arms and hands in populations in the psychosis spectrum. However, based on the current study, L-FV and VS do not seem to be valid measures for dyskinesia and bradykinesia respectively in ASD, and are less sensitive than the AIMS and UPDRS, albeit that the results should be interpreted within the limitation of the low sample size and low numbers of cases.

Generally, with rating scales compared to L-FV and VS, a broader array of movements including the whole body can be taken into account. This is important for dyskinesia, as orofacial dyskinesia or the buccal-lingual masticatory triad is regarded as the core sign of the disorder[37]. Also, bradykinesia can become apparent in body parts other than the hands/arms or when carrying out movements other than required for VS. Thus, for the development of new instrumental or computerized techniques, it is important that the whole body will be covered. Lastly, human perception of biological motion is highly sophisticated and should not be underestimated. Humans are capable of recognizing animacy, individuals, emotional states and intention solely from motion[38-40], and, by inference, of detecting abnormalities in motion as well.

In general, applying both ways of measurement may be the most informative[32]. In ASD specifically, it may be worthwhile to apply any test both with a human test taker, or with social stimuli, and in a digital version with minimal social demands[41, 42]. Possible differences in outcomes can reveal the role of social information processing for a specific function and clarify whether the deficit is a primary component of the disorder or partially due to interference from social information processing.

## Part II. Movement disorders as side effect of antipsychotic medication

In chapter 4, we conducted a meta-analysis of acute MDs associated with the use of second generation antipsychotics (SGAs) in BPD. Data from randomized controlled trials (RCTs) on efficacy and safety of SGAs were used in which MDs were assessed with rating scales. We found no evidence of a heightened risk

of acute MDs associated with the use of low dose SGAs. However, patients in RCTs are a highly selected group and results may not be generalizable to all patients. Particularly relevant in this respect are exclusion criteria pertaining to the absence of comorbid psychiatric disorders and no current use of other psychotropic drugs, as the majority of patients in clinical practice do not fulfill these criteria[43-45]. Although valuable information can be retrieved from RCTs, they should be complemented with results from observational studies.

Rates of antipsychotic drug prescriptions for BPD are with 35%-69% high and prescriptions of SGAs seem to have increased over the last decades[43, 44, 46, 47]. Furthermore, although no psychotropic medication has been officially registered for the treatment of BPD, recent studies show that around 90% of patients with BPD in Europe are prescribed at least one psychotropic drug and more than 70% two or more[43, 46, 47]. Given the significant side-effect profile of most psychotropic drugs and the high rates of polypharmacy, rigorous studies on side effect burden are of utmost importance.



In chapter 5 we examined the effect of switching antipsychotic polypharmacy to antipsychotic monotherapy in long-stay inpatients with psychotic disorders on relapse rate and course of psychotic symptoms. The study focused on patients who were prescribed a combination of at least one FGA and one SGA. For patients randomized to the SWITCH condition, the antipsychotic polypharmacy was switched to one antipsychotic whereas the patients in the STAY condition continued the combined use.

The majority of the patients from the SWITCH group had continued the use of an SGA as monotherapy which was clozapine in most cases, and a minority had continued a long acting injectable FGA. A remarkable result was that patients who had switched from a combination of clozapine and an FGA to clozapine monotherapy, had lower odds of relapse than patients who had continued the combined use. The odds of relapse for patients from the SWITCH group continuing with another antipsychotic did not differ significantly from the odds in the STAY group. Furthermore, in the participants who did not have a relapse nor had dropped out, there was a larger decrease in psychotic symptoms in patients in the SWITCH compared to the STAY group. From these patients, 77% in the SWITCH group were prescribed clozapine.

A hypothesis that may explain the current results concerns the development of supersensitivity for dopamine. The dopamine supersensitivity hypothesis states that long-term blockade of $D_2$ receptors by $D_2$ antagonists leads to an upregula-

tion of $D_2$ receptors and/or the percentage of $D_2$ receptors in high-affinity state ($D_2^{High}$ ), which in turn can lead to dopamine supersensitivity psychosis (DSP)[48]. Criteria for clinical identification of supposed DSP are not rigid, but have been suggested to include the following clinical features in the context of FGA prescription: 1. Rapid relapse after drug discontinuation/dose reduction/switch of antipsychotics, 2. Tolerance to previously observed therapeutic effects, 3. Co-occurring tardive dyskinesia, and 4. Psychotic exacerbation by life stressors[48-51].

The soundest evidence for the existence of DSP comes from animal models. Several studies have shown that administration of antipsychotic medication induces a heightened $D_2$ receptor density and increased levels of $D_2^{High}$ in the caudate-putamen and nucleus accumbens in rats and cats[48, 52, 53]. With regard to humans, one *in vivo* study in patients with schizophrenia found increased $D_2$ receptor availability after discontinuation of antipsychotic treatment[54]. Furthermore, laboratory animals have exhibited behavioral supersensitivity to the indirect dopamine agonist amphetamine after treatment with antipsychotics[55, 56]. See for more comprehensive reviews of the evidence including putative chemical mechanisms leading to DSP Chouinard et al. (2017)[48] and Yin et al. (2017)[50].

Considering DSP in relation to the current study, several characteristics of the included patients increase the likelihood that at least part of them were suffering from DSP; patients were treated on a long-term basis with antipsychotic medication including FGAs which have a high affinity for $D_2$ receptors, patients were prescribed high total defined daily doses (DDDs) of antipsychotics (median DDD=2.5, IQR=1.85), and 87% exhibited tardive dyskinesia. Furthermore, over a period of 9 months, 40% of the patients had relapsed, with a higher percentage of relapses in the STAY group. This may point to the development of tolerance for antipsychotic medication. However, information of a possible more favorable response to antipsychotic monotherapy and/or lower DDD earlier in the treatment history was not available, thus an alternative explanation is that these patients have had treatment resistant schizophrenia from the start of the disease on and had never responded well to antipsychotics. Indeed, various mechanisms of treatment resistant schizophrenia have been proposed, of which DSP is only one potential pathway[57].

Nevertheless, the observation that clozapine monotherapy is more efficacious than clozapine combined with FGAs may be explained by the removal of the putative cause of DSP while continuing an antipsychotic with a relatively low affinity for the $D_2$ receptor but superior antipsychotic effects. Our results are in line with two case series in which switching to clozapine ameliorated DSP[58, 59].

Findings that switching to clozapine is an effective treatment of existing tardive dyskinesia are also congruent with the DSP hypothesis[60]. In the subsequent paper with data from the current study, we will examine the effect of switching to antipsychotic monotherapy and specifically clozapine, on side effects including tardive dyskinesia. Preliminary results show that, as the DSP hypothesis predicts, tardive dyskinesia has significantly improved in the SWITCH group (in preparation). How clozapine exerts its antipsychotic action and may be effective in the treatment of DSP is not exactly known, but research has shown that clozapine is unique with regard to the ratio of dopamine and serotonin binding in favor of the latter, activity on muscarinic and noradrenergic receptors, glycine transporter and brain derived neurotrophic factor (BDNF), and fast dissociation from the $D_2$ receptor[61, 62].

## Part III. Movement disorders as risk factor for mortality



The aim of chapter 6 was to examine if MDs are related to mortality in patients with severe mental illness (SMI). Earlier research suggested that tardive dyskinesia may be associated with a heightened mortality[19, 63]. However, our results showed an association between parkinsonism and mortality, and not between tardive dyskinesia or akathisia and mortality[64]. To our knowledge, the current publication is only the second one demonstrating a relation between parkinsonism and mortality in patients with psychiatric disorders[65]. Therefore, this finding calls for replication. If replicated, the causal mechanisms behind the association should be explored; i.e. does parkinsonism itself lead to a heightened mortality and, if so, what may be the mechanism behind this? It could be that parkinsonism increases the risk of falling and choking. Alternatively, the association may be attributable to a third factor, such as higher illness severity and/or more severe cognitive impairments, which may be related to both parkinsonism and a shorter lifespan. If parkinsonian symptoms themselves are responsible for a heightened mortality, this effect should be considered with regard to prevention and treatment of parkinsonism.

With respect to prevention, expert advice consists of frequent monitoring of parkinsonian signs in the first three months of antipsychotic treatment. Older patients and individuals with a history of parkinsonism are more likely to experience parkinsonism. In these groups it is therefore advised to start with a low dose of the antipsychotic, an antipsychotic with less risk of parkinsonism, or to add an anticholinergic[66].

Considering treatment of existing antipsychotic-induced parkinsonism, guidelines recommend treatment by lowering the antipsychotic dose, short term

addition of anticholinergic medication, or switching to an antipsychotic with a lower $D_2$ affinity[66, 67]. Although there is some evidence for the efficacy of treatment of parkinsonism in non-SMI patients[68, 69], evidence in SMI is scarce and contradictory, and RCTs are lacking[70]. We observed a small but significant effect of switching from antipsychotic polypharmacy to antipsychotic monotherapy on the severity of parkinsonism (in preparation). As mentioned earlier, the majority of the patients who switched to monotherapy continued an SGA, in most cases clozapine[71]. The finding of a reduction in parkinsonism after switching to clozapine monotherapy concurs with results from another study on the efficacy of clozapine in treating MD[72]. However, a naturalistic study conducted in largely the same cohort as the current report on mortality, showed that neither a reduction in antipsychotic dose nor a switch to an SGA, nor a switch to an antipsychotic with a lower $D_2$ affinity, had a significant effect on the severity of parkinsonism. Stopping antipsychotics however did reduce parkinsonism [70]. These results are partly in line with those from another longitudinal study in which antipsychotic dose reduction was not associated with an improvement of parkinsonism. In contrast, switching from an FGA to an SGA did reduce parkinsonism in this study[73].

In this regard, it is insightful to consider the prevalence of parkinsonism in SMI populations, which ranges between 21% and 66%[1, 2, 64, 73]. Even more important, observational cohort studies do not show dramatic decreases in parkinsonism rates over time[2, 64, 74], suggesting either under recognition, under treatment, treatment failure, or some combination of these factors. Similarly, one study showed that more than half of SMI patients in clinical practice exhibit *persistent* parkinsonism[2]. Persistence was defined as the presence of parkinsonism on two consecutive assessments over a period of minimally three months (mean =1.1 years, SD=0.64). Two thirds of the cohort suffered from at least one persistent MD. Strikingly, almost no mention of MDs was found in patients' charts[75], a finding which concurred with other reports[76]. This may suggest little awareness of and/or an attitude of acceptance of MDs including parkinsonism as side effects of antipsychotics for which treatment is not considered a feasible option.

Thus, it is not clear if the relatively high prevalence rates of (persistent) parkinsonism in patients with SMI are the result of under recognition and/or undertreatment, little or no effectiveness of available treatment options, or a combination of both. Further research on this topic is highly needed. With insight into the causes of the high prevalence and persistence rates of parkinsonism, targeted interventions may be designed. Such interventions aimed at state-of-the-art recognition and treatment of parkinsonism, should be studied with regard to

feasibility and effectiveness, and, ultimately, to reveal if they diminish some of the excess mortality in patients with SMI.

## Future directions

Several suggestions for future research arising from the individual studies in this thesis have already been mentioned above. In this paragraph I will firstly take a step back and reflect upon the broader picture of future research directions into MAs in psychiatry. Therefore, I expand the scope from MDs comprising dyskinesia, parkinsonism, akathisia, and dystonia, to MAs including also neurological soft signs and catatonia. To conclude, I will discuss some specific directions for future research.

*General topics*

The first important development and a promising way forward is a renewed interest in MAs across different psychiatric diagnoses and different stages of illness[3, 15, 77, 78]. For example, two systematic reviews on MAs across diagnoses have recently been published[3, 15]. Results show that MAs are prevalent in psychotic disorders, bipolar disorder, major depressive disorder, obsessive-compulsive disorder, ASD, attention deficit hyperactivity disorder (ADHD), Gilles de la Tourette's syndrome, and Alzheimer's Disease[3, 15, 79]. Following these developments and recommendations from influential researchers[15, 79], a sensorimotor domain was added to the US National Institute for Mental Health (NIMH) research domain criteria (RDoC) in 2018[77]. The aim of the formulation of RDoC is to generate knowledge about mental health and illness by studying various levels of psychological functioning, ranging from basic biological components through cognitive processes to overt behavior and subjective experience[80]. Improved understanding of these topics can ultimately inform progress and innovation in mental health care. Within the RDoC framework, research from a dimensional perspective and across the lifespan and stages of illness, rather than within diagnostic categories is encouraged. The study of MAs within the RDoC may prove fruitful as MAs, in contrast to most other symptoms in mental illnesses, are objectively measurable and neurobiological motor pathways are relatively well mapped[79]. Elucidating which MAs are prevalent across different psychiatric illnesses, and which are specific for certain diagnoses or correlate with symptom dimensions such as positive, negative, depressive, and cognitive symptoms, can provide more insight into shared and disorder-specific and/or symptom dimension related underlying processes and neural systems[15, 79]. As there is currently a paucity of research on MAs in diagnoses other than psychotic disorders, studies in populations with other mental illnesses would be of great value.

