MOVEMENT DISORDERS ASSOCIATED WITH NEUROLEPTICS

THE CURAÇAO EXTRAPYRAMIDAL SYNDROMES STUDY

Peter N. van Harten

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Bewegingsstoornissen gerelateerd aan antipsychotica

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(met een samenvatting in het Nederlands)

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voor mijn ouders
voor Sofie en onze boys

Contents

Introduction

This thesis is about extrapyramidal syndromes (EPS) that are related to the use of antipsychotics. These syndromes can be divided into dyskinesia, parkinsonism, akathisia and dystonia. EPS are generally seen in neurological diseases such as Parkinson's disease, Huntington's disease, torsion dystonia, but are also observed during the use of antipsychotics.
The first publication about extrapyramidal syndromes (EPS) during the course of antipsychotic treatment[1,2] appeared one year after the introduction of chlorpromazine.[3-5] In 1954 Steck vividly described EPS: 'since the summer of 1953, we have been impressed by the appearance of a well-developed parkinsonian syndrome in a chronic, cyclically agitated patient who also manifested schizophrenic symptomatology. This patient presented the well-known picture of post-encephalitic parkinsonism with psychomotor rigidity, tremors, facial seborrhea, marked salivation and akathisia.' [6,7]
The tardive complications of antipsychotic treatment were not mentioned in the literature until the late 1950s.[8] Moreover, they were referred to only anecdotally and it was not until the late 1960s that serious epidemiologic studies were undertaken.[9] Since then numerous prevalence surveys have been conducted, particularly with regard to tardive dyskinesia.[10] Nowadays, the subject is well-known and is included in the DSM-IV as a separate category: medication-induced movement disorders.[11] There are several reasons why the members of the DSM-IV work-groups decided to include a section of EPS in the DSM-IV.[12]

- EPS associated with antipsychotics occur very frequently.
- These side effects are often not recognized.
- EPS must be differentiated from Axis I primary mental disorders. For example: bizarre movement may represent acute dystonia or stereotyped movement; restlessness can represent akathisia or psychotic agitation; and psychomotor retardation may occur in parkinsonism, depression, catatonic states, and sedation.
- Many dopamine blocking agents are used in general practice (e.g. metoclopramide or amitriptyline-perphenazine for emesis), yet many physicians do not know that these drugs can induce EPS.
- EPS can cause considerable distress in the form of e.g. pain, anxiety or shame. They can even become life-threatening as in laryngospasm.
- Some of these syndromes have a tendency to become irreversible.
- EPS are often a source for non-compliance, and therefore indirectly a reason for psychotic relapse.

Although EPS associated with antipsychotics are now a separate category there is still a debate about whether EPS are a consequence of antipsychotics or whether they are closely related to the disease process of schizophrenia.[13-16] Whereas, it is not the topic of this thesis it is important to opt for one view or the other because many of the following research questions are based on the

assumption that EPS are associated with antipsychotics. The hypothesis that EPS (particularly the tardive syndromes) are related to schizophrenia is based on (a) descriptions of dystonic and dyskinetic features in schizophrenic patients in the pre-neuroleptic era (b) substantial prevalence of tardive dyskinesia in populations with schizophrenia not treated with neuroleptics (c) the absence of a significant association between the length of time a patient has been receiving antipsychotics and the presence of tardive dyskinesia. However, several arguments strongly support the relationship between tardive syndromes and the use of antipsychotics. Firstly, the absence in many studies of a significant relation between the presence of tardive dyskinesia and the duration of antipsychotic use may be due to the excessive length of time during which patients have received antipsychotics (ceiling effect). This will tend to obscure any relationship between duration of antipsychotic use and the risk of tardive dyskinesia.[16] However, incidence studies with samples of patients in the early years of treatment do show a significant relation between the duration of antipsychotic use and the development of tardive dyskinesia.[17] This relationship is even clearer in older patients receiving antipsychotics for the first time. In these patients a one-year incidence of tardive dyskinesia of 26% and a three-year incidence of 60% has been reported.[18,19] Secondly, there are many case reports of tardive syndromes in non-schizophrenic patients who have used antipsychotics for anxiety, personality disorders, hypochondriasis and other non-psychotic disorders.[20,21] Thirdly, when non-psychiatric patients receive dopamine-blocking agents for non-psychiatric reasons (e.g. metoclopramide in nausea) they also may develop tardive extrapyramidal syndromes, as has been shown in many case reports and in a prevalence study.[20-23] Fourthly, there are case reports of patients in whom tardive dystonia or tardive dyskinesia decreased after withdrawal of classical neuroleptics but increased or reappeared after being rechallenged with these agents.[21,24,25] Fifthly, it is clear that antipsychotics cause acute dystonia, and in a few cases the acute dystonia continued as a persistent dystonia.[20,21] These considerations have led many clinicians and researchers to conclude that antipsychotics are capable of causing or precipitating persistent dyskinesia or dystonia.

Aims and outline of this thesis

The thesis concerns the EPS and is divided into three parts because each part has its own study design. Part 1 focuses on the epidemiology, part 2 on the treatment of tardive dystonia, and part 3 on cocaine as risk factor for acute dystonia.

The main questions of this thesis are:

Part 1

1. **What are the prevalence rates of tardive dyskinesia, parkinsonism, akathisia and tardive dystonia among the total psychiatric inpatient population of the Netherlands Antilles who have used neuroleptics for a long period (at least three months)?**

As will be shown in the introduction of chapter 1.2, most prevalence studies on EPS include one extrapyramidal syndrome; very frequently this is tardive dyskinesia. However, when only one extrapyramidal syndrome is measured this can cause an underestimate of the number of patients suffering from EPS. Therefore, it is important to conduct a study that includes all four syndromes. Furthermore, many studies are flawed by the biased selection of the population, which makes extrapolation uncertain. The Netherlands Antilles, where this study was done, are very suitable for epidemiological research because the natural boundaries of these islands provide a well-defined catchment area. Furthermore, there is only one psychiatric hospital, so the examined population automatically includes all psychiatric inpatients of the Netherlands Antilles; it is a stable population with only one file per patient. Also, a rich amount of data on the island population was generated by a census in January 1992, the year of the study.[26] A benefit in an investigation of EPS is that such a study is relatively independent of language or specific cultural habits, which often constitute a hazard to psychiatric research in foreign cultures.

2. **What is the strength of the inter-relationships between EPS and what are the prevalence rates of each combination of EPS?**

Some EPS are often overlooked or misdiagnosed. Therefore if an extrapyramidal syndrome is significantly associated with another extrapyramidal syndrome diagnosing an extrapyramidal syndrome should alert the clinician to look for the associated extrapyramidal syndrome.
Furthermore, if a patient suffers from one of these EPS, the treatment, if available, is often straightforward. However, having several EPS simultaneously may give rise to clinical dilemmas because treating one extrapyramidal syndrome can worsen the other. Therefore, it is important to know the prevalence of combinations of EPS.

3. **Is there an association between the three lifetime medication variables (cumulative amount of neuroleptics, number of interruptions in treatment with neuroleptics, cumulative amount of anticholinergics)**

and the occurrence and/or severity of tardive dyskinesia?

So far there is no safe and effective treatment for tardive dyskinesia. Therefore, the recognition of risk factors is important. The relative contribution of various medication variables is far from clear. On the basis of the literature it was hypothesized that the cumulative amount of neuroleptics, the number of neuroleptic interruptions, and the cumulative amount of anticholinergics would increase the risk of tardive dyskinesia. The results of the few studies that address the issue of intermittent neuroleptic treatment are not consistent or pertain to highly selective study populations.[27-30] In our study population the selection bias was reduced because our population involved all psychiatric inpatients from a well-defined area. Furthermore, all medication data for a patient could be found in one file and were registered by western trained doctors.

Part 2

4. What is the course of tardive dystonia in chronic psychiatric patients after cessation of neuroleptics and subsequent use of clozapine?

The treatment strategy for tardive dystonia starts with an evaluation of the need for causative drugs, because antipsychotics are regularly prescribed for non-psychotic conditions. However, if antipsychotics have to be continued the dose can be lowered as far as possible. Alternatively, a switch to clozapine could be considered because this drug does not cause tardive syndromes. The effect of clozapine on tardive dystonia has only been reported in a few case reports and results have varied.
The open clinical trial was the first trial to describe the course of tardive dystonia in chronic psychiatric patients after cessation of neuroleptics and subsequent use of clozapine.

Part 3

5. Is cocaine-use a major risk factor for neuroleptic-induced acute dystonia?

Neuroleptic-induced acute dystonia (NIAD) is a common side-effect which almost always occurs within five days in patients who have just started taking neuroleptics or who have had their dosage substantially increased. Because of the sudden onset and unpredictability of NIAD and because it often causes fear and anxiety it is important to know the risk factors for NIAD. Some are well-known, such as male sex, younger age, neuroleptic potency and dose, and a history of NIAD. Two reports, however, have suggested that cocaine might be a

risk factor too. However, the first study (a laboratory study with seven patients) was small and not representative for psychiatric patients, and the retrospective nature of the second study restricted the usefulness of the results.[31,32] Therefore, we conducted a prospective study to test the hypothesis that cocaine is a risk factor for NIAD. Furthermore, when drug abuse is studied as a risk factor a problem arises with regard to polydrug users. In such patients it is almost impossible to determine which particular drug is responsible for NIAD. However, on the island of Curaçao drug abuse is limited almost exclusively to cocaine (or base) and cannabis.

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PART 1

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Raizan

Chapter 1.1

Extrapyramidal syndromes: clinical features and differential diagnosis

Extrapyramidal syndromes associated with antipsychotic treatment are very common and can cause the patient considerable distress. These syndromes are one of the main reasons for patients' non-compliance in medication taking.[1] Since antipsychotic medication is indispensable in the treatment of psychotic disorders, non-compliance can hamper the treatment considerably. Moreover, when long-term treatment with antipsychotics is necessary to lower the risk of a psychotic relapse, extrapyramidal syndromes can be a serious problem. Therefore, it is important to study the prevalences, risk factors and treatment of extrapyramidal syndromes. The importance of iatrogenic movement disorders is also emphasized by the inclusion in the DSM-IV of a separate category of medication-induced movement disorders.[2] There is little doubt that inclusion of these movement disorders in the DSM-IV will improve the recognition of these disorders.[1,2]

Extrapyramidal syndromes can be divided into those with early onset (acute) and those with late onset (tardive). Acute extrapyramidal syndromes appear in the first few days of treatment or follow an increase in the dose of an antipsychotic and can be subdivided into acute dystonia, akathisia and parkinsonism. Late-onset extrapyramidal syndromes usually appear after months or years of antipsychotic exposure and can be subdivided into tardive dyskinesia, tardive akathisia, and tardive dystonia.

Tardive dystonia and acute dystonia are extensively reviewed in chapter 2.1 and chapter 3.1, respectively. This chapter reviews the characteristic phenomena of and differential diagnostic considerations relating to parkinsonism, akathisia and tardive dyskinesia. Several other extrapyramidal syndromes such as tardive myoclonus, tardive tics, tardive tremor, and tardive tourettism, have been associated with the use of antipsychotics,[3,4] but these disorders are beyond the scope of this thesis; for the same reasons some specific extrapyramidal syndromes such as withdrawal dyskinesia, and neuroleptic malignant syndrome are not discussed either.

Characteristics of extrapyramidal syndromes in general

Although movement disorders associated with antipsychotics differ in many aspects they have some characteristics in common. All these involuntary movement disorders (except certain forms of myoclonus) disappear during sleep, particularly during the deep phase of the sleep. The severity of movement disorders may alter with the level of excitement or relaxation. In an anxious patient the disorder may be more severe whereas during relaxation it may decrease. Moreover, volitional motor activity may alter the severity and can reveal or even suppress the extrapyramidal syndromes. For instance, finger tapping or walking may bring out or increase dyskinesia whereas it can suppress akathisia.[5-7] This alteration in severity is sometimes wrongly interpreted as

evidence that the disorder is of psychogenic origin, particularly if the clinician has made the incorrect assumption that movement disorders are static.

The judgment of the severity of the movement disorder can be based on: location, character, amplitude, frequency (i.e. the number of movements occurring in a certain observation time) and persistence (the proportion of an observation period during which the movements are apparent).[8,9] Also the physical or social disability related to the movement disorder is an indicator of the severity.[9,10]

Of the four extrapyramidal syndromes mentioned, the motor phenomena of akathisia differs in principle from the motor phenomena of the other three. Whereas parkinsonism, dyskinesia and dystonia are involuntary abnormal movements, akathisia is a voluntary normal movement (see further under akathisia).