A second step which would benefit the field is to overcome the problem of overlap and ambiguity in concepts referring to different MAs. As briefly discussed in the General Introduction, various paradigms use their own definitions and terminology, making comparisons between diagnoses and developmental stages difficult. Clarity in definitions and clearer boundaries between normal and abnormal movement will enhance progress in the field[15]. Indeed, inclusion of the sensorimotor domain in the RDoC may stimulate a more unified conceptualization and methodology.

*Towards feasible instrumental measurements and greater usefulness in clinical practice*

As discussed in the General Introduction, historically, rating scales have been used most frequently for the measurement of MAs in both research and clinical practice. However, over the last decades several instrumental devices have been developed, such as: the instrument measuring force variability and velocity scaling discussed above, an inkless pen and digitizing tablet for analyses of handwriting kinematics[81, 82], inertial sensors measuring bradykinesia, a glove measuring gestures, and actigraphy for the measurement of the amount of movement[83]. Instrumental measurements have important advantages over rating scales: they tend to have a higher sensitivity and can detect subclinical MAs, they are highly reliable and not prone to observer bias, and the results are linearly related to severity. Yet, drawbacks are that most currently available devices measure only one body part and they require specialized expensive equipment. However, devices are evolving rapidly and new more feasible tools will probably be developed in the near future. For example, accelerometers and gyroscopes integrated into smartphones provide opportunities for easy to use and affordable applications for the measurement of MAs[83, 84]. Indeed, several apps measuring tremor have already been developed[85, 86]. With such apps, and wearable devices which can measure movement continuously, measurements in daily life are possible allowing precise tracking of change over time. This may yield valuable information on, for example worsening of symptoms, or a change in MDs when starting or changing antipsychotic medication. Furthermore, combining such measurements of MAs with the Experience Sampling Method allows for analyses elucidating how symptoms including MAs and environmental variables are related to and interact with each other[78]. Lastly, a huge step forward into the measurement of MAs may be possible when using motion capture techniques currently used in the game and film industries. With motion capture, recordings of movement are translated to digital animations. Importantly, movement of the whole body can be taken into account with this technique, thus overcoming the drawback of many currently available instruments which assess only one part of the body. Considering

developments in artificial intelligence and machine learning, one could imagine that algorithms can learn to analyze such digitized animations and determine the presence and severity of MAs.

MA measurements could also be incorporated into clinical risk calculators to predict the transition to psychosis in young people with clinical high-risk (CHR) or affective syndromes[78]. Currently, risk calculators making use of clinical and neurocognitive variables are becoming increasingly sophisticated with large scale research projects where models are being developed and cross-validated in various settings[87]. Also, machine learning approaches have been applied in order to reach maximum prognostic accuracy. Given the predictive value of MAs for transition in CHR individuals[17, 88, 89], current models could benefit from the inclusion of MAs[78]. As stated before, precise prediction of psychosis risk enables targeted interventions in order to delay or prevent psychosis and ameliorate symptomatic and functional outcomes[23-26].



A similar approach might be undertaken regarding patients presenting with a first psychotic episode in the sense that a combination of symptoms including MAs may be used for prognosis. As far as we know, such a prognostic tool has not been developed yet. However, if, analogue to the risk predictors discussed above, poor outcome such as treatment resistant schizophrenia could be predicted, this may be of benefit in the choice of intervention. One could, for example, think of starting with clozapine for patients with a high probability of poor outcome. In most guidelines, clozapine is currently indicated after two other antipsychotics have been tried without sufficient response. As clozapine has been shown to have superior effectiveness[90], starting directly with clozapine for these patients may accelerate recovery and limit the adverse effects of prolonged psychosis.

## Conclusions

In this thesis, we demonstrated the presence of spontaneous MDs in individuals with AVH in the absence of a diagnosable psychiatric disorder and in children and adolescents with ASD, herewith contributing to a broader knowledge base on MDs across the healthy-abnormal spectrum with regard to psychosis, and in developmental stages in ASD. MD measurements obtained with an instrumental device yielded results in line with earlier findings in psychosis spectrum populations in the healthy individuals with AVH. In contrast, in the children and adolescents with ASD, results from rating scales were more sensitive than instrumental measurement, perhaps pointing at interference from social information processing and different underlying pathophysiology of MDs in ASD than in the psychosis spectrum.

In the realm of antipsychotic-associated MDs, we found no evidence of a heightened prevalence of MDs in patients with BPD using SGAs compared with placebo. As we included only placebo-controlled RCTs in our meta-analysis, results may not be generalizable to the majority of patients with BPD in clinical practice. Observational studies are therefore highly needed.

In the study on switching a combination of FGAs and SGAs to antipsychotic monotherapy in long-stay patients with psychotic disorders, we found beneficial effects of the switch to monotherapy on relapse and psychotic symptoms. The favorable effects were attributable to patients continuing clozapine as monotherapy. Furthermore, yet unpublished work from the same study suggests that switching to monotherapy diminishes MDs. Although more research is needed, we tentatively conclude that patients currently prescribed a combination of FGAs and SGAs can be safely switched to antipsychotic monotherapy consisting of an SGA or a long acting injectable FGA, and that continuation of clozapine as monotherapy is superior in terms of relapse prevention and reduction of psychotic symptoms.

Finally, we showed that parkinsonism may be a risk factor for mortality in patients with SMI. Research suggests that currently, parkinsonism in patients with SMI is either under-recognized, undertreated or, alternatively, that treatment may not be effective. Therefore, effort should be made to clarify this highly important topic and to elucidate if effective recognition and treatment of parkinsonism will reduce the excess mortality in these patients.

## References


1. van Harten PN, Matroos GE, Hoek HW, Kahn RS. The prevalence of tardive dystonia, tardive dyskinesia, parkinsonism and akathisia. The Curaçao Extrapyramidal Syndromes Study: I. *Schizophr Res* 1996;19(195-203).
2. Bakker PR, de Groot IW, van Os J, van Harten PN. Long-Stay Psychiatric Patients: A Prospective Study Revealing Persistent Antipsychotic-Induced Movement Disorder. *PLoS One* 2011;6(10):e25588.
3. Hirjak D, Meyer-Lindenberg A, Fritze S, Sambataro F, Kubera KM, Wolf RC. Motor dysfunction as research domain across bipolar, obsessive-compulsive and neurodevelopmental disorders. *Neuroscience and biobehavioral reviews* Dec 2018;95:315-335.
4. Fritze S, Sambataro F, Kubera KM, Brandt GA, Meyer-Lindenberg A, Wolf RC, Hirjak D. Characterizing the sensorimotor domain in schizophrenia spectrum disorders. *Eur Arch Psychiatry Clin Neurosci* Sep 2022;272(6):1097-1108.
5. Pappa S, Dazzan P. Spontaneous movement disorders in antipsychotic-naive patients with first-episode psychoses: a systematic review. *Psychol Med* 2009;39(07):1065-1076.
6. Koning JP, Tenback DE, van Os J, Aleman A, Kahn RS, van Harten PN. Dyskinesia and parkinsonism in antipsychotic-naive patients with schizophrenia, first-degree relatives and healthy controls: a meta-analysis. *Schizophr Bull* 2010;36(4):723-731.
7. Ayehu M, Shibre T, Milkias B, Fekadu A. Movement disorders in neuroleptic-naïve patients with schizophrenia spectrum disorders. *BMC Psychiatry* Oct 9 2014;14:280.
8. Dean DJ, Mittal VA. Spontaneous parkinsonisms and striatal impairment in neuroleptic free youth at ultrahigh risk for psychosis. *NPJ Schizophr* 2015;1:14006-.
9. Mittal VA, Daley M, Shiode MF, Bearden CE, O'Neill J, Cannon TD. Striatal volumes and dyskinetic movements in youth at high-risk for psychosis. *Schizophr Res* 2010;123(1):68-70.
10. van Harten PN, Bakker PR, Mentzel CL, Tijssen MA, Tenback DE. Movement Disorders and Psychosis, a Complex Marriage. *Frontiers in Psychiatry* 2015-January-09 2015;5(190).
11. Malhotra AK, Litman RE, Pickar D. Adverse effects of antipsychotic drugs. *Drug Saf* Dec 1993;9(6):429-436.
12. van Harten PN, Hoek HW, Matroos GE, van Os J. Incidence of tardive dyskinesia and tardive dystonia in African Caribbean Patients on long-term antipsychotic treatment: the Curaçao Extrapyramidal Syndromes Study V. *The Journal of clinical psychiatry* 2006;67:1920-1927.
13. Gao K, Kemp DE, Ganocy SJ, Gajwani P, Xia G, Calabrese JR. Antipsychotic-induced extrapyramidal side effects in bipolar disorder and schizophrenia. A systematic Review. *J Clin Psychopharmacol* 2008;28(2):203-209.
14. Kapur S, Zipursky RB, Jones C, Remington G, Houle S. Relationship between dopamine D2 occupancy, clinical respons, and side effects: a double-blind PET study of first episode schizophrenia. *Am J Psychiatry* 2000;157(4):514-520.
15. Peralta V, Cuesta MJ. Motor Abnormalities: From Neurodevelopmental to Neurodegenerative Through "Functional" (Neuro)Psychiatric Disorders. *Schizophrenia bulletin* Sep 1 2017;43(5):956-971.

16. Nadesalingam N, Chapellier V, Lefebvre S, et al. Motor abnormalities are associated with poor social and functional outcomes in schizophrenia. *Compr Psychiatry* 2022/05/01/ 2022;115:152307.
17. Pieters LE, Nadesalingam N, Walther S, van Harten PN. A systematic review of the prognostic value of motor abnormalities on clinical outcome in psychosis. *Neuroscience and biobehavioral reviews* Jan 2022;132:691-705.
18. Ballesteros J, González-Pinto A, Bulbena A. Tardive dyskinesia associated with higher mortality in psychiatric patients: results of a meta-analysis of seven independent studies. *J Clin Psychopharmacol* 2000;20(2):188-194.
19. Chong S-A, Tay JAM, Subramaniam M, Pek E, Machin D. Mortality Rates Among Patients With Schizophrenia and Tardive Dyskinesia. *J Clin Psychopharmacol* 2009;29(1):5-8.
20. Willems AE, Sommer IE, Tenback DE, Koning JP, van Harten PN. Instrumental measurements of spontaneous dyskinesia and schizotypy in subjects with auditory verbal hallucinations and healthy controls. *Psychiatry research* Oct 30 2016;244:24-27.
21. Mostert-Kerckhoffs MAL, Willems AE, Tenback DE, Koning JP, Van Harten P, Staal WG. Motor Disturbance in ASD: A Pilot Study Showing Hypokinetic Behavior? *J Autism Dev Disord* Feb 2020;50(2):415-428.
22. Sommer IEC, Daalman K, Rietkerk T, Diederen KM, Bakker S, Wijkstra J, Boks MPM. Healthy Individuals With Auditory Verbal Hallucinations; Who Are They? Psychiatric Assessments of a Selected Sample of 103 Subjects. *Schizophr Bull* May 1, 2010 2010;36(3):633-641.
23. Correll CU, Galling B, Pawar A, et al. Comparison of Early Intervention Services vs Treatment as Usual for Early-Phase Psychosis: A Systematic Review, Meta-analysis, and Meta-regression. *JAMA psychiatry* Jun 1 2018;75(6):555-565.
24. Mei C, van der Gaag M, Nelson B, et al. Preventive interventions for individuals at ultra high risk for psychosis: An updated and extended meta-analysis. *Clin Psychol Rev* Jun 2021;86:102005.
25. Fusar-Poli P, Salazar de Pablo G, Correll CU, et al. Prevention of Psychosis: Advances in Detection, Prognosis, and Intervention. *JAMA psychiatry* Jul 1 2020;77(7):755-765.
26. Salazar de Pablo G, Radua J, Pereira J, et al. Probability of Transition to Psychosis in Individuals at Clinical High Risk: An Updated Meta-analysis. *JAMA psychiatry* Sep 1 2021;78(9):970-978.
27. Daalman K, Diederen KM, Hoekema L, van Lutterveld R, Sommer IE. Five year follow-up of non-psychotic adults with frequent auditory verbal hallucinations: are they still healthy? *Psychological medicine* Jul 2016;46(9):1897-1907.
28. van Harten PN, Tenback DE. Letter to the Editor: Movement disorders should be a criterion for schizophrenia in DSM-V. *Psychol Med* 2009;39(10):1754-1756.
29. Caligiuri MP, Lohr JB. Fine force instability: a quantitative measure of neuroleptic-induced dyskinesia in the hand. *J Neuropsychiatr* 1990;2:395-398.
30. Cortese L, Caligiuri MP, Malla AK, Manchanda R, Takhar J, Haricharan R. Relationship of neuromotor disturbances to psychosis symptoms in first-episode neuroleptic-naive schizophrenia patients. *Schizophr Res* 2005;75(1):65-75.