Parkinsonism

Clinical features

Parkinsonism is an akinetic rigid syndrome with the following cardinal features: tremor at rest, rigidity, bradykinesia, and postural instability.[11] Tremor at rest is a coarse, rhythmic tremor with a frequency of 3 to 5 Hz. It is the characteristic pill-rolling tremor as seen in Parkinson's disease. The tremor is most often localized in one or both hands, but limbs and head are sometimes affected too. When lips are involved it is also referred to as the rabbit syndrome.[12] Emotional stress augments the tremor; the tremor is suppressed or diminished with voluntary movements. The tremor reasserts itself once the limb assumes a new position.[13]

In some patients an atypical action tremor appears; such a tremor has a higher frequency than the rest tremor and is best elicited by holding the arms outstretched with fingers spread apart.[13]

Rigidity is characterized by a persistent increased tone of the muscles, which renders the muscles continuously or intermittently firm and tense. The increased resistance to passive movement leaves the investigator with the impression that he is bending a lead pipe. The rigidity appears to be more prominent in the large flexor muscles groups. A special type of rigidity is the cogwheel phenomenon, in which the investigator encounters a rhythmically interrupted, ratchet-like resistance during passive movement. However, it could be that cogwheel rigidity reflects the presence or absence of an underlying tremor that is masked by the rigidity, but emerges faintly during manipulation.[13,14] Patients with rigidity may complain of generalized muscle tenderness or stiffness, muscle or joint pain, body aching, or lack of coordination during sports.[2,13]

Bradykinesia (slowness of movement) and akinesia (lack of movement) are the most common and sometimes the only manifestations of parkinsonism. They account for monotonous speech with loss of expression, hypomimia, poverty of

movements in general, slowing of movements, muscle fatigue or weakness, stooped posture, slow walking with short steps, and decreased arm swing. Sometimes sialorrhea appear when saliva is not swallowed as fast as it is produced. Also dysarthria or dysphagia can be present. Postural instability is reflected in a reduction or absence of postural response which can be judged with the pull test (a sudden posterior displacement produced by a pull on the shoulders). Parkinsonism may begin only a few days after antipsychotic treatment has started but can also appear after a few months.[15] Signs of parkinsonism are often asymmetrical in distribution.

Differential diagnosis

For the differential diagnosis it is important to have a history of antipsychotic use. If symptoms of parkinsonism were present before antipsychotic treatment started another cause is very likely. Parkinsonian signs can persist after the discontinuation of antipsychotics. However, the longer the time that has elapsed since last antipsychotic exposure, the more likely it is that the symptoms are due to other causes. Somewhat arbitrarily it is suggested that parkinsonian symptoms are not related to antipsychotics if they persist longer than three months if oral antipsychotics have been administered or longer than 12 months if long-acting injectable forms of antipsychotics have been administered.[16]

Idiopathic Parkinson disease is suspected when the parkinsonian signs progress in the absence of an increase in the antipsychotic dose. The differentiation can be made by lowering the dosage of or discontinuing the antipsychotics. Antipsychotic-induced parkinsonism should improve significantly and then resolve, whereas idiopathic Parkinson disease always worsens after the amelioration obtained by stopping the antipsychotic recedes.[11]

Catatonia can be mistaken for parkinsonism but can be differentiated by additional signs of catatonia that differ from parkinsonian symptoms, such as the presence of waxy flexibility versus cogwheel rigidity, muteness versus dysarthria, and negativism versus akinesia. A long list of disorders such as degenerative diseases, toxins, and tumors can also cause parkinsonism.

It is important to differentiate bradykinesia and akinesia from psychomotor retardation associated with depression, sedation, or negative symptoms of schizophrenia. However, it can be extremely difficult to distinguish between negative symptoms as seen in schizophrenia and drug-induced parkinsonism.[17]

Rigidity must be differentiated from spasticity; both have increased resistance to passive movements but spasticity shows no or little resistance when the limb is flexed very slowly. In spasticity a rapid flexion causes rapidly increasing resistance; after an initial free interval up to a certain point, the resistance melts away (the clasp-knife phenomenon).

If the patient is unable to relax tense muscles can mimic parkinsonian rigidity. Therefore, the examiner should try to put the patient at ease and distract the patient during passive movements of the muscles.

Rest tremor must be differentiated from other tremors, particularly those induced by lithium or tricyclics which are often finer and faster.

Postural instability may have many other causes such as cerebellar disorders, Huntington's disease, frontal lobe disorder, drunkenness, and can also develop with age.

Akathisia

Clinical features

Akathisia, which literally means 'not to sit', can be defined as both subjective complaints of restlessness and objective motor movements.[18] The subjective complaints consist of feelings of inner restlessness, most often with reference to the legs. Patients have described the inner restlessness of akathisia in many ways, such as: 'My nerves are just jumping; I feel like I'm wired to the ceiling; I just feel impatient and nasty; I can't concentrate; it's like I got ants in my pants; my nerves are raw; I just feel on the edge; I want to climb the walls'.[19] If the akathisia is of a milder form patients experience vague feelings of apprehension, dysphoria, irritability, or general unease.[2,5,19] These feelings are often accompanied by an inability to remain still. Almost all patients describe a feeling of 'inner restlessness', especially if this description is suggested to them.[5] The subjective complaints may have strong affective components such as fright, terror, anger, and rage and such sensations may result in violent behavior or suicidal impulses. The objective features are typically movements of the legs. Patients complain that they have the utmost difficulty in keeping their legs still and they show movements like rocking from foot to foot, pacing on the place when standing, shuffling or tramping of the legs, or swinging of one leg when sitting. Severe akathisia makes a patient unable to sit or lie for even a few minutes and such patients continually walk or pace about. These movements are described as a response to an irresistible urge to move, but the movement alleviates the urge and distress only temporarily. The urge to move can preoccupy the patient's thinking and akathisia can be more difficult to endure than any of the symptoms for which the patient was originally treated.[5] Akathisia can be provoked by letting the patient stand during informal talking. Lying down often provides some relief.

The term pseudoakathisia describes the condition in which patients manifest the objective motor movements of akathisia but not the subjective complaints. One view of pseudoakathisia is that it represents an end-stage akathisia in which the subjective experience of restlessness has faded.[20] However, one could argue that pseudoakathisia is not a movement disorder but more a habit that falls within the range of normal movements.

Tardive akathisia does not differ from acute akathisia in a phenomenological way. However, the reaction to a change in antipsychotic dosage differs: in acute akathisia an increase in the dose may worsen the akathisia and a decrease may

improve the akathisia, whereas tardive akathisia shares the pharmacological characteristics of tardive dyskinesia in that it is exacerbated by reduction or withdrawal and improved when the dose is increased.[9,20]

Akathisia is the only extrapyramidal syndrome in which the movements are voluntary and not abnormal. In fact the movements are secondary to the subjective distress and it has been debated whether akathisia is a movement disorder, a mental disorder, or both.[21]

Differential diagnosis

Akathisia must be distinguished from the restless legs syndrome that appears only at night or worsens markedly at night and is more severe when the patient is lying down. Akathisia is present the whole day and may increase during standing. Furthermore, restless legs is almost always accompanied by periodic movements during sleep; such movements are rare in akathisia.

The differential diagnosis of akathisia from agitation, particularly psychotic agitation, is most important because psychotic agitation is an indication that antipsychotics should be increased whereas akathisia calls for a decrease in the antipsychotic drug. Some patients experience the akathisia as unnatural or different from previously experienced feelings. In case of doubt, a reduction of the dose is helpful and will reduce akathisia but may worsen the anxiety or agitation.[5]

Substance intoxication (e.g. with cocaine) or substance withdrawal (e.g. from alcohol, nicotine, benzodiazepines, opioids) may also result in agitation. However, if the appropriate patient history is available differentiation from akathisia can often be made.

Tardive dyskinesia

Clinical features

Tardive dyskinesia is characterized by involuntary writhing and purposeless, irregular movements that may or may not be continuous. The core sign is the orofacial dyskinesia, or the buccolinguomasticatory triad. This consists of involuntary movements of the tongue, jaw, lips or face; for example, twisting, curling or 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 movements of trunk and/or limbs are also included such as writhing movements of the fingers (‘piano-playing fingers’) or irregular toe movements, rotation of wrists, arms, ankles, and legs, head nodding, trunk movements, and pelvic thrusting.[9,22] The respiratory musculature and/or the diaphragm can also be affected. This so-called respiratory dyskinesia has the following symptoms: irregularity in the rate and/or rhythm of respiration, gasping, sighing and/or grunting, forceful breathing, shortness of breath, and dyspnea.[23] In most cases of respiratory dyskinesia features of tardive dyskinesia affecting the facio-bucco-lingual region are also present.[24]

Some investigators subdivide tardive dyskinesia into orofacial dyskinesia and limb-truncal dyskinesia because there is some evidence that each of these subsyndromes is associated with different risk factors and a different prognosis.[25-28]

The severity of tardive dyskinesia can vary over time and even during the day.[6,7] Several explanations have been considered such as the fluctuation of physiological processes underlying tardive dyskinesia, examiner bias, variability in the suppression of the disorder, or the presence and fluctuation of other movement disorders.[7] Also, voluntary movements such as moving the tip of the thumb from one finger to another may provoke or aggravate the dyskinesia in other parts of the body. Walking is an example of an activating task that brings out dyskinetic movements in the upper limbs. Lowering the dosage of or discontinuing the antipsychotic drug may increase the severity of the tardive dyskinesia or may even unmask covert tardive dyskinesia. Covert tardive dyskinesia refers to existing tardive dyskinesia that is unmasked when the antipsychotic drug is reduced or discontinued. Increasing the antipsychotic dosage can decrease the severity or (transiently) mask existing tardive dyskinesia.[29]

The patient's lack of awareness of or even denial of dyskinetic movements is often striking and is associated with the cognitive impairment and negative symptoms often present in patients with schizophrenia. Patients with disorders that do not affect cognitive functions such as bipolar or anxiety disorders are more likely to be aware of their movement disorder.[30]

Tardive dyskinesia is a potentially disabling movement disorder. Severe oral dyskinesia may result in dental problems that can progress to ulceration, as well as to muffled or unintelligible speech. Severe orofacial dyskinesia can impair eating and swallowing. Limb and trunk dyskinesia may cause gait disturbances and may leave patients vulnerable to falls.[7,9] Respiratory dyskinesia can induce dyspnea and cyanosis. It is not widely known that tardive dyskinesia can be accompanied by painful sensations which become a source of profound distress for the patient.[31] However, most of the time tardive dyskinesia does not cause physical disabilities; if patients are aware of their dyskinetic movements, social disability is often present. Patients may feel embarrassed, anxious or depressed when they notice that others observe their dyskinetic movements and the presence of obvious odd movements can stigmatize the patients. One study showed that the social acceptability is decreased in patients with orofacial dyskinesia.[32]

Differential diagnosis

The differential diagnosis of tardive dyskinesia is extensive; it can be mistaken for akathisia, and dyskinesia induced by other drugs. If other somatic signs are present besides dyskinesia, diseases such as Huntington's disease, Wilson's disease, Sydenham's chorea, Fahr's syndrome, and Hallervorden-Spatz disease

must be considered. Respiratory dyskinesia is often misdiagnosed as a respiratory disorder or as psychogenic hyperventilation.[23] Stereotypies (purposeless meaningless actions) and mannerisms (peculiar ways of carrying out normal actions) are often repeated less stereotypically than dyskinesia and are quite complex movements in contrast with tardive dyskinesia.[10,33] The differentiation between spontaneous and tardive dyskinesia can sometimes be made with the help of a careful history about the time of onset of the dyskinesia in relation to antipsychotic use. However, when the onset of spontaneous dyskinesia occurs after the use of antipsychotics differentiation may be impossible.

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Chapter 1.2

The prevalence of tardive dystonia, tardive dyskinesia, parkinsonism and akathisia

The Curaçao Extrapyramidal Syndromes Study: I.

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Abstract

A prevalence study of extrapyramidal syndromes was conducted among all psychiatric inpatients of the Netherlands Antilles (N=194; mean age 53.1). The Netherlands Antilles are very suitable for epidemiological research as it is a well-defined catchment area with only one psychiatric hospital and a health care system based on western principles.
In this mainly chronic population, the prevalence was measured of tardive dystonia, tardive dyskinesia, parkinsonism and akathisia using respectively the Fahn-Marsden rating scale, the Abnormal Involuntary Movement Scale, the Unified Parkinson Disease Rating Scale and the Barnes Akathisia Rating Scale. The prevalence numbers were for tardive dystonia 13.4%, tardive dyskinesia 39.7%, parkinsonism 36.1%, akathisia 9.3% and pseudoakathisia 12.9%. The most important conclusions were: (1) The prevalence of tardive dystonia was higher than reported in most other studies and (2) extrapyramidal syndromes are very common in this predominantly Negroid population, with three out of four patients suffering of one or more extrapyramidal syndromes.

Introduction

The prevalence of extrapyramidal syndromes (EPS) induced by neuroleptics is a main issue in epidemiological research concerning the treatment of psychosis. The main EPS are tardive dyskinesia, tardive dystonia, parkinsonism and akathisia.[1] Most prevalence studies include one of these syndromes, very frequently tardive dyskinesia. We conducted a study that included all four syndromes.

Prevalence is defined by two integers, the nominator, depending on case finding and case definition and the denominator depending on the selection of the population under study. Especially the selection of the population often causes a bias and makes extrapolation uncertain. The Netherlands Antilles, where this study was done, are very suitable for epidemiological research. First, there is only one psychiatric hospital, so that the examined population automatically includes all psychiatric inpatients of the Netherlands Antilles. Secondly, because the Netherlands Antilles are islands, the catchment area is well defined. Therefore, a stable population exists with only one file per patient. Thirdly, a rich amount of data of the island population was generated by a census in January 1992, the year of the study.[2] Investigation of EPS has the advantage of being relatively independent of language or specific cultural habits, which are often a hazard to psychiatric research in foreign cultures.

To our knowledge, no study exists which measures simultaneously the prevalence of four main EPS in a restricted geographical area.

The aim of this study was to determine the prevalence of tardive dystonia, tardive dyskinesia, parkinsonism and akathisia among the total psychiatric inpatient population of the Netherlands Antilles that used neuroleptics for a long period (for three months or more).

Patients and methods

Curaçao, Bonaire, Aruba, St. Maarten, St. Eustatius and Saba were six islands of the Antilles, which are closely related to the Netherlands. On the census date (January 1992) Curaçao had 144,097, Aruba 50,777, Bonaire 10,187, St. Maarten 32,221, St. Eustatius 1839 and Saba 1130 inhabitants making a total of 240,251. Because 75% of the psychiatric inpatient population were born on Curaçao we will cite some data from the census of Curaçao. The mean age of the island population of Curaçao is 31.7 years (0-14 years=25.9%, 65+=8.1%). The male-female ratio is 0.9. Of the island population 81.7% was born on Curaçao (87.5% on one of the six islands).[2] The population is mainly Negroid and the health system is based on western (Dutch) principles. Of the nine consultant psychiatrists currently working on Curaçao seven were trained in the Netherlands.

Population under study

The target group comprised all 214 admitted patients at the Dr. David Ricardo Capriles Clinic on the first of June 1992. Nearly all patients had received all their psychiatric care in this hospital. The files were reviewed by two junior medical doctors who were not aware of the existence of movement disorders in the patients. Assessed were age, sex, total duration of admissions and duration of the last admission. The psychiatric diagnoses were based on the chart notes and confirmed in a consensus meeting of the first author and the treating psychiatrist.[3] Neuroleptic medication on the day of the examination was converted to chlorpromazine equivalents (CPZEQ).[4,5] Just before this study started, three patients with tardive dystonia entered an open clinical trial with clozapine.[6] For these patients the data were taken from the start of that trial.

Examination

The patients were each examined simultaneously by two researchers, using a standard protocol. Patients were barefooted, wore shorts or a dress and sat on wooden chairs without armrests. One investigator asked specific questions concerning akathisia while the other investigator counted the eye-blink for one minute. To judge the existence of EPS and to provoke EPS, the patient had to do several tasks: consecutively, stretching arms, making fast alternating hand and foot movements, opening mouth, rising from chair and walking. Also, rigidity and balance were judged. Akathisia was provoked by having the patient standing upright for a few minutes during informal talking. After the examination a joined decision was reached regarding the presence or absence of each EPS and, if present, the ratings were established by consensus. Each examination took 10 to 30 minutes.

Definition and assessment of movement disorders

Tardive dystonia

Dystonia is defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures.[7] For tardive dystonia to be diagnosed, it had to fulfill Burke's criteria.[1] It was rated on the Fahn-Marsden scale.[8] Tardive dystonia was diagnosed if one body area was involved with at least a ‘mild’ rating on a severity factor or if two or more body areas got a ‘slight’ rating. If frequent eye-blinking (a ‘mild’ rating on the item ‘eyes’) was the only symptom at least a ‘moderate’ (blepharospasm) involvement was required for case definition (as frequent eye-blinking can have many other causes.[9] Dystonia was classified by localization in focal, segmental, multifocal and generalized.[7]

Tardive dyskinesia

The core sign of tardive dyskinesia is orofacial dyskinesia, or the

buccolinguomasticatory triad that consists of involuntary choreatic (rapid, irregular, jerking) movements of face, lips, tongue or jaw. Also choreiform purposeless movements of trunk and/or limbs are included.[10]

Assessment of tardive dyskinesia was done with the Abnormal Involuntary Movement Scale.[11] Case definition was based on Schooler and Kane's criteria for probable tardive dyskinesia.[12]

Parkinsonism

Parkinsonism is an akinetic rigid syndrome. The cardinal features are tremor at rest, rigidity, bradykinesia, and postural instability.[13]

The Unified Parkinson Disease Rating Scale (UPDRS) is a valid and reliable instrument and is widely used in research on Parkinson's disease.[14] The motor examination part was used. The items assess speech, facial mobility, resting tremor (face and each limb), action tremor, rigidity (neck and each limb), rapid hand and foot movements, rising from chair, posture, gait, postural stability and body bradykinesia.

Rest-tremor and rigidity being typical of parkinsonism, a ‘mild’ involvement on one of these items led to case definition. If no tremor or rigidity was rated, the cut-off point was at least one ‘moderate’ or two ‘mild’ scores on the other items. This more stringent criterion for items concerning bradykinesia and postural stability was chosen because these symptoms can also be caused by psychiatric syndromes or sedation.

Akathisia

Akathisia can be defined as both subjective complaints of restlessness and objective motor movements, typically movements of the legs.[15]

Akathisia and pseudoakathisia were assessed with the Barnes Akathisia Rating Scale which comprises an objective and a subjective item.[15] If the patient was unable to give the subjective information and showed the characteristic objective akathisia movements, it was rated as pseudoakathisia (on advice of Barnes).

Reliability study

The research protocol, the cut-off points for case definition and the rating methods were extensively discussed and compared during a one-week visit to the Dystonia Clinical Center at Columbia University New York (director S. Fahn) and the Hillside Hospital Long Island Jewish Medical Center (director J.A. Lieberman).

To achieve inter-rater reliability, we held several training sessions in which videotapes of our own patients as well as tapes from other centers were used.

The inter-rater reliability of the four researchers was obtained during the study of 24 patients chosen at random. These 24 patients were examined twice, after which the ratings of the couples of researchers were compared. For these

24 patients the final ratings used for the analysis were based on consensus.

Data analysis

To compare groups a *t*-test or an ANOVA or (when a non-normal distribution was found) a Mann-Whitney *U*-test was performed. Analyses involving CPZEQ concerned only those patients using neuroleptics.

Table 1 *Epidemiological characteristics of the population under study. For comparison of means of males and females the Mann-Whitney U-test was performed. N=194 (male-female ratio=2.7)*

	Total group Mean (SD)	Sex		*z*	*p*
		Males Mean (SD)	Females Mean (SD)		
Age (years)	53.1 (16.7)	50.4 (15.3)	60.3 (18.2)	-3.52	0.0004
Age first admission (years)	26.6 (11.1)	24.6 (8.7)	32.2 (14.6)	-3.62	0.0003
Number of admissions	5.1 (4.3)	5.3 (4.5)	4.6 (3.7)	-0.69	NS
Duration of illness[a]	26.4 (15.8)	25.8 (15.1)	28.0 (17.5)	-0.84	NS
Total duration of admission (years)	20.1 (16.5)	19.6 (16.4)	21.5 (16.7)	-0.65	NS
Duration of last admission (years)	15.6 (16.2)	15.4 (16.2)	16.1 (16.3)	-0.14	NS
Psychiatric diagnosis DSM-III-R					
All diagnoses[b] (%)	Schizophrenia[c] 77.3 Affective disorder 5.2 Dementia 8.2 Mental retardation 4.6 Cocaine abuse[d] 13.9 Other 24.7				
Medication (%)	Benzodiazepines 19.1 Antidepressant 4.6 Lithium 10.3 Other 22.2				

NS, not significant.
[a]Duration of illness is age minus age first admission.
[b]One patient can have several diagnosis, thus the total number exceeds 100%.
[c]Includes 295.1, 295.2, 295.3, 295.4, 295.6, 296.7, 295.9.
[d]On Curaçao addiction to drugs refers almost exclusively to cocaine (base) and cannabis.

To compare categorical data, chi-squared tests were used.

The inter-rater reliability for the EPS case definitions (dichotomous variable) was assessed with Cohen's kappa.[16] Kappa represents the proportion of agreement beyond chance, and is interpreted as moderate between 0.41-0.60; as good between 0.61-0.80 and as very good between 0.81-1.00.[16] Our kappas were: tardive dystonia 0.78, tardive dyskinesia 0.50, UPDRS 0.53 (tremor 0.70,

rigidity 1.0), akathisia 0.65, pseudoakathisia 0.57.

Results

The total inpatient population comprised 214 subjects. Two patients refused to participate and two were too psychotic to be examined. Five patients had obvious organic disturbances that could cause movement disorders and were excluded from the analysis (hydrocephalus (2x), spasticity after cerebral hemorrhage, congenital choreoathetosis, subcortical encephalopathy after alcohol-abuse).

Table 2 *Prevalence of the extrapyramidal syndromes*[a] *and current use of neuroleptics. The prevalence of rest-tremor and rigidity are also reported. (N=194, males=141, females=53)*

Extrapyramidal variants	*N*	%	% of patients currently using neuroleptics
Tardive dystonia	26	13.4	85
Tardive dyskinesia	77	39.7	79
Parkinsonism	70	36.1	91
Rigidity	32	16.5	91
Tremor at rest	26	13.4	96
Akathisia	18	9.3	100
Pseudoakathisia	25	12.9	80

[a]Patients can have one or more extrapyramidal syndromes

Eight patients had never used neuroleptics and three had used neuroleptics in the past for less than 3 months.

The analysis concerns the 194 patients that used neuroleptics during the study or had previously used neuroleptics for more than 3 months. The population was predominantly Negroid (Negroid 94%, white 4%, other 2%). Most patients were chronic psychiatric patients. Of the 194 patients included in this study, 142 lived on chronic wards, 31 on acute wards and 21 in a day-care setting for chronic psychiatric patients. Table 1 shows the epidemiological characteristics of the patients. Note the high prevalence of schizophrenia and the low prevalence of affective disorders.

Neuroleptics were currently used by 167 of them (86.1%), 39.5% of whom also used anticholinergics. Only 6.2% used low-potent neuroleptics and 64.7% was on depot neuroleptics. The neuroleptic users were on a mean CPZEQ-dose of 698 mg/day (SD=695). Most patients took one or two types of antipsychotics. Table 2 shows the prevalence of the EPS and of each syndrome the percentage of patients currently using neuroleptics. Of the population 73.7% had one or more EPS. Male-female ratios of the EPS cannot be given for the group as a whole because the women were significantly older than the men. To solve this we divided the patients into three agegroups without any significant differences

of age by sex. Table 3 shows for each agegroup, the prevalence of EPS by sex and their male-female ratios. In the group of 44 years or younger, males had more tardive dyskinesia and tardive dystonia than females while in the older group the opposite was found. However, none of the male female ratios reached statistical significance.

Table 3 *Prevalence of extrapyramidal syndromes among 194 patients by age bracket*

	Age (years)		
EPS and sex	44 or younger	45-64	65 or older
Tardive dystonia			
– Men	16.7%	10.7%	8.0%
– Women	7.7%	11.1%	22.7%
– Male/female ratio	2.2	1.0	0.4
Tardive dyskinesia			
– Men	33.3%	39.3%	52.0%
– Women	7.7%	38.9%	63.6%
– Male/female ratio	4.3	1.0	0.8
Parkinsonism			
– Men	25.0%	46.4%	36%
– Women	30.8%	33.3%	45.5%
– Male/female ratio	0.8	1.4	0.8
Akathisia			
– Men	16.7%	3.6%	4.0%
– Women	15.4%	5.6%	9.1%
– Male/female ratio	1.1	0.6	0.4
Pseudo-akathisia			
– Men	13.3%	8.9%	16.0%
– Women	15.4%	0.0%	27.3%
– Male/female ratio	0.9	—	0.6
Total number of patients			
– Men	60	56	25
– Women	13	18	22

Table 4 shows the difference of the mean age between patients with and without EPS. Also, the difference of the mean dose of CPZEQ is presented. Because CPZEQ and age were inversely related ($r=-0.24$, 95% CI $-0.38<r<-0.09$) the difference in CPZEQ for patients with or without one of the EPS was corrected for age by using age as a covariate.

Of the patients with tardive dystonia 35% had focal, 39% segmental, 19% multifocal and 8% generalized dystonia.

Five of the patients with pseudoakathisia were unable to give information about the subjective item so some of them might actually have had akathisia.
Of the patients with parkinsonism 30% had no Parkinson tremor and no rigidity.

Discussion

This study examined the prevalence of four EPS in the total psychiatric inpatient population of a well-defined catchment area. The most important findings were a high prevalence of tardive dystonia (13.4%), and the fact that as many as 73.7% of the patients had at least one extrapyramidal syndrome.