31. Koning JP, Kahn R, Tenback DE, van Schelven LJ, van Harten PN. Movement disorders in nonpsychotic siblings of patients with nonaffective psychosis. *Psychiatry Res* 2011;188(1):133-137.
32. Dean CE, Russel JM, Kuskowski MA, Caligiuri MP, Nugent SM. Clinical rating scales and instruments. How do they compare in assessing abnormal involuntary movements? *Journal of clinical psychopharmacology* 2004;24:298-304.
33. Mittal VA, Dean DJ, Pelletier A, Caligiuri M. Associations between spontaneous movement abnormalities and psychotic-like experiences in the general population. *Schizophr Res* 2011;132:194-196.
34. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb)* 2012;22(3):276-282.
35. Koning JP. Movement disorders in patients with schizophrenia and their siblings; symptoms, side effects and mechanical measurements. *Utrecht: Psychiatry* 2011.
36. Caligiuri MP, Lohr JB, Ruck RK. Scaling of movement velocity: A measure of neuromotor retardation in individuals with psychopathology. *Psychophysiology* 1998;35(4):431-437.
37. Van Harten PN. *Movement disorders associated with neuroleptics. The Curacao extrapyramidal syndromes study*. Utrecht, Universiteit Utrecht; 1998.
38. Thurman SM, Giese MA, Grossman ED. Perceptual and computational analysis of critical features for biological motion. *Journal of Vision* 2010;10(12):15-15.
39. Bachmann J, Munzert J, Krüger B. Neural Underpinnings of the Perception of Emotional States Derived From Biological Human Motion: A Review of Neuroimaging Research. *Front Psychol* 2018;9:1763.
40. Schultz J, Bülthoff HH. Perceiving animacy purely from visual motion cues involves intraparietal sulcus. *Neuroimage* 2019/08/15/ 2019;197:120-132.
41. Ozonoff S. Reliability and validity of the Wisconsin Card Sorting Test in studies of autism. *Neuropsychology* 1995;9(4):491-500.
42. Dichter GS, Belger A. Social stimuli interfere with cognitive control in autism. *Neuroimage* Apr 15 2007;35(3):1219-1230.
43. Paton C, Crawford MJ, Bhatti SF, Patel MX, Barnes TR. The use of psychotropic medication in patients with emotionally unstable personality disorder under the care of UK mental health services. *The Journal of clinical psychiatry* Apr 2015;76(4):e512-518.
44. Pascual JC, Martín-Blanco A, Soler J. Twenty-Year Trends in the Psychopharmacological Treatment of Outpatients with Borderline Personality Disorder: A Cross-Sectional Naturalistic Study in Spain. *CNS drugs* Sep 2021;35(9):1023-1032.
45. Soler J, Casellas-Pujol E, Fernández-Felipe I, Martín-Blanco A, Almenta D, Pascual JC. "Skills for pills": The dialectical-behavioural therapy skills training reduces polypharmacy in borderline personality disorder. *Acta psychiatrica Scandinavica* Apr 2022;145(4):332-342.
46. Bridler R, Häberle A, Müller ST, Cattapan K, Grohmann R, Toto S, Kasper S, Greil W. Psychopharmacological treatment of 2195 in-patients with borderline personality disorder: A comparison with other psychiatric disorders. *Eur Neuropsychopharmacol* Jun 2015;25(6):763-772.
47. Martín-Blanco A, Ancochea A, Soler J, Elices M, Carmona C, Pascual JC. Changes over the last 15 years in the psychopharmacological management of persons with

borderline personality disorder. *Acta psychiatrica Scandinavica* Sep 2017;136(3):323-331.
48. Chouinard G, Samaha AN, Chouinard VA, Peretti CS, Kanahara N, Takase M, Iyo M. Antipsychotic-Induced Dopamine Supersensitivity Psychosis: Pharmacology, Criteria, and Therapy. *Psychotherapy and Psychosomatics* 2017;86(4):189-219.
49. Chouinard G. Severe cases of neuroleptic-induced supersensitivity psychosis. Diagnostic criteria for the disorder and its treatment. *Schizophrenia research* Jul-Aug 1991;5(1):21-33.
50. Yin J, Barr AM, Ramos-Miguel A, Procyshyn RM. Antipsychotic Induced Dopamine Supersensitivity Psychosis: A Comprehensive Review. *Current neuropharmacology* 2017;15(1):174-183.
51. Chouinard G, Jones BD. Neuroleptic-induced supersensitivity psychosis: clinical and pharmacologic characteristics. *The American journal of psychiatry* Jan 1980;137(1):16-21.
52. O'Dell SJ, La Hoste GJ, Widmark CB, Shapiro RM, Potkin SG, Marshall JF. Chronic treatment with clozapine or haloperidol differentially regulates dopamine and serotonin receptors in rat brain. *Synapse* 1990;6(2):146-153.
53. Ginovart N, Wilson AA, Hussey D, Houle S, Kapur S. D2-receptor upregulation is dependent upon temporal course of D2-occupancy: a longitudinal [11C]-raclopride PET study in cats. *Neuropsychopharmacology* Feb 2009;34(3):662-671.
54. Silvestri S, Seeman MV, Negrete JC, et al. Increased dopamine D2 receptor binding after long-term treatment with antipsychotics in humans: a clinical PET study. *Psychopharmacology* Oct 2000;152(2):174-180.
55. Samaha AN, Seeman P, Stewart J, Rajabi H, Kapur S. "Breakthrough" dopamine supersensitivity during ongoing antipsychotic treatment leads to treatment failure over time. *J Neurosci* Mar 14 2007;27(11):2979-2986.
56. Montanaro N, Dall'Olio R, Gandolfi O, Vaccheri A. Differential enhancement of behavioral sensitivity to apomorphine following chronic treatment of rats with (-)-sulpiride and haloperidol. *Eur J Pharmacol* Jun 16 1982;81(1):1-9.
57. Potkin SG, Kane JM, Correll CU, Lindenmayer JP, Agid O, Marder SR, Olfson M, Howes OD. The neurobiology of treatment-resistant schizophrenia: paths to antipsychotic resistance and a roadmap for future research. *NPJ Schizophr* Jan 7 2020;6(1):1.
58. Chouinard G, Vainer JL, Bélanger MC, Turnier L, Beaudry P, Roy JY, Miller R. Risperidone and clozapine in the treatment of drug-resistant schizophrenia and neuroleptic-induced supersensitivity psychosis. *Progress in neuro-psychopharmacology & biological psychiatry* Nov 1994;18(7):1129-1141.
59. Nakata Y, Kanahara N, Kimura H, Watanabe H, Iyo M. Efficacy of clozapine on dopamine supersensitivity psychosis in schizophrenia. *International clinical psychopharmacology* May 2017;32(3):169-173.
60. Mentzel TQ, van der Snoek R, Lieverse R, Oorschot M, Viechtbauer W, Bloemen O, van Harten PN. Clozapine Monotherapy as a Treatment for Antipsychotic-Induced Tardive Dyskinesia: A Meta-Analysis. *The Journal of clinical psychiatry* Sep 18 2018;79(6).
61. Aringhieri S, Carli M, Kolachalam S, et al. Molecular targets of atypical antipsychotics: From mechanism of action to clinical differences. *Pharmacol Ther* Dec 2018;192:20-41.

62. Seeman P. Clozapine, a fast-off-D2 antipsychotic. *ACS chemical neuroscience* Jan 15 2014;5(1):24-29.
63. Ballesteros J, Gonzáles-Pinto A, Bulbena A. Tardive dyskinesia associated with higher mortality in psychiatric patients: results of a meta-analysis of seven independent studies. *J Clin Psychopharmacol* 2000;20(2):188-194.
64. Willems AE, Mentzel CL, Bakker PR, et al. Movement Disorders and Mortality in Severely Mentally Ill Patients: The Curacao Extrapyramidal Syndromes Study XIV. *Schizophrenia bulletin* Jun 21 2022;48(4):766-773.
65. Schoepf D, Uppal H, Potluri R, Heun R. Physical comorbidity and its relevance on mortality in schizophrenia: a naturalistic 12-year follow-up in general hospital admissions. *Eur Arch Psychiatry Clin Neurosci* 2014;264(1):3-28.
66. Van Harten PN. *Bewegingsstoornissen door antipsychotica; diagnostiek en behandeling*. Amsterdam: Boom; 2000.
67. Van Alphen A, Ammeraal M, Blanke C, et al. Multidisciplinaire richtlijn schizofrenie. 2012.
68. Ritchie CW, Chiu E, Harrigan S, et al. The impact upon extra-pyramidal side effects, clinical symptoms and quality of life of a switch from conventional to atypical antipsychotics (risperidone or olanzapine) in elderly patients with schizophrenia. *Int J Geriatr Psychiatry* May 2003;18(5):432-440.
69. Ritchie CW, Chiu E, Harrigan S, et al. A comparison of the efficacy and safety of olanzapine and risperidone in the treatment of elderly patients with schizophrenia: an open study of six months duration. *Int J Geriatr Psychiatry* 2006;21(2):171-179.
70. Mentzel CL, Bakker PR, van Os J, Drukker M, Matroos GE, Hoek HW, Tijssen MA, van Harten PN. Effect of Antipsychotic Type and Dose Changes on Tardive Dyskinesia and Parkinsonism Severity in Patients With a Serious Mental Illness: The Curaçao Extrapyramidal Syndromes Study XII. *The Journal of clinical psychiatry* Mar 2017;78(3):e279-e285.
71. Shakir M, Willems AE, van Harten PN, van Lutterveld R, Tenback DE. The effect on relapse rate and psychiatric symptomatology: Switching a combination of first- and second-generation antipsychotic polypharmacy to antipsychotic monotherapy in long-term inpatients with schizophrenia and related disorders. A pragmatic randomized open-label trial (SwAP trial). *Schizophr Res* 2022/05/01/ 2022;243:187-194.
72. Spivak B, Mester R, Abesgaus J, Wittenberg N, Adlersberg S, Gonen N, Weizman A. Clozapine treatment for neuroleptic-induced tardive dyskinesia, parkinsonism, and chronic akathisia in schizophrenic patients. *The Journal of clinical psychiatry* Jul 1997;58(7):318-322.
73. Parksepp M, Ljubajev U, Taht K, Janno S. Prevalence of neuroleptic-induced movement disorders: an 8-year follow-up study in chronic schizophrenia inpatients. *Nordic Journal of Psychiatry* 2016;70(7):498-502.
74. Modestin J, Wehrli MV, Stephan PL, Agarwalla P. Evolution of neuroleptic-induced extrapyramidal syndromes under long-term neuroleptic treatment. *Schizophr Res* 2008;100(1-3):97-107.
75. Bakker PR. *Drug-induced movement disorders in long-stay psychiatric patients. Genetic and non-genetic risk factors: A prospective study*. Maastricht, Maastricht University; 2012.
76. Friedman JH, Fernandez HH, Trieschmann MM. Parkinsonism in a nursing home: underrecognition. *J Geriatr Psychiatry Neurol* Mar 2004;17(1):39-41.