A possible explanation for the high prevalence of tardive dystonia might be that being Negroid is a risk factor. Of the nine studies that examined the prevalence of tardive dystonia,[17-25] three mentioned race.[20,21,23] Chiu[23] found an extremely low prevalence of tardive dystonia (0.4%) in a large Hong-Kong Chinese inpatient population. She suggested that the Asian race may be less sensitive to EPS.[23] However, a Japanese study found a prevalence of 2.1%[21] which was similar to four western studies.[17-19,22] Sethi compared Negroid and Caucasian patients in one population and found no difference.[20]

Another possibility could be that some cases of dystonia might have been labeled dyskinesia by other investigators, e.g. blepharospasm, or dystonic postures of the fingers, making the prevalence of dystonia lower. However, according to the definition of dystonia mentioned, these abnormal movements should be classified as dystonia.
Another possible explanation could be that tardive dystonia is more common than is often thought. Our way of case finding with two investigators, a comprehensive rating scale and a standard examination to reveal dystonic features, may well increase the chance of case-finding. Three studies found comparable numbers respectively 6.2%,[25] 11%,[24] and 21.6%.[20] Most studies do not specify their case definition and the studies with a prevalence of about 2% may include only moderate to severe cases. If we define moderate to severe tardive dystonia as involving at least two body areas moderately or one severely, our prevalence falls to 2.9%.

We found no significant difference in the prevalence of tardive dystonia with males and females. However, the prevalence of tardive dystonia was higher among males of 44 years or younger, while females were more affected in the group of 65 and older. Friedman et al.[19] found a higher prevalence for men but he excluded patients older than 70 years. This exclusion criterion is important because in our study, 62.5% of the females with tardive dystonia were between 70 and 91 years old, while all males with tardive dystonia were under 70 years of age. Others provide different male female ratios.[17,18,21,23,26]

The prevalence of tardive dyskinesia was 39.7%, which is within the range of many other studies.[27-30] An interesting study for comparison is the Nithsdale schizophrenia survey because it was also carried out in a restricted area and

assessed TD, akathisia and parkinsonism.[31] Their mean age was lower, which may have caused their lower prevalence of TD.[32] The influence of race on TD has been studied by Glazer et al.[33] who found that being Negroid almost doubles the incidence of TD. On the other hand, Sramek et al.[34] found no difference between Negroid and Caucasian patients. Age is the most consistently reported risk factor of TD.[10,27,32] We also found that the patients with TD were significantly older than those without.

Table 4 *The mean age and the mean dose of chlorpromazine-equivalents (CPZEQ) by extrapyramidal syndrome*

	Age (years)[a]			CPZEQ (mg/d)[b]		
	Mean (SD)	*t*	*p*	Adjusted mean (SD)	*F*	*p*
Tardive dystonia						
YES	53.3 (18.1)			522 (427)		
		-0.07	NS		1.52	NS
NO	53.0 (16.5)			713 (724)		
Tardive dyskinesia						
YES	58.3 (16.5)			576 (508)		
		-3.62	0.0001		2.87	0.09
NO	49.6 (16.0)			757 (768)		
Parkinsonism						
YES	55.5 (16.2)			803 (815)		
		-0.513	NS		2.82	0.10
NO	51.7 (16.9)			620 (609)		
Akathisia						
YES	46.5 (15.1)			919 (612)		
		-1.76	NS		1.79	NS
NO	53.7 (16.7)			692 (701)		
Pseudoakathisia						
YES	58.1 (18.0)			836 (1033)		
		-1.61	NS		1.28	NS
NO	52.3 (16.4)			653 (639)		

[a]Total population (n=194). To compare the mean of age, a *t*-test was used.
[b]Of the patients currently using neuroleptics (n=167). To compare the mean of CPZEQ an ANOVA was used. Because CPZEQ was inversely correlated with age ($r=-0.24$, $p<0.01$), the means of CPZEQ were adjusted for age by using age as a covariate.
NS not significant

The prevalence of parkinsonism was 36.1%, which is roughly similar to the Nithsdale number of 31%.[31] Prevalence numbers of other studies varied from 8.6 to 72%.[30,35]

The prevalence of akathisia was low (9.3%) compared with two studies using

the same rating scale.[36,37] However, many studies of patients with a long neuroleptic history show considerable variation.[1]

The kappa's for inter-rater reliability varied substantial between the different EPS, with tardive dyskinesia, UPDRS and pseudoakathisia having moderate, and akathisia and tardive dystonia having a good agreement. This variation is partly due to the fact that only a small number of patients (24) were rated twice, influencing Cohen's kappa, together with the low prevalence of most EPS, (base-rate problem). However, our kappa's are comparable to those of other studies with also values of moderate to good agreement.[14,36,38]

Can we generalize our results to other (Negroid) populations? The inclusion of nearly all psychiatric inpatients in a circumscribed area is a point strongly in favor of extrapolation. Furthermore the census gives us reliable information about the origin of our population. In our case the admittance rate of 1.8 promille[1] would justify extrapolation as it is comparable to that in a western country.

How representative is our population under study? Some epidemiological data are similar to those in western studies, like the percentage of schizophrenic patients, the lower age of first admission for males compared with females, the mean age of the patients and the mean dose of currently used neuroleptics. However, the cultural setting may influence the characteristics of the population, such as the high male-female ratio and the low prevalence of affective disorders.

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Chapter I.3

The inter-relationships of tardive dyskinesia, parkinsonism, akathisia and tardive dystonia

The Curaçao Extrapyramidal Syndromes Study: II.

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Abstract

A study of the four extrapyramidal syndromes (EPS), tardive dyskinesia, parkinsonism, akathisia and tardive dystonia was performed in the Netherlands Antilles, a well-defined catchment area with only one psychiatric hospital. The population under study (N=194; mean age 53.1) was mainly Afro-Caribbean, and most patients were chronic. The severity of each EPS was measured with valid and reliable rating scales. The purpose was to study both the strength of the inter-relationships of EPS and the prevalence of combinations of EPS. The inter-relationships between the EPS were analyzed by means of logistic regression.

The adjusted odds ratios between the various EPS revealed strong connections between the hyperkinetic syndromes (tardive dyskinesia, tardive dystonia and akathisia). Parkinsonism was found to be inversely related to tardive dyskinesia and to tardive dystonia.

Almost 30% of the patients suffered from two or more EPS. The highest prevalence rates of combinations were: tardive dyskinesia combined with parkinsonism 12.9%, tardive dyskinesia combined with tardive dystonia 9.8%, and tardive dyskinesia combined with akathisia 5.2%.

Our findings show a strong positive correlation between hyperkinetic forms of EPS. Furthermore, chronic psychiatric inpatients regularly suffer from combinations of EPS. Different treatment strategies are suggested for various combinations of EPS.

Introduction

Extrapyramidal syndromes (EPS) that are related to the long-term use of neuroleptics can be classified by the time of onset (acute vs. tardive) and by phenomenology. In a study of mainly chronic psychiatric patients a phenomenological classification is preferable; EPS can be divided into four categories: tardive dyskinesia, parkinsonism, (tardive) akathisia and tardive dystonia. If a patient suffers from one of these EPS, the treatment, if available, is often straightforward. However, having several EPS simultaneously may give rise to clinical dilemmas.[1] Many prevalence studies have investigated one extrapyramidal syndrome only[1,2] and some studies have investigated two[3-7] or three EPS.[8-12] In most cases the extrapyramidal syndrome concerned was tardive dyskinesia and or parkinsonism. Only two studies have measured all four EPS simultaneously.[13,14] However, neither study used valid scales to assess all four EPS and neither was located in a well-defined catchment area. Only two studies have measured the prevalence of EPS in a well-defined catchment area[12,15] O'Hara et al.[15] measured two EPS and McCreadie et al.[12] three EPS. None of the studies[12-15] used multivariate techniques to analyze the inter-relationships. If a study design is to overcome the limitations mentioned above, it should satisfy three criteria:

1) All four EPS should be measured simultaneously using valid and reliable rating scales.
2) The study should be conducted in a geographically circumscribed area.
3) Multivariate statistical analysis should be used, because multiple intercorrelated variables are involved.

Some of the earlier studies fulfill one criterion, but no study fulfills two criteria, let alone all three. We designed a study that fulfilled all three criteria in order to estimate the strength of the inter-relationships between the EPS and how often combinations of EPS occur. Our study was performed in the Netherlands Antilles, a well-defined catchment area with only one psychiatric hospital and a health care system based on western principles. Therefore, the area is uniquely suitable for epidemiological research. All four EPS were measured simultaneously with the use of valid and reliable rating scales. The purpose of the study was to assess the strength of the inter-relationships between EPS and to estimate the prevalence of each combination of EPS.

Methods

Patients and methods

The methods have been described in detail previously.[16] In short, the study was performed in the Dr. D.R. Capriles Hospital located on Curaçao. The population

of Curaçao is mainly of Afro-Caribbean origin. Most patients (75%) in the clinic were born on Curaçao. Twelve per cent of the patients came from Aruba, an island that formerly belonged to the Netherlands Antilles but now has a special status.

On the first of June 1992 there were 214 psychiatric inpatients in the Dr. David Ricardo Capriles Clinic. Almost all patients (95%) were of Afro-Caribbean origin. The inclusion criteria for this study were: (i) no organic disorders that could cause movement disorders; (ii) a history of neuroleptic use for at least three months; and (iii) informed consent. There were 194 patients who fulfilled the inclusion criteria.[16]

The research criteria and the case definitions of each extrapyramidal syndrome have been described in detail previously.[16] Tardive dyskinesia was assessed with the Abnormal Involuntary Movement Scale (AIMS),[17,18] parkinsonism with the motor examination part of the Unified Parkinson Disease Rating Scale (UPDRS),[19] akathisia with the Barnes Akathisia Rating Scale[20,21] and tardive dystonia with the Fahn-Marsden scale.[22,23]

Four raters had been trained for a week in the use of a movement disorder examination protocol at the Dystonia Clinical Research Center at Columbia University, New York (Director: Dr. S. Fahn). Each patient was examined simultaneously by two raters. The way in which the inter-rater reliability was measured has been described previously.[16] The inter-rater statistics were assessed with Cohen's kappa. Our kappas were: tardive dystonia 0.78, tardive dyskinesia 0.50, UPDRS 0.53 (tremor 0.70, rigidity 1.0), and akathisia 0.65.

The medical files were reviewed by two medical doctors who had no knowledge of the existence of movement disorders in the patients. The following data were collected about each patient: age, sex, age on first admission to the psychiatric hospital, number of admissions, total duration of stays in the clinic, and duration of the last stay. The DSM-III-R diagnosis at the time of the study[24] was assessed on the basis of the chart notes and confirmed at a consensus meeting attended by the first author (P.N.vH.) and the treating psychiatrist. Furthermore, diabetes mellitus and leukotomy were measured as separate variables because they occurred fairly frequently and are known to influence the prevalence of tardive dyskinesia.[25] Finally, the use of medication was assessed, neuroleptics being converted into chlorpromazine equivalents (CPZEQ), and anticholinergics, benzodiazepines, antidepressants and other medication being converted into yes/no variables.[26,27]

Data analysis

The relationships between the various EPS were analyzed by multiple logistic regression analysis.[28] This was done in the following way: a specific extrapyramidal syndrome (e.g. tardive dyskinesia defined by case definition) was entered into the analysis as the dependent variable. Another extrapyramidal syndrome (e.g., parkinsonism) was entered as the independent variable, together

with the following potential confounders: age, sex, age on first admission, number of admissions, total duration of stay(s) (in years) and duration of the last stay (in years), psychiatric diagnosis (for each category see Table 1), diabetes mellitus, leukotomy, neuroleptic dose in chlorpromazine equivalents, anticholinergics, benzodiazepines, lithium, antidepressants and other medication. The resulting regression coefficient for the independent variable (e.g., parkinsonism) describes the relationship between tardive dyskinesia and parkinsonism corrected for the confounding effects of the other variables in the equation.

Table 1 *Characteristics of the study population (N=194)*

Characteristic	%	Mean	SD
Males	72.7		
Psychiatric diagnosis DSM-III-R[a]			
Schizophrenia	77.3		
Affective disorder	5.2		
Dementia	8.2		
Mental retardation	4.6		
Cocaine abuse[b]	13.9		
Other	24.7		
Leukotomy in the past	11.9		
Diabetes mellitus	9.3		
Current medication			
Neuroleptics	86.1		
Depot medication	55.7		
Anticholinergics	34.0		
Benzodiazepines	19.1		
Antidepressants	4.6		
Lithium	10.3		
Other	22.2		
Age (years)		53.1	16.7
Age on first admission		26.6	11.1
Total duration of stays in hospital (years)		20.1	16.5
Duration of last stay in hospital (years)		15.6	16.2
Number of times admitted		5.1	4.3
Neuroleptic dose (CPZEQ mg/day)[c]		698	695

[a]A patient can have multiple diagnoses.
[b]On Curaçao, addiction to drugs refers almost exclusively to cocaine (mostly used as base) and cannabis.
[c]Of the 86% of the patients currently using neuroleptics.
CPZEQ=chlorpromazine equivalents.