77. Mittal VA, Walther S. As Motor System Pathophysiology Returns to the Forefront of Psychosis Research, Clinical Implications Should Hold Center Stage. *Schizophrenia bulletin* Apr 25 2019;45(3):495-497.
78. van Harten PN, Pieters LE. Clinical Consequences of Motor Behavior as Transdiagnostic Phenomenon. *Schizophrenia bulletin* Mar 17 2022.
79. Bernard JA, Mittal VA. Updating the research domain criteria: the utility of a motor dimension. *Psychological medicine* Oct 2015;45(13):2685-2689.
80. NIMH. https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/about-rdoc. *National Institute of Mental Health*. Accessed January 9 2023, 2023.
81. Caligiuri MP, Teulings HL, Filoteo JV, Song D, Lohr JB. Quantitative measurement of handwriting in the assessment of drug-induced parkinsonism. *Human movement science* Oct 2006;25(4-5):510-522.
82. Caligiuri MP, Teulings H-L, Dean CE, Niculescu Iii AB, Lohr JB. Handwriting movement kinematics for quantifying extrapyramidal side effects in patients treated with atypical antipsychotics. *Psychiatry Res* 2010;177:77-83.
83. van Harten PN, Walther S, Kent JS, Sponheim SR, Mittal VA. The clinical and prognostic value of motor abnormalities in psychosis, and the importance of instrumental assessment. *Neuroscience and biobehavioral reviews* Sep 2017;80:476-487.
84. Mentzel CL. The course, recognition and treatment of movement disorders in severe mental illness. *Datawyse/Universitaire Pers Maastricht: Maastricht* 2017.
85. Kubben PL, Kuijf ML, Ackermans LP, Leentjens AF, Temel Y. TREMOR12: An Open-Source Mobile App for Tremor Quantification. *Stereotact Funct Neurosurg* 2016;94(3):182-186.
86. Kuosmanen E, Wolling F, Vega J, et al. Smartphone-Based Monitoring of Parkinson Disease: Quasi-Experimental Study to Quantify Hand Tremor Severity and Medication Effectiveness. *JMIR Mhealth Uhealth* Nov 26 2020;8(11):e21543.
87. Koutsouleris N, Worthington M, Dwyer DB, et al. Toward Generalizable and Transdiagnostic Tools for Psychosis Prediction: An Independent Validation and Improvement of the NAPLS-2 Risk Calculator in the Multisite PRONIA Cohort. *Biological psychiatry* Nov 1 2021;90(9):632-642.
88. Callaway DA, Perkins DO, Woods SW, Liu L, Addington J. Movement abnormalities predict transitioning to psychosis in individuals at clinical high risk for psychosis. *Schizophr Res* 2014;159(2-3):263-266.
89. Mittal VA, Walker EF. Movement abnormalities predict conversion to Axis I psychosis among prodromal adolescents. *J Abnorm Psychol* 2007;116(4):796-803.
90. Wagner E, Siafis S, Fernando P, et al. Efficacy and safety of clozapine in psychotic disorders-a systematic quantitative meta-review. *Transl Psychiatry* Sep 22 2021;11(1):487.

# Summary


## General introduction

Movement disorders (MDs) occur often in psychiatric disorders[1-3]. Although many MDs exist, this thesis focuses on the following three MDs:

*Dyskinesia* is a hyperkinetic MD which present itself in involuntary, writhing, irregular movements which are generally fluid. These movements can happen in any body part, but the orofacial area and upper limbs are affected most often.

*Parkinsonism* is a hypokinetic MD consisting of bradykinesia, rigidity, tremor at rest and postural instability.

*Akathisia* consists of subjective feelings of inner restlessness and objective motor movements, typically occurring in the legs.

We examined these MDs from three perspectives: in Part I. the focus is on MDs as symptom of the underlying psychiatric disorder, in Part II. the focus in on MDs as adverse effect of antipsychotic medication, and in Part III we analyzed if MDs may be a risk factor for a shorter lifespan.

In clinical practice and in research, MDs are mostly measured with observation-based rating scales. However, over the last decades, several instruments have been developed which can measure MDs[4]. In the studies described in chapter 2 and 3, we used a mechanical instrument for the measurement of dyskinesia, bradykinesia, and tremor.

### *Part I. Movement disorders as symptom*

In chapter 2 we aimed to shed light on the relation between psychotic-like experiences and dyskinesia[5]. We studied spontaneous dyskinesia in 34 individuals with auditory verbal hallucinations in the absence of a psychotic disorder, and 31 matched healthy control participants. Dyskinesia was assessed mechanically by measuring force variability in the 0-3 Hz range[6, 7]. Schizotypy was assessed using the Schizotypal Personality Questionnaire[8]. Dyskinesia and schizotypy showed a significant positive correlation in the total group (Spearman's rho=0.32, p=0.005). Furthermore, when using a cut-off point based on the 95$^{th}$ percentile score of force variability in the control group, a larger proportion of subjects in the hallucinating group displayed dyskinesia (n=8, 23.5%) than in the control group (n=1, 3.2%; p=0,019). These results underscore the intrinsic relation between

MDs and AVH, and they are in line with the concept of psychosis as a continuous phenomenon.

The objective of chapter 3 was to assess the presence of MDs in children and adolescents/young adults with autism spectrum disorder (ASD)[9]. Therefore, parkinsonism and dyskinesia were measured in 44 subjects with ASD and 49 typically developing control individuals who were matched for sex, age, and IQ. MDs were measured both with rating scales and a mechanical instrument[6, 7, 10, 11]. Using the Unified Parkinson's Disease Rating Scale (UPDRS), we found more cases with bradykinesia in both age groups with ASD compared to the typically developing control groups ($p<0.0001$ for both age groups). The adolescent/young adult group with ASD also displayed more rigidity than the control group ($p<0.0001$). No group differences were observed using the instrumental measurements. The finding of a higher sensitivity of the UPDRS compared to the mechanical instrument was puzzling, since instrumental measurements have generally been shown to be more sensitive than rating scales in the psychosis spectrum[7, 12]. We hypothesized that the current findings of an opposite pattern in ASD may point at different underlying neuropathology and possibly interference from social information processing in the rating scale measurements.

***Part II. Movement disorders as side effect***

Chapter 4 sought to determine the risk of antipsychotic-induced MDs in borderline personality disorder (BPD)[13]. Antipsychotic medication is often prescribed off-label for BPD. However, MDs in BPD have received little research attention. We conducted meta-analyses on measurements of parkinsonism, akathisia, and dyskinesia from placebo-controlled RCTs on efficacy and safety of olanzapine (n=3)[14-16] and ziprasidone (n=1)[17]. We found no evidence of a higher risk of MDs in patients receiving an antipsychotic drug versus placebo. The current findings are in line with observations that low to moderate doses of olanzapine (5-10 mg/day) do not seem to occupy more than 78% of striatal dopamine D2 receptors, which has shown to be the threshold above which parkinsonism generally arises[18, 19]. Although such a threshold is not as clear for akathisia and (tardive) dyskinesia, these MDs are also more likely to develop with higher doses and higher potency antipsychotic drugs[20-22]. Furthermore, olanzapine has some of the lowest risks of inducing acute MDs among the SGAs[23], which is thought to be at least partly due to its anticholinergic properties[24]. A limitation of the study was that by including only RCTs, selection bias may have arisen. Therefore, caution should be taken in generalizing the results to all patients with BPD.

In chapter 5, the first report from an open label RCT on the effects of switching from a combination of FGA(s) and SGA(s) to antipsychotic monotherapy, is presented[25]. Antipsychotic polypharmacy is commonly used in the treatment of inpatients with schizophrenia[26], although the evidence for its efficacy and effectiveness is inconclusive[27, 28]. The current study investigated the effects of switching a combination of FGA(s) and SGA(s) to antipsychotic monotherapy on relapse rate and psychiatric symptoms. Patients with psychotic disorders treated at long-stay wards were eligible. Included patients (n=136) were randomized to a SWITCH or a STAY group. The SWITCH group discontinued either the FGA(s) or the SGA(s) over a period of maximum three months, and the STAY group continued the combination treatment. Psychiatric symptoms were measured at baseline and at follow-ups at three, six and nine months using the Brief Psychiatric Rating Scale (BPRS)[29]. Relapse was defined as (i) an increase in the BPRS of at least 2 points in any item, or (ii) an increase of at least 4 points in the total BPRS score in combination with the need to adjust the antipsychotic medication. A logistic regression model corrected for sex, showed that the odds for relapse was significantly lower in the SWITCH group OR=0.29 (95% CI=0.13-0.62). The protective effect was attributable to patients continuing clozapine as monotherapy. For patients who did not experience a relapse nor dropped out, the BPRS total scores decreased significantly more in the SWITCH group ($p$=0.0001). The current results show that switching from a combination of FGA(s) and SGA(s) is safe with respect to the risk of relapse. Switching to clozapine monotherapy may even reduce the risk.

***Part III. Movement disorders as risk factor for mortality***

Chapter 6 aimed to investigate if MDs are related to mortality in patients with severe mental illness (SMI)[30]. There is a substantial gap in life expectancy between patients with SMI and the general population[31, 32] and it is important to understand which factors contribute to this difference. Some research has suggested that MDs are associated with a heightened mortality, but results have been inconclusive[33-35]. We examined if tardive dyskinesia, parkinsonism, and akathisia, would be related to mortality in patients with SMI. We studied a cohort of 157 Afro-Caribbean inpatients with predominantly schizophrenia on the island of Curacao. Tardive dyskinesia, parkinsonism, and akathisia were assessed with rating scales on eight occasions over a period of eighteen years. Twenty-four years after baseline, survival status and if applicable, date of death, were determined. Cox regression models were used to calculate hazard ratios (HRs) for MDs. Sex, age, use of antipsychotics, antidepressants, and benzodiazepines at each measurement occasion were tested as covariates. The results showed that parkinsonism was a significant risk factor with a HR of 1.02 per point on the

UPDRS (range 0-56). The SD for cases with parkinsonism was around 10 points and an increase of 10 points would lead to an increase in the HR for mortality of 21%. Tardive dyskinesia and akathisia did not show a significant association with mortality. The finding that parkinsonism was a significant risk factor is in line with results from studies in older individuals[36] and in patients with Alzheimer's and Parkinson's disease[37, 38]. The present finding in patients with SMI needs to be replicated. If it is confirmed in other studies, it may provide a starting point for new interventions that ultimately may help to reduce the excess mortality in SMI patients.

## General Discussion

In the General discussion, the most important results of the studies in this theses are summarized, and some notable results are discussed into more depth or in a broader context.

We considered the findings of the study on dyskinesia in individuals with AVH in light of a possible prognostic value of MDs for a poor outcome. Our findings demonstrated a higher proportion of dyskinesia in the AVH group (24%) compared with the healthy control group (3%). A follow-up study on the mental health of the individuals with AVH had shown that five years after the baseline measurement, a relatively large proportion of these people (39%) had developed a need for mental health care and a somewhat larger proportion than would be expected had developed psychosis (6%)[39]. Numerous studies have shown that MDs have prognostic value for developing psychosis in individuals at clinical high risk (CHR) or ultra-high risk (UHR) for psychosis, and for a poor outcome in first episode psychosis and chronic psychosis[40, 41]. Therefore, we suggest that MDs may also help in predicting which individuals with AVH may be the most vulnerable for developing psychosis or a need for mental health care.

A surprising finding from the study on MDs in children and adolescents with ASD was the lack of agreement between the rating scales and the instrumental measurements. These results were discussed into more detail and a mini review was conducted on earlier research into the sensitivity and validity of the instrumental measurements. These earlier studies focused on MDs in patients with psychotic disorders[7, 10-12, 42]. Taken together, there is some evidence than the instrumental measurements are generally more sensitive than rating scales. Results on concurrent validity were mixed. Part of the disagreement between the instrumental measurements and the rating scales can be explained by the fact that these instrumental measurements only include the arms/hands whereas with rating scales, the whole body is included.

Remarkable in the study on switching antipsychotic polypharmacy to monotherapy was the finding that patients who had switched to clozapine monotherapy, had significant lower odds of relapse than patients who had continued antipsychotic polypharmacy (clozapine in combination with at least one FGA). We tried to explain the results using the dopamine supersensitivity hypothesis. This hypothesis states that long-term blockade of $D_2$ receptors by $D_2$ antagonists leads to an upregulation of $D_2$ receptors and/or the percentage of $D_2$ receptors in high-affinity state ($D_2^{High}$ ), which in turn can lead to dopamine supersensitivity psychosis[43]. Dopamine super sensitivity might have been present in a large proportion of the patients included in the current study. Supported by several earlier reports, we suggested that switching to clozapine monotherapy may have improved this condition[44, 45].

Regarding the finding that parkinsonism may be a risk factor for a heightened mortality in patients with SMI, we discussed ways to proceed from here, ultimately aiming at reducing the excess mortality in patients with SMI.

An important question to start with is that of causation: how does parkinsonism lead to a shorter lifespan? Future studies should focus on this topic and determine if the heightened mortality is attributable to parkinsonism itself, or to a third factor. If the parkinsonian symptoms are responsible for the association, this would stress the need for more awareness of parkinsonism as a serious condition in clinical practice. Research suggests that currently, parkinsonism in patients with SMI is either under recognized, under treated, or that available treatments are not effective in this population. Clarification of what happens in clinical practice can provide starting points for improvement in prevention and treatment of parkinsonism and may ultimately help in reducing the excess mortality in SMI patients.

## Future directions

An important development in the field of movement abnormalities (MAs, including, but not limited to, the MDs studied in this thesis) in psychiatry is a renewed interest into MAs across different diagnoses and stages of illness[1, 2]. This is exemplified by the addition of a sensorimotor domain to the Research Domain Criteria (RDoC) of the National Institute for Mental Health (NIMH)[46]. Elucidating which MAs are prevalent across different psychiatric illnesses, and which are specific for certain diagnoses or correlate with symptom dimensions such as positive, negative, depressive, and cognitive symptoms, can provide more insight into shared and disorder-specific and/or symptom dimension related underlying processes and neural systems[2, 47]

Furthermore, inclusion of the sensorimotor domain in the RDoC may help to overcome the problem of overlap and ambiguity in concepts referring to different MAs and the distinction between normal and abnormal motor functioning.

Another promising way forward is the development of increasingly sophisticated electronical devices and apps for the measurement of MAs[4]. Important for the development of new devices is that they should take the whole body into account.

Given the prognostic value for unfavorable symptomatic and functional outcomes of MAs in psychotic disorders, future studies should determine if risk calculators for the development of psychosis in high-risk subjects can be improved by including MAs. Also, risk calculators assessing risk of adverse outcomes in first episode psychosis may be developed in which MAs may be included. Such risk calculators may be helpful in choosing optimal interventions for patients presenting with first episode psychosis.

# Nederlandse samenvatting

## Algemene inleiding

Bewegingsstoornissen vormen een integraal onderdeel van meerdere psychiatrische aandoeningen[1-3]. Hoewel er veel verschillende bewegingsstoornissen onderscheiden worden, richt dit proefschrift zich op de volgende drie bewegingsstoornissen:

*Dyskinesie*: een hyperkinetische bewegingsstoornis die tot uiting komt in onwillekeurige, onregelmatige en veelal vloeiende bewegingen. Deze bewegingen kunnen zich in het gehele lichaam voordoen maar het orofaciale gebied en de bovenste ledematen zijn het meest frequent aangedaan.

*Parkinsonisme*: een hypokinetische bewegingsstoornis die wordt gekenmerkt door bradykinesie, rusttremor en houdingsinstabiliteit.

*Acathisie*: een bewegingsstoornis bestaande uit een gevoel van rusteloosheid (het subjectieve symptoom) hetgeen veelal leidt tot bewegingen (objectieve symptomen). De rusteloosheid wordt vaak ervaren in de benen.

In dit proefschrift hebben we bewegingsstoornissen onderzocht vanuit drie perspectieven: in Deel I. bestudeerden we bewegingsstoornissen als symptoom van de onderliggende psychiatrische aandoening, in Deel II. bekeken we bewegingsstoornissen als bijwerking van antipsychotische medicatie, en in Deel III. onderzochten we of bewegingsstoornissen een risicofactor vormen voor een verkorte levensduur.

Zowel in de klinische praktijk als in wetenschappelijk onderzoek worden bewegingsstoornissen over het algemeen gemeten met behulp van meetschalen die zijn gebaseerd op observatie van de patiënt. In de afgelopen decennia zijn echter ook verschillende instrumenten ontwikkeld voor het meten van bewegingsstoornissen[4]. In de studies beschreven in hoofdstuk 2 en 3 hebben we een dergelijk instrument gebruikt voor het meten van dyskinesie, bradykinesie en tremor.

***Deel I. Bewegingsstoornissen als symptoom***

Het doel van hoofdstuk 2 was om inzicht te verkrijgen in de relatie tussen psychotische ervaringen en dyskinesie[5]. Om deze vraag te beantwoorden hebben we dyskinesie gemeten bij 34 mensen die auditieve verbale hallucinaties (AVHs) hadden zonder dat zij in aanmerking kwamen voor een psychiatrische diagnose

en een controlegroep van 31 gezonde mensen zonder AVHs. Dyskinesie werd vastgesteld door het meten van de variatie in uitgeoefende druk in de range van 0-3 Hz[6, 7]. De mate van schizotypie werd gemeten met de Schizotypal Personality Questionnaire. Dyskinesie en schizotypie lieten een significante positieve correlatie zien in de totale groep (Spearman's rho=0.32, p=0.005). Daarnaast keken we of er een verschil was in het percentage van personen die dyskinesie vertoonden in de groep met AVHS versus de controlegroep. Als definitie voor dyskinesie gebruikten we een afkappunt gebaseerd op de 95$^{ste}$ percentielscore in drukvariatie in de controlegroep. Een hoger percentage van de mensen in de AVH-groep (n=8, 23.5%) dan in de controlegroep (n=1, 3.2%;) had dyskinesie ($p$=0,019). De resultaten onderschrijven de intrinsieke relatie tussen bewegingsstoornissen en AVHs en ze zijn in overeenstemming met het concept van psychose als continu fenomeen.

In hoofdstuk 3 onderzochten we de aanwezigheid van bewegingsstoornissen bij kinderen en adolescenten/jong volwassenen met autismespectrumstoornissen (ASS)[8]. Parkinsonisme en dyskinesie werden gemeten bij 44 individuen met ASS en 49 zich 'normaal' ontwikkelende kinderen en jongeren die waren gematcht voor geslacht, leeftijd en IQ. De bewegingsstoornissen werden zowel met meetschalen, als met een mechanisch instrument[6, 7, 9, 10] gemeten. De analyses werden apart uitgevoerd voor kinderen (leeftijd 6-12 jaar) en adolescenten/jong volwassenen (leeftijd 13-26 jaar).

Met de Unified Parkinson's Disease Rating Scale (UPDRS) vonden we meer cases met bradykinesie in beide leeftijdscategorieën in de ASS-groep dan in de controlegroep ($p$<0.0001 voor beide leeftijdscategorieën). Bij de adolescenten/jong volwassenen zagen we meer rigiditeit in de ASS-groep dan in de controlegroep ($p$<0.0001). De instrumentele metingen lieten geen groepsverschillen zien.

De bevinding van een hogere sensitiviteit van de UPDRS vergeleken met het mechanische instrument was verrassend aangezien eerder onderzoek liet zien dat vergelijkbare instrumentele metingen over het algemeen sensitiever zijn dan meetschalen[7, 11]. Deze studies waren voornamelijk uitgevoerd bij patiënten met psychotische stoornissen. Om deze resultaten te verklaren hebben we als voorlopige hypothese gesteld dat de bewegingsstoornissen bij ASS veroorzaakt worden door andere onderliggende neuropathologie dan bij psychotische stoornissen. Bij kinderen en jongeren met ASS kan een verstorend effect van sociale informatieverwerking hebben opgetreden bij het uitvoeren van de bewegingen die gevraagd worden bij het afnemen van de meetschalen.

***Deel II. Bewegingsstoornissen als bijwerking***

De doelstelling van hoofdstuk 4 was om het risico op antipsychotica-geïnduceerde bewegingsstoornissen bij borderline persoonlijkheidsstoornis (BPS) te bepalen[12]. Antipsychotica worden vaak off-label voorgeschreven BPS. Er is echter nog nauwelijks onderzoek gedaan naar bewegingsstoornissen bij deze patiënten. Wij voerden een meta-analyse uit naar het voorkomen van parkinsonisme, acathisie en dyskinesie. Daarbij maakten we gebruik van metingen van deze bewegingsstoornissen uit gerandomiseerde, placebogecontroleerde studies die de effectiviteit en bijwerkingen van antipsychotica bij BPD onderzochten. Er werden drie studies naar olanzapine[13-15] en één studie naar ziprazidon[16] geïncludeerd. De resultaten lieten geen hoger risico op bewegingsstoornissen zien bij de patiënten die een antipsychoticum kregen voorgeschreven in vergelijking met een placebo. Deze bevindingen komen overeen met observaties dat lage tot gemiddelde doseringen van olanzapine (5-10 mg/dag) minder dan 78% van de striatale dopamine $D_2$ receptors bezetten, hetgeen de drempelwaarde is waarboven parkinsonisme over het algemeen ontstaat[17, 18]. Hoewel er voor acathisie en dyskinesie geen dergelijke duidelijke drempelwaarde is, hebben ook deze bewegingsstoornissen een grotere kans om op te treden bij hogere doseringen van antipsychotica en middelen met een hogere affiniteit voor de $D_2$ receptor[19-21]. Daarnaast dragen de anticholinerge eigenschappen van olanzapine waarschijnlijk bij aan het lage risico op bewegingsstoornissen van dit antipsychoticum[22, 23]. Een beperking van de studie was dat door het uitsluitend includeren van gerandomiseerde, placebogecontroleerde studies, er waarschijnlijk selectiebias is opgetreden. Terughoudendheid is daarom geboden met het generaliseren van de resultaten naar alle patiënten met BPS.

In hoofdstuk 5 presenteerden we de eerste publicatie van een open label gerandomiseerde studie naar de effecten van het switchen van een combinatie van eerste en tweede generatie antipsychotica naar antipsychotische monotherapie[24]. Ondanks dat de evidentie voor de effectiviteit van antipsychotische polyfarmacie tegenstrijdig is[25, 26], worden combinaties vaak voorgeschreven aan langdurig opgenomen patiënten met schizofrenie[27]. De huidige studie onderzocht de effecten van het switchen van een combinatie van eerste en twee generatie antipsychotica naar één antipsychoticum op de mate van terugval en psychiatrische symptomen. Patiënten met psychotische stoornissen die behandeld werden op langdurige opnameafdelingen konden deelnemen aan de studie. De geïncludeerde patiënten (n=136) werden gerandomiseerd naar een afbouw- en een controlegroep. Bij de patiënten in de afbouwgroep werden ofwel de eerste generatie antipsychotica, ofwel de tweede generatie antipsychotica afgebouwd over een periode van maximaal drie maanden. Patiënten in de controlegroep

zetten de antipsychotische polyfarmacie voort. Psychiatrische symptomen werden gemeten met de Brief Psychiatric Rating Scale (BPRS) op baseline en bij follow-ups bij drie, zes en negen maanden. Terugval was gedefinieerd als (i) een toename van de BPRS van 2 punten of meer in een afzonderlijk item of (ii) een toename van 4 punten of meer in de BPRS-totaalscore, in combinatie met de noodzaak tot aanpassing van de antipsychotische medicatie. Een logistisch regressiemodel gecorrigeerd voor geslacht liet zien dat de odds voor terugval significant lager was in de afbouw- dan in de controlegroep, odds ratio=0.29 (95% betrouwbaarheidsinterval=0.13-0.62). Uit post-hoc analyses bleek dat het beschermende effect van afbouwen toe te schrijven was aan de patiënten die clozapine behielden als monotherapie. Bij de patiënten die geen terugval hadden en niet uitgevallen waren, nam de BPRS-totaalscore sterker af in de afbouw- dan in de controlegroep ($p$=0.0001). De resultaten van de studie laten zien dat het afbouwen van een combinatie van eerste en tweede generatie antipsychotica naar één antipsychoticum veilig is wat betreft het risico op terugval. Bij patiënten die clozapine in combinatie met een eerste generatie antipsychoticum voorgeschreven krijgen kan afbouwen naar clozapine monotherapie dit risico zelfs verminderen.