Trend tests were carried out to see whether a gradual change in one extrapyramidal syndrome alters the probability of having another. Trend tests were computed by treating each extrapyramidal syndrome (when it was put into the analysis as an independent variable) as an ordinal variable, by which the

total score was recoded in three categories (0,1,2 with 0 as the reference group. 0= zero point on the scale, 1= 1 to median, 2= median to highest score. The median was calculated using all patients with a score higher than zero).

This paper focuses on the inter-relationships of EPS controlled for all other factors measured. Therefore, the contribution of these other factors to the prevalence of each extrapyramidal syndrome will not be discussed.

Results

Table 1 shows the characteristics of our sample. Of the 108 patients using depot neuroleptics, 42% used fluphenazine and 23% haloperidol. Less than 15% of patients were on the depot neuroleptic zuclopentixol, flupentixol or penfluridol. Oral neuroleptics alone were used by 59 patients. Of these 59 patients 46% used haloperidol. Risperidone, the only atypical neuroleptic, was used by nine patients.

Table 2 shows the odds ratios (OR), adjusted for the variables mentioned, of tardive dyskinesia with other EPS and consecutively of parkinsonism, akathisia and tardive dystonia with other EPS.

Life-time medication data concerning the neuroleptics and the anticholinergics were available in 161 patients. The mean lifetime dose of neuroleptics was 3.3 kg CPZEQ (SD=3.2) and the mean life-time dose of anticholinergics was 22.64 g benztropine equivalents (SD=22.60) (conversion table to benztropine equivalents see ref 27). When life-time medication data are added as potential confounders and the analysis of Table 2 is repeated (then the analysis involves only the 161 patients for whom life-time medication data were available) the results do not change significantly.

Of the 77 patients with tardive dyskinesia, 39% had that disorder only, 17% had tardive dyskinesia with parkinsonism only. Other combinations with tardive dyskinesia were relatively rare (fewer than seven patients).

Of the 70 patients with parkinsonism, 53% had parkinsonism only, 19% had parkinsonism with tardive dyskinesia only. Any other combination with parkinsonism was found in fewer than ten patients.

Of the 18 patients with akathisia, 33% had this disorder only, 28% had akathisia with tardive dyskinesia only. Any other combination with akathisia was seen in fewer than four patients.

Of the 26 patients with tardive dystonia, 19% had tardive dystonia only, 27% had tardive dystonia with tardive dyskinesia only. Any other combination with tardive dystonia was seen in fewer than six patients.

Of the total population, 26% had no EPS, 45% had one, 20% two, 8% three and one patient (0.5%) had all four syndromes.

Table 3 shows the prevalence of all possible combinations of EPS.

Discussion

This study examined both the inter-relationships of various EPS and the prevalence of combinations of EPS in the entire psychiatric inpatient population of a well-defined catchment area. We have found statistically and clinically significant associations between the hyperkinetic syndromes (tardive dyskinesia, tardive dystonia and akathisia). Clinically significant is the finding that having tardive dyskinesia increases the probability of akathisia six-fold. This conclusion may help in the differential diagnosis of akathisia. Akathisia is often overlooked or misdiagnosed (and then treated incorrectly) as psychotic restlessness.

Table 2 *Adjusted odds ratios (OR) with 95% confidence intervals (95% CI)*[a]

Independent variable	Dependent variables			
	Tardive dyskinesia OR (95% CI)	Parkinsonism OR (95% CI)	Akathisia OR (95% CI)	Tardive dystonia OR (95% CI)
Tardive dyskinesia[b]	—	0.6 (0.3-1.3)	6.2 (1.6-24.1)	8.7 (2.3-32.1)
AIMS (1)[c]	—	0.5 (0.2-1.2)	2.2 (0.5-10.1)	1.7 (0.4-7.3)
AIMS (2) [c]	—	0.4 (0.2-1.0)	22.9 (3.3-156.6)	11.0 (2.5-49.2)
Parkinsonism[b]	0.7 (0.3-1.4)	—	0.4 (0.1-1.6)	0.9 (0.3-2.7)
UPDRS (1)[d]	0.4 (0.2-1.0)	—	0.4 (0.1-1.8)	0.1 (0.0-0.5)
UPDRS (2)[d]	0.4 (0.1-0.9)	—	0.5 (0.1-2.1)	0.3 (0.1-1.2)
Akathisia[b]	6.6 (1.8-24.0)	0.4 (0.1-1.5)	—	1.7 (0.3-10.5)
Tardive dystonia[b]	7.5 (2.0-28.5)	1.1 (0.4-3.1)	1.3 (0.2-7.8)	—
FMS (1)[e]	1.6 (0.4-6.4)	2.7 (0.7-9.6)	not computable due to zero cells	—
FMS (2)[e]	13.6 (3.0-60.6)	0.3 (0.0-1.5)	2.5 (0.4-17.2)	—

[a]Each odds ratio is the result of an equation in a logistic regression analysis with one extrapyramidal syndrome as dependent variable and one other extrapyramidal syndrome as independent variable adjusted for all other variables measured; e.g., in patients with tardive dyskinesia the probability of having akathisia is increased 6.6 times compared to patients without tardive dyskinesia.

[b]As defined by case definition (see Methods).

[c] AIMS converted to a trichotomous variable:
AIMS score of 0 is the reference category;
AIMS (1) is AIMS score of 1-9;
AIMS (2) is AIMS score of 10 to highest score.

[d]UPDRS converted to a trichotomous variable:
UPDRS score of 0 is the reference category;
UPDRS (1) is UPDRS score of 1-11;
UPDRS (2) is UPDRS score of 12 to highest score.

[e]Fahn-Marsden rating scale score converted to a trichotomous variable:
Fahn-Marsden scale score of 0 is the reference category;
FMS (1) is Fahn-Marsden score of 1-9;
FMS (2) is Fahn-Marsden score of 10 to highest score.

Our finding indicates that any clinician diagnosing tardive dyskinesia in a patient should also search for akathisia. However, according to the following analysis this conclusion may be valid only in patients receiving moderate to high doses of neuroleptics. The unadjusted odds ratio between tardive dyskinesia and akathisia was not significant. Therefore, we assessed which factor in the logistic regression analysis increased the adjusted OR between tardive dyskinesia and akathisia. The neuroleptic dose appeared to be a strong factor. In fact, when the neuroleptic dose was converted into a dichotomous variable, a strong interaction effect appeared (neuroleptic dose split into above and below 500 mg CPZEQ, which is often considered as a border between low and moderate to high dose). In the patients with less than 500 mg CPZEQ, having tardive dyskinesia reduced the probability of having akathisia (OR of 0.3), whereas the opposite was the case in patients using more than 500 mg CPZEQ; in the latter, tardive dyskinesia increased the probability of having akathisia (OR 8.8).

In patients with tardive dyskinesia, the probability of having tardive dystonia as well is strikingly increased. One clinical consequence of this finding is that diagnosing tardive dyskinesia must alert the clinician to look for tardive dystonia, a disorder that is often overlooked. Since tardive dystonia causes more distress to the patient than tardive dyskinesia,[22] switching to an atypical neuroleptic like clozapine may be a successful strategy.[29]

Another finding in this study was that parkinsonism was inversely related to both tardive dyskinesia and tardive dystonia. The inverse relationship between tardive dyskinesia and parkinsonism has also been reported by others.[5,8,30-32] Previously, it was hypothesized that tardive dyskinesia and parkinsonism represented opposite pathophysiological states, with an excess of dopamine in the former and a deficiency of dopamine in the latter. However, quite often both syndromes co-exist, which makes such a hypothesis less likely. A possible alternative hypothesis is that parkinsonism is a forerunner of tardive dyskinesia, as has been proposed by several authors.[3,33] As far as we know, we are the first to report that having parkinsonism reduces the probability of having tardive dystonia. A possible explanation is that tardive dystonia and tardive dyskinesia share a common etiology. In the past many researchers have considered dystonic features a variant of tardive dyskinesia.[2] Burke,[22] on the other hand, argued that tardive dystonia should be regarded as distinct from classic tardive dyskinesia because (1) it has different phenomenologic manifestations, (2) patients with tardive dystonia are younger at onset, and lack the female predominance seen with tardive dyskinesia, and (3) the pharmacological reactions involved are different (tardive dystonia is sometimes alleviated by anticholinergics and tardive dyskinesia is sometimes exacerbated by anticholinergics).

This study shows that EPS are a common phenomenon in this population: only one quarter of the patients had no signs of EPS whereas almost 30% had

two or more EPS. Furthermore, in the subgroups of our patients with at least one extrapyramidal syndrome most had two or more EPS. As mentioned above, we are aware of only two studies that have been conducted in a geographically well-defined catchment area.[12,15] The Nithsdale schizophrenia study assessed tardive dyskinesia, parkinsonism and akathisia simultaneously; results showed that 44% of the patients in that study had no EPS whereas 20% had two or more EPS.[12] The lower prevalence of EPS in the Nithsdale schizophrenia study may have been due to the lower mean age of that population. The study by O'Hara et al.[15] assessed tardive dyskinesia and parkinsonism simultaneously in long-term psychiatric patients in day-care in south London and reported prevalences of 15% and 21%, respectively. These percentages are much lower than ours and also lower than those reported by others.[2] The authors did not provide any explanation for the difference.[15] In many other studies the prevalence of the combination of tardive dyskinesia with parkinsonism in the population studied ranges from 5.5 to 24%.[3,34,35] However, an obvious problem in comparing the studies is the heterogeneity of the populations and the measurements employed.

Table 3 *Prevalence of combinations of extrapyramidal syndromes (N=194) (percentages in descending order)*

Combination of EPS	*N*	*%*
Tardive dyskinesia and parkinsonism	25	12.9
Tardive dyskinesia and tardive dystonia	19	9.8
Tardive dyskinesia and akathisia	10	5.2
Parkinsonism and tardive dystonia	9	4.6
Parkinsonism and akathisia	5	2.6
Akathisia and tardive dystonia	2	1.0

Although there is an inverse relationship between tardive dyskinesia and parkinsonism, the prevalence of the coexistence was as high as 12.9%. This combination constitutes another clinical dilemma, since administering anticholinergics relieves parkinsonism, but may increase the severity of tardive dyskinesia.[36] Currently, there is no method of treating both simultaneously. However, in clinical practice it is advisable to treat the condition about which the patient complains most; very often this is parkinsonism.[37]

We like to stress that the inter-relationships between the EPS were revealed in this study by the use of multivariate techniques; most relationships disappeared when only the crude OR was computed. This may partly explain why other studies that used only univariate techniques did not find these associations,[13,21] and shows the importance of taking into account the effect of possible confounders.

The cross-sectional design of our study does not permit us to distinguish between factors that affect EPS development and factors that affect the course

of the EPS once it has occurred. Therefore, this study cannot address relationships between different EPS over time. Furthermore, cross-sectional studies are particular vulnerable to selection biases. The inclusion of nearly all psychiatric inpatients in a circumscribed area reduces the selection bias. This, in combination with the fact that the medical history of these patients is documented in a single file by Western doctors, should mean that the data can be extrapolated to other psychiatric inpatients. However, it could be possible that in our area, with a mainly Afro-Caribbean population, the cultural setting did influence the characteristics of the population. Indeed, the population has some unusual characteristics: a male-female ratio of 2.7, a low prevalence of affective disorders, and a 12% prevalence of leukotomy. These variables were controlled for in the analysis.

One might wonder whether the raters were able to make a clear distinction between the various EPS, in particular between the hyperkinetic syndromes (tardive dyskinesia, akathisia, tardive dystonia). As was mentioned, however, the raters were well trained and most of the time they were able to differentiate between the pattern of normal, restless movements of akathisia, the abnormal movements of dyskinesia and the twisted movements of dystonia. Moreover, akathisia was defined as both subjective complaints of restlessness and objective motor movements, typically movements of the legs.[20] However, no differentiation could be made between akathisia and tardive akathisia.

In conclusion, our study has shown that there are strongly positive correlations between hyperkinetic forms of EPS. More specifically, the probability of having akathisia, which is often neglected or misdiagnosed, is markedly increased in a patient suffering from tardive dyskinesia. Furthermore, it is quite common for chronic psychiatric inpatients to suffer from combinations of EPS. Therefore, it is definitely advisable that psychiatrists dealing with such patient groups should be familiar with treatment strategies for minimizing these EPS and should regularly check on the state of the EPS.

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Chapter 1.4

Intermittent neuroleptic treatment is a risk factor for tardive dyskinesia

The Curaçao Extrapyramidal Syndromes Study: III.

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Abstract

Objective

We examined the association between three lifetime medication variables (cumulative amount of neuroleptics, number of interruptions in treatment with neuroleptics, cumulative amount of anticholinergics) and the occurrence and/or severity of tardive dyskinesia (TD).