***Deel III. Bewegingsstoornissen als risicofactor voor mortaliteit***

De studie beschreven in hoofdstuk 6 had als doel om een mogelijk verband tussen bewegingsstoornissen en mortaliteit bij patiënten met ernstige psychiatrische aandoeningen (EPA) te onderzoeken[28]. Patiënten met EPA hebben een fors verkorte levensverwachting ten opzichte van mensen uit de algemene bevolking[29, 30] en het is van belang te achterhalen welke factoren hierop van invloed zijn. Sommige studies lieten zien dat bewegingsstoornissen samenhangen met een verhoogde mortaliteit maar andere vonden geen verband[31-33]. Wij onderzochten of tardieve dyskinesie, parkinsonisme en acathisie, samenhangen met mortaliteit bij Afro-Caribische opgenomen patiënten met EPA. Daarvoor gebruikten we data van een cohort van 157 patiënten met voornamelijk schizofrenie die behandeld werden in het enige psychiatrische ziekenhuis van Curaçao. Tardieve dyskinesie, parkinsonisme en acathisie waren acht keer gemeten met meetschalen over een periode van achttien jaar. Vierentwintig jaar na de baselinemeting werd vastgesteld welke patiënten wanneer overleden waren. We gebruikten Cox regressie modellen om hazard ratio's (HRs) te berekenen voor de drie bewegingsstoornissen. Geslacht, leeftijd en het gebruik van antipsychotica, antidepressiva en benzodiazepines op ieder meetmoment werden getest als covariaten. De resultaten wezen uit dat parkinsonisme een significante risicofactor was met een HR van 1.02 per punt op de UPDRS (range 0-56). De standaarddeviatie lag rond de tien punten, en een toename van tien punten zou leiden tot een toename in de HR

voor mortaliteit van 21%. Tardieve dyskinesie en acathisie vertoonden geen significant verband met mortaliteit. De bevinding van parkinsonisme als significante risicofactor komt overeen met resultaten bij ouderen[34] en bij patiënten met de ziekte van Alzheimer en Parksinon[35, 36]. Deze bevinding bij patiënten met EPA dient gerepliceerd te worden. Bij voldoende evidentie kan zij dienen als aanknopingspunt voor nieuwe interventies. Dergelijke interventies zouden op den duur kunnen helpen om de oversterfte bij patiënten met EPA terug te dringen.

## Algemene discussie

In de Algemene discussie werden de belangrijkste resultaten van de studies in dit proefschrift samengevat en sommige opvallende resultaten werden nader en in een bredere context besproken.

We beschouwden de bevindingen uit de studie naar dyskinesie bij mensen met AVH in het licht van een mogelijke prognostische waarde van bewegingsstoornissen voor een ongunstig beloop. In onze studie troffen we vaker dyskinesie aan in de AVH groep (24%) dan in controlegroep (3%). Een follow-up studie naar de geestelijke gezondheid van de mensen met AVH had laten zien dat vijf jaar na de baseline meting, een relatief hoog percentage (39%) van deze mensen een hulpvraag naar geestelijke gezondheidszorg had ontwikkeld[37]. Ook was bij een wat hoger percentage dan verwacht op basis van gegevens uit de algemene bevolking een psychose ontstaan (6%). Talrijke studies hebben aangetoond dat bewegingsstoornissen een prognostische waarde hebben voor het ontwikkelen van een psychose bij jongeren geclassificeerd als clinical high-risk (CHR) of ultra high-risk (UHR) voor psychose en voor een ongunstig beloop zowel bij mensen met een eerste psychose als chronische psychotische aandoeningen[38, 39]. Onze verwachting is daarom dat bewegingsstoornissen ook bij mensen met AVH een prognostische waarde kunnen hebben voor het ontwikkelen van een psychose of een hulpvraag naar geestelijke gezondheidszorg.

Een verrassende uitkomst van de studie naar bewegingsstoornissen bij kinderen en adolescenten/jong volwassenen met ASS was het gebrek aan overeenkomst in de uitkomsten van de meetschalen en het mechanische instrument. Deze resultaten zijn nader besproken in een mini review van eerdere studies naar de sensitiviteit en validiteit van de gebruikte instrumentele methode. Deze eerdere studies waren voornamelijk uitgevoerd bij patiënten met psychotische stoornissen[7, 9-11, 40]. We concludeerden dat er enige onderbouwing is dat deze instrumentele metingen over het algemeen gevoeliger zijn dan meetschalen. De resultaten ten aanzien van de concurrente validiteit waren niet eenduidig. Een deel van het gebrek aan overeenkomst tussen beide meetmethoden kan verklaard worden

doordat met het instrument alleen de armen/handen gemeten worden terwijl bij de meetschalen het hele lichaam in ogenschouw genomen wordt.

Bij de studie naar het switchen van antipsychotische polyfarmacie naar monotherapie was een opvallend resultaat dat de patiënten die overgestapt waren naar clozapine monotherapie, een lagere kans op terugval hadden dan de patiënten die de antipsychotische polyfarmacie voortgezet hadden (clozapine in combinatie met ten minste één eerste generatie middel). Deze bevinding hebben we geprobeerd te verklaren vanuit de dopamine supersensitiviteitshypothese. Deze hypothese luidt dat langdurige blokkade van dopamine $D_2$ receptoren door dopamine antagonisten leidt tot een upregulatie van de $D_2$ receptoren en/of het percentage van de $D_2$ receptoren in een staat van verhoogde affiniteit ($D_2^{Hoog}$), hetgeen kan leiden tot dopamine supersensitiviteitspsychose[41]. Mogelijk was er bij een groot deel van de patiënten die deelnamen aan onze studie, sprake van dopamine supersensitiviteit. Ondersteund door enkele eerdere publicaties stelden wij dat de overstap naar clozapine monotherapie vermindering van de dopamine supersensitiviteit kan hebben bewerkstelligd en op deze manier tot een verminderde kans op terugval heeft geleid[42, 43].

De belangrijkste uitkomst van de studie naar bewegingsstoornissen en mortaliteit was dat parkinsonisme het risico op vroegtijdig overlijden bij patiënten met EPA lijkt te verhogen. We behandelden de vraag welke vervolgstappen genomen zouden kunnen worden om uiteindelijk de oversterfte bij mensen met EPA te verminderen. Een eerste vraag voor vervolgonderzoek is hoe het oorzakelijk verband in elkaar steekt. Hierbij is het essentieel om te achterhalen of de verhoogde mortaliteit is toe te schrijven aan het parkinsonisme zelf, of aan andere factoren. Als symptomen van parkinsonisme zelf leiden tot een verhoogde mortaliteit is het van belang het bewustzijn dat parkinsonisme een ernstige aandoening is, te verhogen in de klinische praktijk. Onderzoek heeft uitgewezen dat parkinsonisme bij patiënten met EPA onvoldoende herkend en/of onvoldoende behandeld wordt, of dat de beschikbare behandelopties slechts een beperkte effectiviteit hebben bij deze mensen. Meer duidelijkheid ten aanzien van huidige behandelpraktijken kan als aanknopingspunt dienen om de situatie te verbeteren en uiteindelijk mogelijk de oversterfte bij EPA-patiënten te verminderen.

## Suggesties voor toekomstig onderzoek

Een belangrijke ontwikkeling in het onderzoek naar bewegingsafwijkingen in de psychiatrie is een vernieuwde interesse in bewegingsafwijkingen bij meerdere psychiatrische ziektebeelden en gedurende verschillende ziektestadia[1, 2]. Een uiting hiervan is de toevoeging van een sensorimotor domein aan de Research

Domain Criteria (RDoC) van het National Institute for Mental Health (NIMH)[44]. Meer kennis over welke bewegingsafwijkingen voorkomen bij meerdere psychiatrische aandoeningen en welke specifiek zijn voor bepaalde diagnoses, en welke bewegingsafwijkingen samenhangen met andere symptoomdimensies zoals positieve, negatieve, depressieve en cognitieve symptomen, kan helpen met het verhelderen van onderliggende mentale processen[2, 45].

Daarnaast kan de toevoeging van het sensorimotor domein aan de RDoC zorgen voor meer duidelijkheid in de definities en afbakeningen van verschillende bewegingsafwijkingen en het onderscheid tussen normaal en abnormaal motorisch functioneren.

Een andere veelbelovende weg vooruit is de ontwikkeling van steeds geavanceerdere elektronische apparaten en apps voor met meten van bewegingsafwijkingen[4]. Voor een compleet beeld van de bewegingsafwijkingen is het van belang dat nieuwe instrumenten het gehele lichaam of in ieder geval meer dan een gebied, in ogenschouw nemen. Bewegingsafwijkingen hebben een prognostische waarde voor een ongunstig beloop van psychotische stoornissen. Recent ontwikkelde algoritmes voor het berekenen van het risico op psychose bij risicogroepen[46], zouden daarom verbeterd kunnen worden door toevoeging van bewegingsmetingen. Ook kunnen vergelijkbare algoritmes ontwikkeld worden om een inschatting te maken van de kans op een ongunstig beloop bij patiënten met een eerste psychose. Dit zou behulpzaam kunnen zijn voor clinici bij het kiezen van optimale interventies voor deze patiënten.

# References/Referenties


1. Hirjak D, Meyer-Lindenberg A, Fritze S, Sambataro F, Kubera KM, Wolf RC. Motor dysfunction as research domain across bipolar, obsessive-compulsive and neurodevelopmental disorders. *Neuroscience and biobehavioral reviews* Dec 2018;95:315-335.
2. Peralta V, Cuesta MJ. Motor Abnormalities: From Neurodevelopmental to Neurodegenerative Through "Functional" (Neuro)Psychiatric Disorders. *Schizophrenia bulletin* Sep 1 2017;43(5):956-971.
3. van Harten PN, Bakker PR, Mentzel CL, Tijssen MA, Tenback DE. Movement Disorders and Psychosis, a Complex Marriage. *Frontiers in Psychiatry* 2015-January-09 2015;5(190).
4. van Harten PN, Walther S, Kent JS, Sponheim SR, Mittal VA. The clinical and prognostic value of motor abnormalities in psychosis, and the importance of instrumental assessment. *Neuroscience and biobehavioral reviews* Sep 2017;80:476-487.
5. Willems AE, Sommer IE, Tenback DE, Koning JP, van Harten PN. Instrumental measurements of spontaneous dyskinesia and schizotypy in subjects with auditory verbal hallucinations and healthy controls. *Psychiatry research* Oct 30 2016;244:24-27.
6. Lohr JB, Caligiuri MP. Quantitative instrumental measurement of tardive dyskinesia: a review. *Neuropsychopharmacology* 1992;6(4):231-239.
7. Koning JP, Kahn R, Tenback DE, van Schelven LJ, van Harten PN. Movement disorders in nonpsychotic siblings of patients with nonaffective psychosis. *Psychiatry Res* 2011;188(1):133-137.
8. Mostert-Kerckhoffs MAL, Willems AE, Tenback DE, Koning JP, Van Harten P, Staal WG. Motor Disturbance in ASD: A Pilot Study Showing Hypokinetic Behavior? *J Autism Dev Disord* Feb 2020;50(2):415-428.
9. Caligiuri MP, Lohr JB. Fine force instability: a quantitative measure of neuroleptic-induced dyskinesia in the hand. *J Neuropsychiatr* 1990;2:395-398.
10. Caligiuri MP, Lohr JB, Ruck RK. Scaling of movement velocity: A measure of neuromotor retardation in individuals with psychopathology. *Psychophysiology* 1998;35(4):431-437.
11. Cortese L, Caligiuri MP, Malla AK, Manchanda R, Takhar J, Haricharan R. Relationship of neuromotor disturbances to psychosis symptoms in first-episode neuroleptic-naive schizophrenia patients. *Schizophr Res* 2005;75(1):65-75.
12. Willems AE, Tenback DE, Ingenhoven TJ, van Harten PN. Acute movement disorders associated with the use of second-generation antipsychotics in borderline personality disorder: a meta-analysis. *Journal of clinical psychopharmacology* Aug 2014;34(4):520-522.
13. Soler J, Pascual JC, Campins J, Barrachina J, Puigdemont D, Alvarez E, Perez V. Double-Blind, Placebo-Controlled Study of Dialectical Behavior Therapy Plus Olanzapine for Borderline Personality Disorder. *The American journal of psychiatry* Jun 2005;162(6):1221-1224.
14. Schulz S, Zanarini MC, Bateman A, et al. Olanzapine for the treatment of borderline personality disorder: Variable dose 12-week randomised double-blind placebo-controlled study. *British Journal of Psychiatry* Dec 2008;193(6):485-492.