Method

The study (N=133, mean age 51.5 years) was conducted in the only psychiatric hospital of a well-defined catchment area (the Netherlands Antilles). The presence and the severity of TD were measured using the Abnormal Involuntary Movement Scale.

Results

Of the three lifetime medication variables, only the number of neuroleptic interruptions was significantly related to TD (adjusted OR 1.3, 95% CI 1.07-1.62). If the number of neuroleptic interruptions is dichotomized into less than or equal to two and more than two the resulting adjusted OR is 3.3 (95% CI 1.27-8.49).

Conclusions

Our finding supports the schizophrenia protocol that recommends long-term neuroleptic treatment rather than targeted or intermittent neuroleptic treatment. More than two interruptions increase the risk of TD more than threefold.

In the absence of a safe and effective treatment for tardive dyskinesia (TD), recognition of risk factors is important. There is a relatively good consensus about demographic and clinical risk-factors such as age, and some degree of consensus about risk-factors such as female gender, brain damage, diabetes mellitus, and early development of extrapyramidal side effects.[1-3] However, the relative contribution of various medication variables is far from clear.[1,2]

On the basis of the literature it was hypothesized that the cumulative amount of neuroleptics, the number of neuroleptic interruptions, and the cumulative amount of anticholinergics would increase the risk of TD.[1,2] Intermittent neuroleptic treatment lowers the cumulative amount of neuroleptics. In the seventies such treatment was advocated as a strategy for reducing the risk of TD.[4,5] The results of the few studies that address this issue are not consistent. Jeste et al. reported drug-free intervals as a risk factor for persistent TD. However, his results were based on a small sample of patients all aged over 50 years.[6] Two studies with a larger sample did not find that drug-free periods were a risk factor.[7,8] A few studies have compared intermittent with continuous neuroleptic treatment. Some found no difference while others found an increase in the risk of TD in the group with intermittent neuroleptic treatment.[1,2,4,9] However, these results pertain to highly selective study populations, which makes generalizations difficult. In our study population the selection bias was reduced because our population involved all psychiatric inpatients from a well-defined area.[10]

The goal of our study was to examine the association between the three lifetime medication variables mentioned and TD.

Patients and Methods

The study was performed in the only psychiatric hospital on Curaçao, which is the main island of the Netherlands Antilles. The target group comprised all inpatients in this hospital on 1st June, 1992.[10] The population is mainly of Afro-Caribbean origin. To be eligible for the study a patient had to fulfill the following criteria: (i) informed consent, (ii) no organic disorders that could cause movement disorders, (iii) a history of neuroleptic use for at least three months, and (iv) currently using neuroleptics. The last inclusion criterion was used because it was impossible to find out whether a patient was suffering from TD at the time when neuroleptic treatment was discontinued.

One hundred and sixty-six patients fulfilled the inclusion criteria.

The psychiatric diagnoses (DSM-III-R American Psychiatric Association, 1987) were based on the chart notes and confirmed in a consensus meeting between the first author and the treating psychiatrist.

TD was assessed with the Abnormal Involuntary Movement Scale (AIMS)[11] with case definition according to Schooler and Kane's criteria.[12] The severity of TD was measured by the AIMS as the sum of the first seven items.

The lifetime medication data were reviewed by two junior medical doctors who had no knowledge of the existence of movement disorders in the patients. All medication data for a patient could be found in one file and were registered by western trained doctors. The junior doctors were instructed to mark missing or puzzling data. Lifetime medication data were considered valid when they were clearly indicated in the chart notes for at least 90% of the time in which medication had been taken. Neuroleptics were converted into chlorpromazine equivalents (CPZEQ), and anticholinergics into benztropine equivalents.[13]

Data analysis

For each of the three lifetime medication variables a separate multiple logistic regression analysis and multiple linear regression analysis was applied, incorporating the following potential confounders age, sex, diagnosis (schizophrenia yes/no), diabetes mellitus, leukotomy, current dosage of neuroleptics, and current use of anticholinergics, lithium, antidepressants, benzodiazepines and other medication.[1,14] The resulting OR's and regression coefficients can be interpreted as a measure of the effect of the risk factor corrected for all potential confounders.

Results

Lifetime medication data were considered valid in 133 (80%) patients. The characteristics of the 133 patients were as follows: male 73.7%, diagnosis of schizophrenia 84.2%, diabetes mellitus 11.3%, and leukotomy 12.8%, mean age 51.5 years, SD 15.3 (males' mean age=49.4 yrs, SD=14.2, females' mean age=57.3 yrs, SD=16.8). Medication used at the time of the assessment consisted of: anticholinergics (34.6%), benzodiazepines (18.0%), antidepressants (4.5%), lithium (10.5%), other medication (21.8%), and the mean neuroleptic dose was 717 CPZEQ (SD=748) (male's mean neuroleptic dose=724 CPZEQ, SD=700, female's mean neuroleptic dose=700 CPZEQ, SD=879). The prevalence of TD was 36.1%. Table 1 shows the relationship between the three lifetime medication variables and the occurrence of TD. Only the number of neuroleptic interruptions was significantly related to the occurrence of TD. If the number of neuroleptic interruptions is dichotomized into less than or equal to two and more than two the resulting adjusted OR is 3.3. The linear regression analysis, which refers to the relation between the three lifetime medication variables and the severity of TD, showed no significant effect for the lifetime intake of neuroleptics (ß=-0.17, t= -1.29, df=120, p=0.2) and the lifetime intake of anticholinergics (ß=-0.03, t=-1.91, df=120, p=0.06), but did show a significant effect for the number of neuroleptic interruptions (ß=0.36, t=2.43, df=120, p=0.02).

Discussion

The most important finding is that intermittent neuroleptic treatment increases the risk of TD. This finding supports the schizophrenia protocol that recommends long-term low-dose neuroleptic treatment rather than targeted or intermittent neuroleptic treatment.

Table 1 *The relation of the three lifetime medication variables to the occurrence of TD*

		Logistic regression analysis	
Lifetime medication variable	Mean (SD)	Adjusted OR[#]	95% CI
Lifetime intake of neuroleptics (Kg CPZEQ)	3.8 (3.3)	0.93[a]	0.78-1.11
Number of neuroleptic interruptions each longer than three months	1.7 (2.2)	1.32[b]	1.07-1.62
Number of neuroleptic interruptions dichotomized: ≤ 2 versus > 2		3.29[c]	1.27-8.49
Lifetime intake of anticholinergics (gram benztropine equivalents)	25.2 (22.5)	0.99[d]	0.97-1.01

[#]Each odds ratio (OR) was adjusted for potential confounders (see data analysis)
[a]Wald χ^2=0.63 df=1 p=0.426
[b]Wald χ^2=6.57 df=1 p=0.010
[c]Wald χ^2=6.03 df=1 p=0.014
[d]Wald χ^2=0.99 df=1 p=0.321

Our finding is in line with animal studies,[4] e.g. a study in rats showed that following neuroleptic withdrawal it was only the intermittently treated group which developed persistent increases in vacuous chewing movements.[15] It could be that repeated 'on-off' manipulations of some dopaminergic systems may have a greater negative impact then continuous dopaminergic activity.

Our finding that intermittent neuroleptic treatment is a risk-factor for TD is further supported by the fact that it was a risk-factor not only for the presence but also for the severity of TD. Furthermore, if our data are analyzed with the use of stepwise logistic regression in which a stepwise algorithm generates the 'best' model for predicting TD,[7,8,14] the number of interruptions in neuroleptic treatment turns out to be the second factor after the well-known risk-factor age.

Our inability to find a relationship between the cumulative amount of neuroleptics used and TD may be due to the long duration of neuroleptic treatment in most of the patients of our sample; only seven patients had used neuroleptics for less than two years. It may be that cumulative dosage as a risk factor for TD is important only during the first few years of neuroleptic

treatment.[1,2,4]
The fact that we found no relation between the cumulative amount of anticholinergics and TD is consistent with results of others who suggested that anticholinergics increase the severity of existing TD but do not cause TD.[1,2]

This study has some limitations. First, the number of interruptions in treatment with neuroleptics was measured retrospectively; therefore the resulting measurement error could produce a bias. However, all medication data of a patient were noted in one file, mainly by western trained doctors. Second, a group of 33 patients was excluded from the analysis because no valid lifetime-medication data were available for these patients. In this group the prevalence and the severity of TD was the same, which makes it less likely that the inclusion of this group would have changed the results significantly. Third, a retrospective study of risk-factors is particularly vulnerable to selection biases. However, the inclusion of nearly all psychiatric inpatients in a circumscribed area reduces the selection bias considerably. Fourth, it could be that in some patients the expression of TD was masked by the neuroleptics. However, this is inevitable for any prevalence study in which patients are on neuroleptics. Fifth, patients not currently using neuroleptics were excluded because no data about TD were available at time the neuroleptics were discontinued. However, if this group had been added to the analysis (using the current status of TD) the results would not have changed significantly.

In conclusion, if treatment with neuroleptics is required, the treatment should preferably not be given intermittently; more than two interruptions increase the risk of TD more than threefold.

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PART 2

Mijn eigen stem zelfs,
deze diepe winternacht,
lijkt niet de mijne.

Otsuji

Chapter 2.1

TARDIVE DYSTONIA

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Abstract

This paper provides an overview of the phenomenology, epidemiology and treatment of tardive dystonia. Tardive dystonia is one of the extrapyramidal syndromes that starts after long-term use of dopamine receptor antagonists. The diagnosis is based on the presence of chronic dystonia, being defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures. Furthermore, the patient must develop dystonia either during or within 3 months of a course of antipsychotic treatment and other causes such as Wilson's disease, acute dystonia or a conversion reaction must be ruled out.

Tardive dystonia occurs in about 5% of patients on long-term antipsychotic treatment. Some probable risk factors for tardive dystonia are younger age, male, and the presence of tardive dyskinesia.

The treatment of tardive dystonia starts with an evaluation of the need for using the causative drug. If antipsychotics have to be continued, a switch to an atypical antipsychotic may be helpful. However, since these agents can only be taken orally they may affect the compliance of medication-taking in patients who were previously on depot antipsychotics.

If the dystonia is relatively localized, an effective but not well-known treatment possibility is to use botulinum toxin. If tardive dystonia is more extensive, either dopamine depleting drugs or high dosages of anticholinergics can be tried.

Tardive dystonia is one of the extrapyramidal syndromes that starts after long-term use of dopamine receptor antagonists. Tardive dystonia is underdiagnosed or often misdiagnosed; some of the treatment possibilities are hardly known among psychiatrists. This paper provides a survey of the diagnosis, epidemiology and treatment of tardive dystonia. Dystonia is defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures.[1] The term 'dystonia tarda' was coined by Keejan and Rajput in 1973.[2] However, it was not until 1982 that Burke et al.[3] published a series of case reports on 42 patients with tardive dystonia and since 1982 more than 300 cases have been added to the literature.[4]

Tardive dystonia should be considered as distinct from tardive dyskinesia because (1) it has different phenomenological manifestations, (2) patients with tardive dystonia are younger at onset, and lack the female predominance seen with tardive dyskinesia, and (3) different reactions to anticholinergics: such drugs can alleviate tardive dystonia but exacerbate tardive dyskinesia.[4,5]

It has been hypothesized that tardive extrapyramidal syndromes are not side-effects of antipsychotics but are closely related to the disease process of schizophrenia.[6-8] This hypothesis is based on descriptions of dyskinetic and dystonic movements in psychiatric patients in the pre-neuroleptic era[9,10] and on three prevalence studies showing that extrapyramidal syndromes are not uncommon among neuroleptic-naive psychiatric patients.[8,11,12] However, this hypothesis is in conflict with many case reports that describe the development of tardive dystonia in non-schizophrenic patients who use antipsychotics for anxiety or personality disorders. In addition, tardive dystonia has been reported to be a consequence of dopamine-blocking agents that are used as anti-emetics. Moreover, there are case-reports in which tardive dystonia disappears after withdrawal of antipsychotics and reappears after re-exposure to antipsychotics; such on-off phenomena make a causal relationship very plausible.[5,13] Furthermore, animal studies have shown that long-term use of antipsychotics can cause movement disorders comparable to tardive dyskinesia/dystonia.[14]

In line with the view that tardive dystonia is a separate entity and is caused by dopamine-blocking agents, Burke et al.[3] suggested the following diagnostic criteria: (1) the patient must have dystonia, as defined above (2) the dystonia must have developed either during or within 3 months of a course of neuroleptic treatment, (3) Wilson's disease must be ruled out and there must be no other neurological signs to suggest one of the many causes of secondary dystonia, (4) there must be a negative family history for dystonia.