15. Zanarini MC, Schulz SC, Holland CD, et al. A dose comparison of olanzapine for the treatment of borderline personality disorder: a 12-week randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2011;72(10):1353-1362.
16. Pascual JC, Soler J, Puigdemont D, Pérez-Egea R, Tiana T, Alvarez E, Pérez V. Ziprasidone in the treatment of borderline personality disorder: a double blind, placebo controlled, randomized study. *J Clin Psychiatry* 2008;69(4):603-608.
17. Kapur S, Zipursky RB, Jones C, Remington G, Houle S. Relationship between dopamine D2 occupancy, clinical respons, and side effects: a double-blind PET study of first episode schizophrenia. *Am J Psychiatry* 2000;157(4):514-520.
18. Frankle WG, Gil R, Hackett E, et al. Occupancy of dopamine D2; receptors by the atypical antipsychotic drugs risperidone and olanzapine: theoretical implications. *Psychopharmacology (Berl)* 2004;175(4):473-480.
19. Sachdev P. The epidemiology of drug-induced akathisia: Part I. Acute akathisia. *Schizophrenia bulletin* 1995;21(3):431-449.
20. Miller CH, Fleischhacker WW. Managing antipsychotic-induced acute and chronic akathisia. *Drug Saf* Jan 2000;22(1):73-81.
21. Tenback DE, van Harten PN, Slooff CJ, Belger MA, van Os J. Effects of antipsychotic treatment on tardive dyskinesia: a 6-month evaluation of patients from the European Schizophrenia Outpatient Health Outcomes (SOHO) Study. *The Journal of clinical psychiatry* Sep 2005;66(9):1130-1133.
22. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Kissling W, Davis JM, Leucht S. Second-Generation Antipsychotic Drugs and Extrapyramidal Side Effects: A Systematic Review and Meta-analysis of Head-to-Head Comparisons. *Schizophr Bull* January 1, 2012 2010;38(1):167-177.
23. Chew ML, Mulsant BH, Pollock BG, et al. A model of anticholinergic activity of atypical antipsychotic medications. *Schizophr Res* 2006;88(1-3):63-72.
24. Shakir M, Willems AE, van Harten PN, van Lutterveld R, Tenback DE. The effect on relapse rate and psychiatric symptomatology: Switching a combination of first- and second-generation antipsychotic polypharmacy to antipsychotic monotherapy in long-term inpatients with schizophrenia and related disorders. A pragmatic randomized open-label trial (SwAP trial). *Schizophr Res* 2022/05/01/ 2022;243:187-194.
25. Galling B, Roldan A, Hagi K, et al. Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis. *World psychiatry : official journal of the World Psychiatric Association (WPA)* Feb 2017;16(1):77-89.
26. Tiihonen J, Taipale H, Mehtälä J, Vattulainen P, Correll CU, Tanskanen A. Association of Antipsychotic Polypharmacy vs Monotherapy With Psychiatric Rehospitalization Among Adults With Schizophrenia. *JAMA psychiatry* May 1 2019;76(5):499-507.
27. Gallego JA, Bonetti J, Zhang J, Kane JM, Correll CU. Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. *Schizophrenia research* Jun 2012;138(1):18-28.
28. Willems AE, Mentzel CL, Bakker PR, et al. Movement Disorders and Mortality in Severely Mentally Ill Patients: The Curacao Extrapyramidal Syndromes Study XIV. *Schizophrenia bulletin* Jun 21 2022;48(4):766-773.

29. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? *Archives of General Psychiatry* 2007;64(10):1123-1131.
30. Lomholt LH, Andersen DV, Sejrsgaard-Jacobsen C, et al. Mortality rate trends in patients diagnosed with schizophrenia or bipolar disorder: a nationwide study with 20 years of follow-up. *International Journal of Bipolar Disorders* 2019/03/01 2019;7(1):6.
31. Ballesteros J, Gonzáles-Pinto A, Bulbena A. Tardive dyskinesia associated with higher mortality in psychiatric patients: results of a meta-analysis of seven independent studies. *J Clin Psychopharmacol* 2000;20(2):188-194.
32. Modestin J, Vogt Wehrli M, Stephan PL, Agarwalla P. Relationship between Neuroleptic Extrapyramidal Syndromes and Patients' All-Cause Mortality. *Pharmacopsychiatry* 2009;42(02):57-60.
33. Schoepf D, Uppal H, Potluri R, Heun R. Physical comorbidity and its relevance on mortality in schizophrenia: a naturalistic 12-year follow-up in general hospital admissions. *Eur Arch Psychiatry Clin Neurosci* 2014;264(1):3-28.
34. Bennett DA, Beckett LA, Murray AM, Shannon KM, Goetz CG, Pilgrim DM, Evans DA. Prevalence of Parkinsonian Signs and Associated Mortality in a Community Population of Older People. *N Engl J Med* 1996;334(2):71-76.
35. Mitchell SL, Rockwood K. The Association Between Parkinsonism, Alzheimer's Disease, and Mortality: A Comprehensive Approach. *J Am Geriatr Soc* 2000;48(4):422-425.
36. Santos-García D, Suárez-Castro E, Ernandez J, et al. Predictors of Mortality in Nondemented Patients With Parkinson Disease: Motor Symptoms Versus Nonmotor Symptoms. *J Geriatr Psychiatry Neurol* 2018;31(1):19-26.
37. Daalman K, Diederen KM, Hoekema L, van Lutterveld R, Sommer IE. Five year follow-up of non-psychotic adults with frequent auditory verbal hallucinations: are they still healthy? *Psychological medicine* Jul 2016;46(9):1897-1907.
38. Pieters LE, Nadesalingam N, Walther S, van Harten PN. A systematic review of the prognostic value of motor abnormalities on clinical outcome in psychosis. *Neuroscience and biobehavioral reviews* Jan 2022;132:691-705.
39. Nadesalingam N, Chapellier V, Lefebvre S, et al. Motor abnormalities are associated with poor social and functional outcomes in schizophrenia. *Compr Psychiatry* 2022/05/01/ 2022;115:152307.
40. Dean CE, Russel JM, Kuskowski MA, Caligiuri MP, Nugent SM. Clinical rating scales and instruments. How do they compare in assessing abnormal involuntary movements? *Journal of clinical psychopharmacology* 2004;24:298-304.
41. Chouinard G, Samaha AN, Chouinard VA, Peretti CS, Kanahara N, Takase M, Iyo M. Antipsychotic-Induced Dopamine Supersensitivity Psychosis: Pharmacology, Criteria, and Therapy. *Psychotherapy and Psychosomatics* 2017;86(4):189-219.
42. Chouinard G, Vainer JL, Bélanger MC, Turnier L, Beaudry P, Roy JY, Miller R. Risperidone and clozapine in the treatment of drug-resistant schizophrenia and neuroleptic-induced supersensitivity psychosis. *Progress in neuro-psychopharmacology & biological psychiatry* Nov 1994;18(7):1129-1141.
43. Nakata Y, Kanahara N, Kimura H, Watanabe H, Iyo M. Efficacy of clozapine on dopamine supersensitivity psychosis in schizophrenia. *International clinical psychopharmacology* May 2017;32(3):169-173.

44. NIMH. https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/about-rdoc. *National Institute of Mental Health*. Accessed January 9 2023, 2023.
45. Bernard JA, Mittal VA. Updating the research domain criteria: the utility of a motor dimension. *Psychological medicine* Oct 2015;45(13):2685-2689.
46. Koutsouleris N, Worthington M, Dwyer DB, et al. Toward Generalizable and Transdiagnostic Tools for Psychosis Prediction: An Independent Validation and Improvement of the NAPLS-2 Risk Calculator in the Multisite PRONIA Cohort. *Biological psychiatry* Nov 1 2021;90(9):632-642.

# Impact

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

# References


1. van Harten PN, Matroos GE, Hoek HW, Kahn RS. The prevalence of tardive dystonia, tardive dyskinesia, parkinsonism and akathisia. The Curaçao Extrapyramidal Syndromes Study: I. *Schizophr Res* 1996;19(195-203).
2. Bakker PR, de Groot IW, van Os J, van Harten PN. Long-Stay Psychiatric Patients: A Prospective Study Revealing Persistent Antipsychotic-Induced Movement Disorder. *PLoS One* 2011;6(10):e25588.
3. Peralta V, Cuesta MJ. Motor Abnormalities: From Neurodevelopmental to Neurodegenerative Through "Functional" (Neuro)Psychiatric Disorders. *Schizophrenia bulletin* Sep 1 2017;43(5):956-971.
4. Hirjak D, Meyer-Lindenberg A, Fritze S, Sambataro F, Kubera KM, Wolf RC. Motor dysfunction as research domain across bipolar, obsessive-compulsive and neurodevelopmental disorders. *Neuroscience and biobehavioral reviews* Dec 2018;95:315-335.
5. Koning JPF, Tenback DE, van Os J, Aleman A, Kahn RS, van Harten PN. Dyskinesia and Parkinsonism in Antipsychotic-Naive Patients With Schizophrenia, First-Degree Relatives and Healthy Controls: A Meta-analysis. *Schizophr Bull* July 1, 2010 2010;36(4):723-731.
6. Pappa S, Dazzan P. Spontaneous movement disorders in antipsychotic-naive patients with first-episode psychoses: a systematic review. *Psychol Med* 2009;39(07):1065-1076.
7. Ayehu M, Shibre T, Milkias B, Fekadu A. Movement disorders in neuroleptic-naïve patients with schizophrenia spectrum disorders. *BMC Psychiatry* Oct 9 2014;14:280.
8. Dean DJ, Mittal VA. Spontaneous parkinsonisms and striatal impairment in neuroleptic free youth at ultrahigh risk for psychosis. *NPJ Schizophr* 2015;1:14006-.
9. Mittal VA, Neumann C, Saczawa M, Walker EF. Longitudinal progression of movement abnormalities in relation to psychotic symptoms in adolescents at high risk of schizophrenia. *Archives of General Psychiatry* 2008;65(2):165-171.
10. Dean DJ, Bernard JA, Damme KSF, O'Reilly R, Orr JM, Mittal VA. Longitudinal Assessment and Functional Neuroimaging of Movement Variability Reveal Novel Insights Into Motor Dysfunction in Clinical High Risk for Psychosis. *Schizophrenia bulletin* Dec 1 2020;46(6):1567-1576.
11. Peralta V, Cuesta MJ. The effect of antipsychotic medication on neuromotor abnormalities in neuroleptic-naive nonaffective psychotic patients: a naturalistic study with haloperidol, risperidone, or olanzapine. *Prim Care Companion J Clin Psychiatry* 2010;12(2).
12. Ballesteros J, Gonzáles-Pinto A, Bulbena A. Tardive dyskinesia associated with higher mortality in psychiatric patients: results of a meta-analysis of seven independent studies. *J Clin Psychopharmacol* 2000;20(2):188-194.
13. Schoepf D, Uppal H, Potluri R, Heun R. Physical comorbidity and its relevance on mortality in schizophrenia: a naturalistic 12-year follow-up in general hospital admissions. *Eur Arch Psychiatry Clin Neurosci* 2014;264(1):3-28.
14. Dean CE, Thuras PD. Mortality and tardive dyskinesia: long-term study using the US National Death Index. *The British Journal of Psychiatry* 2009-04-01 00:00:00 2009;194(4):360-364.