Clinical features

Tardive dystonia is usually divided into four categories: focal (single body part affected), segmental (two or more contiguous body parts), multifocal (two or more non-contiguous body parts) and generalized (combined involvement of at

least one leg and trunk and any other body part).[15]

Patients develop tardive dystonia after varying periods of exposure to antipsychotics, ranging from a few days to many years.[3,16,17] In contrast to tardive dyskinesia, tardive dystonia often begins after a relatively short period of exposure to antipsychotics, about one fifth of the cases occurring in the first year, and half of the cases in the first five years of exposure.[17]

Tardive dystonia can affect every body area in the form of torti-retro-laterocollis, blepharospasm, oromandibular, laryngeal, arm, trunk, and leg dystonia. Oculogyric crises are a well-known form of acute dystonia but a tardive form has also been reported.[18,19] The most common site for tardive dystonia is the cranial and neck region but the involvement of the arms is common too.[3,17]

Tardive dystonia often starts insidiously, about two thirds of the onset being located in face and or neck. Onset in an arm is less common and tardive dystonia starting in a leg is very rare. In about three quarters of the patients the dystonia progresses to a segmental state, but progression to a generalized state is uncommon.[3,17] There seems to be a relation between the age of onset of dystonia and the final severity; patients with generalized dystonia were younger than those with focal dystonia.[3,17]

The onset of tardive dystonia seems to occur earlier in males than in females[3,17,20-22] and we also found this in a study we conducted in Curaçao (age of onset in males 38.4 versus females 59.0 years; N=22; F=9.08 $p<0.007$, unpublished data).[23] Remarkable features of tardive dystonia are the 'sensory tricks' which are tactile or proprioceptive stimuli that may relieve the severity or the subjective discomfort of the dystonia; e.g. a patient with torticollis obtains relief by touching his chin.[15] The severity of tardive dystonia can increase with fatigue and stress but tends to be suppressed through relaxation, hypnosis and sleep. Mania and psychosis can alter the severity of tardive dystonia; some authors have reported a worsening[13] and others an improvement.[24,25] Sometimes tardive dystonia can cause severe pain[3,26] and even a rib fracture has been reported.[27]

All agents that block dopamine-receptors in the central nervous system such as antipsychotics, anti-emetics (e.g. prochlorpromazine, metoclopramide), and the antidepressant amoxapine, can cause tardive dystonia.[3,5,28,29] Cocaine has been reported to exacerbate existing tardive dystonia.[30]

Differential Diagnosis

The differential diagnosis starts with the identification of the type of involuntary movement. Dystonia can be confused with tardive dyskinesia, myoclonus, tremor, and tics. Tardive dyskinesia is characterized by writhing, purposeless, irregular movements and is located most of the time in the face, lips, tongue or jaw and less frequently in limbs or trunk.[14] Myoclonus is characterized by

sudden, shock-like contractions of a muscle or a group of muscles. Tremor is a rhythmic, regular, oscillating movement. Tics are sudden, stereotyped, complex, repetitive, normally coordinated but inappropriate movements.[31]

When dystonia has been diagnosed the first possibility to consider is acute dystonia. Acute dystonia almost always occurs within five days of beginning antipsychotics or after a substantial increase in dosage and responds very well to the administration of anticholinergics.

The next possibility is Wilson's disease, an inborn error in copper metabolism that can express itself as dystonia. Since Wilson's disease is treatable it must be carefully ruled out by ascertaining a normal serum ceruloplasmin level and the absence of the Kayser-Fleischer ring.[32]

There are numerous other neurological causes of dystonia. However, they should be ruled out only if other progressive neurological signs are present besides dystonia.[5] If dystonia is not accompanied by other neurological signs one should consider: (1) a conversion reaction, (2) dystonia caused by other compounds, and (3) idiopathic dystonia.

In contrast with organic dystonia, a conversion reaction generally does not show normal progression over time and does not tend to increase during activity. Furthermore, a conversion reaction shows a static abnormal posture and lacks the dynamic component of organic dystonia.[33,34] However, in clinical practice the differentiation can be very difficult.[34,35] A rule of thumb is that the presence of other tardive syndromes supports the diagnosis of tardive dystonia.[5,15]

Dystonia can also be caused by compounds other than antipsychotics, e.g. levodopa,[36] carbamazepine,[37,38] dextroamphetamine,[39] and diphenylhydantoin.[40] Generally the dystonia disappears after the dose is reduced or the causative drug is stopped.

Idiopathic or primary dystonia can often be distinguished from tardive dystonia by taking a careful history about the time of onset of the dystonia in relation to start of antipsychotics. Furthermore, the prevalence of idiopathic dystonia in the general population is only 0.03% which is a much lower percentage than the prevalence of tardive dystonia.[41]

Etiology

The pathophysiology of tardive dyskinesia and of tardive dystonia is not clear. It is thought to result from postsynaptic supersensitivity induced by sustained inhibition of dopaminergic neurotransmission.[42] It is also possible that the anti-noradrenergic action of the antipsychotics plays an important role, because in idiopathic torsion dystonia a reduction of the amount of noradrenaline in the hypothalamus, mammillary body, subthalamic nucleus and locus ceruleus was found.[43] Furthermore, antipsychotics have strong affinities to sigma receptors and there is a relationship between the sigma receptors and dystonia.[44]

A search for a genetic cause of tardive dystonia was done on the DYT1 gene on chromosome 9q34; early-onset primary dystonia in most Ashkenazi Jews is due to a single founder mutation in this gene. However, there was no evidence that the DYT1 founder mutation contributes to tardive dystonia.[45]

Prevalence and risk factors

Prevalence

Prevalence rates come from population-based studies and are highly dependent on the patient characteristics of the population involved and the method of case finding.

Table 1 *Prevalence studies of tardive dystonia*

Study	*N*	Prevalence (%)[a]
Owens et al. 1982[11]	411	2.7
Yassa et al. 1986[48]	351	2.0
Friedman et al. 1987[52]	331	1.5
Yassa et al.1989[22]	555	1.4
Sethi et al. 1990[55]	125	21.6
Inada et al. 1991[47]	716	2.1
Sachdev 1991[46]	100	1.0
Chiu et al. 1992[49]	917	0.4
Micheli et al. 1993[51]	878	0.9
Hoffman et al. 1994[53]	119	11.0
Pourcher et al. 1995[54]	64	6.3
Raja 1995[50]	200	4.0
van Harten et al.1996[23]	194	13.4

[a]Mean ± SD = 5.3% ± 6.4%

As far as we know, there have been thirteen prevalence studies on tardive dystonia; these are shown in table 1. Only one study was conducted in an outpatient setting,[46] all other studies were conducted in a psychiatric hospital. Most studies used the diagnostic criteria of Burke[22,23,46-51] and some added a cut-off point on a rating scale.[23,52,53] About half of the studies used rating scales.[22,23,48,52-55] It is difficult to compare the prevalence rates because of the diversity of the rating scales used and the lack of consensus about a cut-off point. The prevalence figures reported in earlier studies[11,22,48,52] tended to be lower than those reported in more recent studies.[23,53-55] A possible reason for this difference is that in earlier studies only patients with moderate to severe forms of tardive dystonia were considered as cases, whereas in later studies the diagnosis was also applied to mild cases. This is supported by our own study which reported a prevalence of 13.4% when mild cases were included and a prevalence of only 2.9% when only moderate to severe cases of tardive dystonia

were considered.[23] Also the high prevalence found by Sethi et al.[55] is due to inclusion of very mild cases; only 20% of cases were symptomatic.

An estimate of the prevalence of tardive dystonia, calculated by taking the mean of all thirteen prevalence rates, would be 5.3%. In such a calculation each study is given equal weight; this method was also used in a review that estimated the prevalence of tardive dyskinesia.[56]

Risk factors

To predict individual susceptibility and to develop preventive strategies one needs to be able to identify risk factors. Crucial to the definition of a risk factor is that it should precede the occurrence of the illness. Therefore, the most valid way to establish risk factors would be to conduct a prospective longitudinal study in a population without tardive dystonia and measure the risk factors in that population.[57] Such a study could distinguish between factors that cause tardive dystonia and factors that affect the course of tardive dystonia once it has occurred. However, no such study has been carried out for tardive dystonia. Therefore, we have to derive our evidence from cross-sectional studies and case series. Table 2 shows the putative risk factors found in the literature.

Table 2 *Risk factors for tardive dystonia derived from case studies and cross-sectional studies*

Risk factors	Comment
Age	Patients with tardive dystonia are younger than patients with tardive dyskinesia.[22,23,49,50,58] Age of onset of tardive dystonia is lower than age of onset of tardive dyskinesia.[20,50,53,58-60]
Sex	Male preponderance.[3,,22,48,52,59,61] Some found no difference.[17,20,23,47,49,60]
Race	Extremely low prevalence in a Hong-Kong Chinese inpatient population.[49] A Japanese study found rates similar to those in western studies.[47] No difference in prevalence rates between Afro-Americans and white patients.[55]
Other extrapyramidal syndrome	Increased risk of tardive dystonia in patients with tardive dyskinesia.[23,53] One study found no relationship.[55]
Other factors that may increase the risk	History of acute dystonia.[62] Affective disorder.[21] Mental retardation.[3,20,52] History of ECT.[52]

Treatment

The treatment strategy for tardive dystonia starts with an evaluation of the need for causative drugs, because antipsychotics are often prescribed for non-psychotic conditions.[3,63] However, if antipsychotics have to be continued one can lower the dose as much as possible. Alternatively, a switch to an atypical antipsychotic can considered since these antipsychotics are less likely to cause extrapyramidal side effects. However, so far no controlled trials have been conducted to measure the effect of such a switch on patients with tardive dystonia. Several case reports have described dramatic improvements in tardive dystonia upon administration of clozapine.[13,64-67] If tardive dystonia does not improve after a switch to an atypical antipsychotic the addition of a benzodiazepine such as diazepam, clonazepam or lorazepam may be beneficial.[68,69] If the dystonia is relatively localized as in focal or mild segmental forms, botulinum toxin should be considered. Botulinum toxin is the most potent biological poison known and at the same time it is an important development in the treatment of dystonic features. It is injected in minute quantities into the contorted muscles and causes a permanent blockade of neurotransmission at the motor endplates by inhibiting acetylcholine release from nerve endings. This induces prolonged muscle weakness without systemic toxicity. The paralytic effect of botulinum toxin subsides over a period of 8 to 12 weeks as new nerve terminals develop. Reinjecting the muscles restores the original beneficial effect.[70] According to several controlled clinical trials botulinum toxin is the treatment of choice in idiopathic focal dystonias, such as blepharospasm, cervical dystonia, oromandibular dystonia, laryngeal dystonia and limb dystonia.[70] Although these trials were promising, they did not include patients with tardive dystonia. Recently, an open-label study showed that botulinum toxin is also effective in tardive dystonia. Thirty-four patients with relatively localized forms of tardive dystonia unresponsive to oral medications were treated with injections of botulinum toxin. Cervical dystonia was the most frequent manifestation in this group of patients. There was marked or moderate improvement in 29 of the 34 patients.[71] A few case reports support this treatment option.[72-75] If the dystonia is too comprehensive to use botulinum toxin, a trial can be conducted with either dopamine depleting drugs (reserpine, metyrosine or tetrabenazine) or high dosages of anticholinergics. However, the results are often disappointing.[3,17] Lisuride was studied in 42 patients with various types of dystonia. Eight patients improved and the response was confirmed by double-blind placebo substitution.[76]

Other agents that have been described as helpful in case reports are bromocriptine,[77] deanol,[78] baclofen,[79] ceruletide,[80] and verapamil.[81] Some case reports describe a dramatic improvement after electroconvulsion therapy;[82-85] one case report however, described a worsening of the dystonia.[86]

Although classical antipsychotics should be avoided, they have the ability to

suppress dystonia and they are used in patients for whom all treatment strategies have failed or in patients to whom the dystonia causes severe pain or muscle damage.[5,17]

Peripheral and brain-surgical methods have been used in idiopathic or torsion dystonia[87] but they are seldomly used in tardive dystonia.[3]

Discussion

About 5% of the patients on long-term treatment with dopamine receptor antagonists develop tardive dystonia, a syndrome that often causes substantial distress. Tardive dystonia does not require the same treatment as tardive dyskinesia. In patients with relatively localized forms of dystonia the use of botulinum toxin could be advocated.

If classical antipsychotics are continued it is unlikely that tardive dystonia will disappear.[3,5] Therefore, as mentioned, a switch from a classical antipsychotic to an atypical antipsychotic may alleviate the dystonia. However, because atypical antipsychotics are only available in oral form, such a switch may induce non-compliance in patients whose motivation for medication taking is very limited. In patients who tolerate depot antipsychotics but are not expected to take daily oral medication, such a switch may decrease the dystonic features but increase the risk of psychotic deterioration. On the other hand, it should be emphasized that non-compliance in some patients is caused by the side-effects of the classical antipsychotics and such patients can become compliant after a switch to an atypical antipsychotic.

Future studies will have to focus on the incidence and identification of risk factors in a longitudinal study. Furthermore, double-blind randomized trials with the atypical antipsychotics are needed to find out how effective a switch to an atypical antipsychotic would be for psychiatric patients suffering from tardive dystonia.