15. Modestin J, Vogt Wehrli M, Stephan PL, Agarwalla P. Relationship between Neuroleptic Extrapyramidal Syndromes and Patients' All-Cause Mortality. *Pharmacopsychiatry* 2009;42(02):57-60.
16. Willems AE, Sommer IE, Tenback DE, Koning JP, van Harten PN. Instrumental measurements of spontaneous dyskinesia and schizotypy in subjects with auditory verbal hallucinations and healthy controls. *Psychiatry research* Oct 30 2016;244:24-27.
17. Raine A. The SPQ: A Scale for the Assessment of Schizotypal Personality Based on DSM-III-R Criteria. *Schizophr Bull* January 1, 1991 1991;17(4):555-564.
18. Vollema MG, Sitskoorn MM, Appels MCM, Kahn RS. Does the Schizotypal Personality Questionnaire reflect the biological -genetic vulnerability to schizophrenia? *Schizophr Res* 2002;54(1-2):39-45.
19. Caligiuri MP, Lohr JB. Fine force instability: a quantitative measure of neuroleptic-induced dyskinesia in the hand. *J Neuropsychiatr* 1990;2:395-398.
20. Dean CE, Russel JM, Kuskowski MA, Caligiuri MP, Nugent SM. Clinical rating scales and instruments. How do they compare in assessing abnormal involuntary movements? *Journal of clinical psychopharmacology* 2004;24:298-304.
21. Cortese L, Caligiuri MP, Malla AK, Manchanda R, Takhar J, Haricharan R. Relationship of neuromotor disturbances to psychosis symptoms in first-episode neuroleptic-naive schizophrenia patients. *Schizophr Res* 2005;75(1):65-75.
22. Koning JP, Kahn R, Tenback DE, van Schelven LJ, van Harten PN. Movement disorders in nonpsychotic siblings of patients with nonaffective psychosis. *Psychiatry Res* 2011;188(1):133-137.
23. van Os J, Hanssen M, Bijl RV, Ravelli A. Strauss (1969) revisited: a psychosis continuum in the general population? *Schizophr Res* 2000;45(1-2):11-20.
24. Sommer IE. The continuum hypothesis of psychosis: David's criticisms are timely. *Psychol Med* 2010;40(12):1959-1961.
25. van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychol Med* 2009;39(02):179-195.
26. Baumeister D, Sedgwick O, Howes O, Peters E. Auditory verbal hallucinations and continuum models of psychosis: A systematic review of the healthy voice-hearer literature. *Clin Psychol Rev* Feb 2017;51:125-141.
27. Mostert-Kerckhoffs MAL, Willems AE, Tenback DE, Koning JP, Van Harten P, Staal WG. Motor Disturbance in ASD: A Pilot Study Showing Hypokinetic Behavior? *J Autism Dev Disord* Feb 2020;50(2):415-428.
28. Ozonoff S. Reliability and validity of the Wisconsin Card Sorting Test in studies of autism. *Neuropsychology* 1995;9(4):491-500.
29. Willems AE, Tenback DE, Ingenhoven TJ, van Harten PN. Acute movement disorders associated with the use of second-generation antipsychotics in borderline personality disorder: a meta-analysis. *Journal of clinical psychopharmacology* Aug 2014;34(4):520-522.
30. Soler J, Pascual JC, Campins J, Barrachina J, Puigdemont D, Alvarez E, Perez V. Double-Blind, Placebo-Controlled Study of Dialectical Behavior Therapy Plus Olanzapine for Borderline Personality Disorder. *The American journal of psychiatry* Jun 2005;162(6):1221-1224.

31. Schulz S, Zanarini MC, Bateman A, et al. Olanzapine for the treatment of borderline personality disorder: Variable dose 12-week randomised double-blind placebo-controlled study. *British Journal of Psychiatry* Dec 2008;193(6):485-492.
32. Zanarini MC, Schulz SC, Holland CD, et al. A dose comparison of olanzapine for the treatment of borderline personality disorder: a 12-week randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2011;72(10):1353-1362.
33. Pascual JC, Soler J, Puigdemont D, Pérez-Egea R, Tiana T, Alvarez E, Pérez V. Ziprasidone in the treatment of borderline personality disorder: a double blind, placebo controlled, randomized study. *J Clin Psychiatry* 2008;69(4):603-608.
34. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Kissling W, Davis JM, Leucht S. Second-Generation Antipsychotic Drugs and Extrapyramidal Side Effects: A Systematic Review and Meta-analysis of Head-to-Head Comparisons. *Schizophr Bull* January 1, 2012 2010;38(1):167-177.
35. Kapur S, Zipursky RB, Remington G, Jones C, DaSilva J, Wilson AA, Houle S. 5-HT2 and D2 receptor occupancy ol olanzapine in schizophrenia: a PET investigation. *Am J Psychiatry* 1998;155(7):8.
36. Shakir M, Willems AE, van Harten PN, van Lutterveld R, Tenback DE. The effect on relapse rate and psychiatric symptomatology: Switching a combination of first- and second-generation antipsychotic polypharmacy to antipsychotic monotherapy in long-term inpatients with schizophrenia and related disorders. A pragmatic randomized open-label trial (SwAP trial). *Schizophr Res* 2022/05/01/ 2022;243:187-194.
37. Seeman P, Corbett R, Van Tol HHM. Atypical Neuroleptics Have Low Affinity for Dopamine D2 Receptors or Are Selective for D4 Receptors. *Neuropsychopharmacology* 1997/02/01 1997;16(2):93-110.
38. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *The Lancet* 2009/1/9/ 2009;373(9657):31-41.
39. Gründer G, Hippius H, Carlsson A. The 'atypicality' of antipsychotics: a concept re-examined and re-defined. *Nat Rev Drug Discov* Mar 2009;8(3):197-202.
40. Stuurgroep multidisciplinaire richtlijnontwikkeling GGZ. Multidisciplinaire richtlijn schizofrenie (Dutch Clinical guideline for Schizophrenia). 2012.
41. Willems AE, Mentzel CL, Bakker PR, et al. Movement Disorders and Mortality in Severely Mentally Ill Patients: The Curacao Extrapyramidal Syndromes Study XIV. *Schizophrenia bulletin* Jun 21 2022;48(4):766-773.
42. Laursen TM. Life expectancy among persons with schizophrenia or bipolar affective disorder. *Schizophr Res* 2011;131(1-3):101-104.
43. Crump C, Winkleby MA, Sundquist K, Sundquist J. Comorbidities and Mortality in Persons With Schizophrenia: A Swedish National Cohort Study. *Am J Psychiatry* 2013;170(3):324-333.
44. Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, Haukka J. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *The Lancet* 2009/8/28/ 2009;374(9690):620-627.
45. Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and mortality in bipolar disorder: A swedish national cohort study. *JAMA psychiatry* 2013;70(9):931-939.

46. Heald A, Pendlebury J, Anderson S, Narayan V, Guy M, Gibson M, Haddad P, Livingston M. Lifestyle factors and the metabolic syndrome in Schizophrenia: a cross-sectional study. *Annals of General Psychiatry* 2017;16(1):12.
47. De Hert M, Correll CU, Bobes J, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World psychiatry : official journal of the World Psychiatric Association (WPA)* 2011;10:52-77.
48. Lei C, Sunzi K, Dai F, Liu X, Wang Y, Zhang B, He L, Ju M. Effects of virtual reality rehabilitation training on gait and balance in patients with Parkinson's disease: A systematic review. *PLoS One* 2019;14(11):e0224819.
49. Hulzinga F, de Rond V, Vandendoorent B, Gilat M, Ginis P, D'Cruz N, Schlenstedt C, Nieuwboer A. Repeated Gait Perturbation Training in Parkinson's Disease and Healthy Older Adults: A Systematic Review and Meta-Analysis. *Front Hum Neurosci* 2021;15:732648.
50. Liu WY, Tung TH, Zhang C, Shi L. Systematic review for the prevention and management of falls and fear of falling in patients with Parkinson's disease. *Brain Behav* Aug 2022;12(8):e2690.
51. Bakker PR. *Drug-induced movement disorders in long-stay psychiatric patients. Genetic and non-genetic risk factors: A prospective study.* Maastricht, Maastricht University; 2012.

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*"There can be no doubt, I thought, pushing aside the newspaper, that our mean lives, unsightly as they are, put on splendour and have meaning only under the eyes of love*"

*- Virginia Woolf, the Waves.*

# Curriculum vitae

Anna (Anne) Eliza Willems werd geboren op 25 mei 1982 te Leiden, Nederland. In 2001 behaalde zij haar gymnasium diploma aan het Stedelijk Gymnasium Leiden. Zij studeerde Psychologie met als specialisatie Neuropsychologie aan de Universiteit Utrecht, waarvoor zij in 2006 haar doctoraal/MSc behaalde. Vervolgens werkte zij een jaar als onderzoeksmedewerker bij het Universitair Medisch Centrum Utrecht. In 2008 startte zij bij GGz Centraal (destijds Symfora Groep) en werd binnen een jaar coördinator wetenschappelijk onderzoek. In 2013 werd zij master Klinische Epidemiologie aan het Netherlands Institute for Health Sciences. In 2012 begon zij, naast haar werk als onderzoekscoördinator, met het promotietraject aan de Universiteit Maastricht met als promotieteam prof. dr. P.N. van Harten en dr. D.E. Tenback. Bij GGz Centraal heeft ze bijgedragen aan de valorisatie van Routine Outcome Monitoring (ROM) data. Ze analyseerde de gegevens van de instelling op teamniveau en gaf terugkoppeling aan de betreffende teams in presentaties en workshops. Daarnaast verwierf ze een subsidie voor het onderzoek ‘Therapie op Maat’ dat gericht was op meer eigen regie en het bevorderen van de gezondheid van cliënten in de langdurige klinische zorg. Ze was projectleider van ditzelfde onderzoek. In 2019 won de ze de posterprijs bij Voorjaarscongres van de Nederlandse Vereniging voor Psychiatrie. Op 1 mei 2023 is zij begonnen als postdoctoraal onderzoeker 'Toekomstbestendige Gezondheidszorg' bij het Nivel.

Anna (Anne) Eliza Willems was born on May 25, 1982 in Leiden, the Netherlands. She completed secondary school at Stedelijk Gymnasium Leiden in 2001. In 2006, she obtained her MSc in Psychology specializing in Neuropsychology. Subsequently, she worked for a year as a research assistant at the University Medical Centre Utrecht. In 2008, she started at GGz Centraal (at the time known as Symfora Groep), and became research coordinator within a year. In 2013, she graduated with a Masters in Clinical Epidemiology at the Netherlands Institute for Health Sciences. She started as a PhD candidate in 2012 at Maastricht University under the supervision of prof. P.N. van Harten and D.E. Tenback, in addition to her work as a research coordinator at GGz Centraal. While here, she also contributed to the valorization of routine outcome monitoring (ROM) data. She analyzed the ROM data from the institution at team level and presented results back to the teams. Furthermore, she obtained funding and was project leader for the study ‘Personalized Therapy’. This project aimed at the implementation of shared decision making and improvement of health for inpatients in long-term psychiatric care. In 2019, she won the poster prize at the Spring Congress of the

Dutch Association for Psychiatry. On May 1, 2023, she has started with a post-doctoral position ‘Future-Proof Health Care’ at Nivel.

# Publication list

1. Willems AE, Mentzel CL, Bakker PR, et al. Movement Disorders and Mortality in Severely Mentally Ill Patients: The Curacao Extrapyramidal Syndromes Study XIV. *Schizophrenia bulletin* Jun 21 2022;48(4):766-773.

2. Shakir M, Willems AE, van Harten PN, van Lutterveld R, Tenback DE. The effect on relapse rate and psychiatric symptomatology: Switching a combination of first- and second-generation antipsychotic polypharmacy to antipsychotic monotherapy in long-term inpatients with schizophrenia and related disorders. A pragmatic randomized open-label trial (SwAP trial). *Schizophr Res* 2022/05/01/ 2022;243:187-194.

3. Mostert-Kerckhoffs MAL, Willems AE, Tenback DE, Koning JP, Van Harten P, Staal WG. Motor Disturbance in ASD: A Pilot Study Showing Hypokinetic Behavior? *J Autism Dev Disord* Feb 2020;50(2):415-428.

4. Van Riel L, Ingenhoven TJ, Polak MG, Vollema MG, Willems AE, Berghuis H, Van Megen H. Borderline or Schizotypal? Differential Psychodynamic Assessment in Severe Personality Disorders. *J Psychiatr Pract* Mar 2017;23(2):101-113.

5. Willems AE, Sommer IE, Tenback DE, Koning JP, van Harten PN. Instrumental measurements of spontaneous dyskinesia and schizotypy in subjects with auditory verbal hallucinations and healthy controls. *Psychiatry research* Oct 30 2016;244:24-27.

6. Willems AE, Tenback DE, Ingenhoven TJ, van Harten PN. Acute movement disorders associated with the use of second-generation antipsychotics in borderline personality disorder: a meta-analysis. *Journal of clinical psychopharmacology* Aug 2014;34(4):520-522.

7. van Lutterveld R, Oranje B, Kemner C, et al. Increased psychophysiological parameters of attention in non-psychotic individuals with auditory verbal hallucinations. *Schizophrenia research* Aug 2010;121(1-3):153-159.

A summary of the article on movement disorders and mortality[1] was published in the Dutch journal 'Tijdschrift voor Psychiatrie' in the rubric 'Dutch/Flemish Top Research': Willems. A. Ernstige psychiatrische aandoeningen, bewegingsstoornissen en mortaliteit. *Tijdschrift voor Psychiatrie* 2022;9.