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Chapter 2.2

Use of clozapine in tardive dystonia

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Abstract

This open clinical trial (N=7) measured the course of severe tardive dystonia in chronic psychiatric patients after discontinuation of neuroleptics and subsequent use of clozapine.
The dystonia was regularly assessed using the Fahn-Marsden Rating Scale. The eventual concomitant tardive dyskinesia was assessed using the Abnormal Involuntary Movement Scale. The mean follow-up was 103 weeks.
The results for the tardive dystonia: four patients recovered totally, two improved considerably and one did not recover.
The results for the concomitant tardive dyskinesia: five of the seven patients had also dyskinesia, one patient had a total and three a partly remission. One patient worsened and one developed dyskinesia.
It is suggested to consider clozapine for patients with tardive dystonia who have to continue antipsychotic treatment.

Introduction

Although dopamine antagonists are effective antipsychotics, they induce considerable side-effects. One late-onset side effect is tardive dystonia. The prevalence of tardive dystonia among chronic psychiatric patients is reported as 1 to 2% in most studies, but when mild cases are included, the prevalence may increase to 21%.[1] Tardive dystonia can start at every age, the average age being around 40. It frequently begins in the face or neck and is often accompanied by tardive dyskinesia. Once dystonia develops, the indication for neuroleptics should be reconsidered. For treatment the first choice agents are dopamine depletors such as tetrabenazine and reserpine or high dosages of anticholinergics. Many alternatives are described in case reports.[1,2] Despite treatment the dystonia often persists, especially if neuroleptics have to be continued.[3] In such cases clozapine could be an alternative. Clozapine is an atypical neuroleptic with a low incidence of extra-pyramidal side effects.[4]

The effect of clozapine on tardive dystonia has been published in several case reports with different results. Three patients were treated without results.[5,6] One patient with Meige syndrome improved[7] and another report described one patient who recovered partially and two patients who recovered completely.[8] Two patients only improved after clonazepam was added.[9] In an open study which also included seven patients with tardive dystonia, four patients improved considerably.[10]

The goal of the present study, an open clinical trial, is to describe the course of tardive dystonia in seven chronic psychiatric patients after cessation of neuroleptics and subsequent use of clozapine.

Methods

Patients

All patients gave their written informed consent. All the patients were Negroid and chronic schizophrenics and all diagnostic assessments were within normal limits. Only patient 5, who had a congenital hemiparesis, showed a large lesion on the CT scan. In his case tardive dystonia was diagnosed, as the chronic neurologic syndrome was considered stable and dystonia developed during neuroleptic intake.

The mean total duration of admittance (total days in the clinic) was 5.3 years (SD=4.4, median 4.3, range 0.6-12.9).

Table 1 gives individual data of the seven patients involved.

Assessments

After the start of clozapine treatment, first a weekly (till 18 weeks) and then a monthly blood test was done. Tardive dystonia was diagnosed by the criteria of Burke.[1] Also an EEG and/or a brain CT scan was done.

At what we will call baseline the dystonia was assessed with the Fahn-Marsden rating scale[11] and the classical neuroleptics were discontinued gradually in one week's time. The Fahn Marsden scale comprises a movement and a disability scale and ranges from 0 to 150. A concomitant tardive dyskinesia was rated on the Abnormal Involuntary Movement Scale (AIMS) using Schooler and Kane criteria.[12,13] The AIMS starts with seven items dividing the body into different areas. The authors report the sum of these seven items, ranging from 0 to 28. Psychiatric symptoms were rated with the Brief Psychiatric Rating Scale.[14] Patients were examined simultaneously by two investigators in a standard setting in the afternoon.

Table 1 *Characteristics of the seven patients in the study*

Case Number	Age at start of the study (years)	Age first neuroleptic intake (years)	Interval between first neuroleptic intake and dystonia onset (years)	Duration dystonia prior to baseline (years)
1	24	19	3	1.5
2	41	22	4	15.3
3	35	20	10	4.7
4	30	19	8	3.4
5	54	29	10	15.1
6	25	18	*	0.2
7	37	9	15	2.5

*The dystonia developed three years after neuroleptic intake (in the Netherlands). After a year clozapine was started and the dystonia disappeared. Returning to Curaçao clozapine was discontinued and flupenthixol decanoate 40 mg/2 weeks was added. Five months later a recidive occurred. Two months thereafter the patient entered the study.

Results

Four patients had a neuroleptic free period after baseline with a mean of 9 weeks (SD=9.6, range 1-24). Six patients used clozapine for more than a year with a mean dose of 508 mg/d.

All bloodcounts were within normal limits.

The mean duration of follow-up was 103.3 weeks (SD 51.7, range 38-167).

The mean age at onset of the four patients with total or near total remission of their tardive dystonia was lower than that of the three patients without remission (mean 27.1 versus 31.9 years), and the mean duration of dystonia was shorter (1.9 versus 11.6 years).

The interaction between dystonia and dyskinesia is quite complex.

(Figure 1-7 shows the interaction between tardive dystonia and tardive dyskinesia during follow-up. The dystonia rating is on the left Y-axis and the dyskinesia on the right Y-axis. The X-axis represents the time in weeks.

To compare the patients both axes have been standardized on the highest score in our sample. For dystonia this was 53 and for dyskinesia 16.)

Case 1.
At baseline the patient had a very disabling dystonia containing a severe backward bending, severe retrocollis, and dystonia of both arms and mouth. He also had dyskinesia of facial muscles and the arms. Both the dystonia and the dyskinesia decreased. This patient improved dramatically (Fig. 1).

Case 2.
Patient had a torticollis, involvement of both arms and bending of the trunk. At baseline no dyskinesia was assessed, although it had been reported previously, so that it may have been masked at baseline by neuroleptics. In this case there first seemed to be a negative correlation: while dystonia decreased dyskinesia increased. But later, when the dystonia increased the dyskinesia remained stable. In fact this patient showed hardly any improvement even after almost three years of follow-up (Fig. 2).

Case 3.
Patient had a blepharospasm, a dystonia of the mouth and involvement of the speech. He also had a dyskinesia involving all body areas except the neck. This patient had a very irregular intake of clozapine, for he regularly refused blood tests because of paranoid ideation. There was an overall positive correlation between dyskinesia and dystonia ratings: in the first 20 weeks they both decreased (especially in the few weeks when the patient used a high dose of clozapine) and then without clozapine they increased again (Fig. 3).

Case 4.
At baseline he had a torticollis and trunk dystonia and no dyskinesia. A mild rating of dyskinesia was assessed after a few weeks but it decreased to zero in some weeks without any medication. This patient gained total remission. After a year he discontinued his medication for two weeks but no dystonia returned. (Fig. 4)

Case 5.
Patient had a blepharospasm, mouth opening dystonia, antecollis alternating with a retrocollis and dystonia of the left arm. He also had a myoclonus of the upper palatum and a tremor of the jaw and sometimes the tongue, which also showed dyskinetic movements. He had an overall decrease of dystonia and an increase of dyskinesia (Fig. 5).

Case 6.
At baseline he had a mouth dystonia, dystonia of both arms, and frequent eye-blinking. Dyskinesia involved the lips, tongue, upper and lower extremities. There was a simultaneous decrease of dyskinesia and dystonia ratings with finally a total remission of dystonia and a partly remission of dyskinesia (Fig. 6).

Case 7.
Patient had dystonia of both arms and frequent eye-blinking and a dyskinesia of facial muscles, jaw and arms. The dystonia disappeared completely although frequent eye-blinking remained. The dyskinesia improved partially (Fig. 7).

Three patients (#s 1,4,6) had a history before baseline of transient improvement of the dystonic symptoms after withdrawal of neuroleptics and a worsening after resumption of the neuroleptics.
Patient 1 stopped the neuroleptics half a year before he entered the study. At that time the dystonic symptoms caused such a severe backward bending that he could not see where he was walking. A neuroleptic free period of a few weeks resulted in a partial improvement of the dystonia. However, an increase of psychotic symptoms and aggressive outbursts justified the resumption of neuroleptics (penfluridol 20mg/week), causing an increase of the dystonic symptoms to the same level as before.

In patient 4 penfluridol (20mg/week) was discontinued for 4 weeks, because of severe torticollis, two years before he entered the study. The torticollis improved dramatically, however the psychiatric state worsened and penfluridol was reintroduced with complete return of the torticollis. Then the medication was changed into thioridazine. The torticollis improved somewhat but the psychiatric state worsened. Then flupentixol 100 mg every 2 weeks was introduced, improving the psychiatric state but causing a complete return of the torticollis.

Patient 6, while living in the Netherlands, developed a mouth dystonia, three years after the start of neuroleptics. A year later clozapine was started and the mouth dystonia disappeared. A year thereafter the patient returned to Curaçao, where clozapine was not available, and was replaced by flupenthixol 40 mg every two weeks. Five months later the mouth dystonia reappeared.

Discussion

This study is limited by its open nature and because it included only seven patients. However the results suggest that, even if antipsychotic treatment has to be continued, tardive dystonia is better reversible than is often thought.[3] Four patients had a total or near total remission of their tardive dystonia.

Five of the seven patients had a concomitant tardive dyskinesia at baseline. Of these five patients, one had a total, two a partial remission, one had a very fluctuating rating, and in one patient the tardive dyskinesia worsened. One patient had no tardive dyskinesia at baseline and developed it during the study.

The number of treated patients is too small to reach conclusions about predictors for remission. However, in accordance with the literature the authors found younger age at onset of dystonia and shorter duration of dystonia as possible predictors of remission of tardive dystonia.[3]

The question arises whether the improvement of tardive dystonia is due to the passage of time in the absence of neuroleptics or if clozapine is a suppressing or even a therapeutic agent. Figures 1,4 and 6 clearly show that at least these patients improved already considerably during the non-neuroleptic period, suggesting that time is a main factor.

The interruption of the use of clozapine by patient 5, resulted in a psychotic relapse and an increase of more than 100% on the dystonia scale. With clozapine the dystonia decreased to the previous level in three weeks. This might point to an active suppressing effect of clozapine on the dystonia which is similar to a case described by Lieberman et al.[10] On the other hand discontinuation of clozapine by patient 4, when already in total remission, did not give a relapse. This corresponds with two other case-reports from the same study of Lieberman et al.[10]

Finally one should note the histories of cases 1,4 and 6 before baseline. Their dystonia decreased after withdrawal of classical neuroleptics and it increased or

reappeared after rechallenge with classical neuroleptics. This suggests that with a history of tardive dystonia there is a proneness to develop it again.

Conclusion

On the whole there would seem to be clear indications that the use of clozapine, as in the present study, could benefit some patients with tardive dystonia who cannot do without antipsychotic treatment.

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PART 3

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Joso

Chapter 3.1

Acute Dystonia

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Abstract

This article provides a review of acute dystonia and is intended as a guide for the clinician. A description is given of the clinical features, differential diagnosis, epidemiology, pathophysiology, treatment and the advantages and disadvantages of prophylaxis.
The risk of acute dystonia increases when one or more of the following factors are present: young age, male sex, use of cocaine, past history of acute dystonia and a normal dosage of a high-potency neuroleptic. In most cases, acute dystonia appears after the start of treatment with a dopamine blocking agent or after the dose has been increased. It is often overlooked that when dopamine blocking agents are used not as antipsychotics but for instance as anti-emetics, they may also cause acute dystonia. Anticholinergics are highly effective in both the treatment and prevention of acute dystonia. In any case it is advisable to administer a prophylactic to patients at risk.

Although antipsychotics (neuroleptics) are indispensable in the treatment of psychotic disorders; they can cause the patient great distress because of the extrapyramidal side effects. One of these side effects is acute dystonia, which may appear at a very early stage of the treatment.

Clinical features

The DSM-IV describes 'neuroleptic-induced acute dystonia' as 'sustained abnormal postures or muscle spasms that develop within 7 days of starting or rapidly raising the dose of the neuroleptic medication, or of reducing a medication used to treat (or prevent) acute extrapyramidal symptoms (e.g. anticholinergic agents)'.[1]

In 95% of all cases acute dystonia appears within 96 hours of starting antipsychotics, or after a considerable increase in the dose.[2-4] Sometimes, acute dystonia is also diagnosed during maintenance treatment with a depot antipsychotic, always within a few days after the depot has been administered.[5] The dystonia may appear in all muscle groups, but is observed mainly in the head and neck area. This can lead to a variety of forms of dystonia, such as torti-retro-latero- or ante-collis, trismus, mouth-opening dystonia, grimacing, dysarthria, oculogyric crisis, blepharospasm, swallowing difficulties and badly articulated speech due to a thick or protruding tongue.[2-4] A tense tongue or throat may indicate a moderate form of acute dystonia. Sometimes, only the hands or just a few fingers may be affected. Quite frequently, acute dystonia worsens when one or more muscle groups are activated, for instance during walking. Sometimes, the dystonia is only visible during activity but not at rest. Acute dystonia may appear in a generalized form, affecting for instance the jaw, neck, axial musculature and extremities. This may lead to the imposing state of a seriously dystonic patient in opisthotonos. Very occasionally dangerous dystonias appear, for example stridor due to a laryngospasm.[2-4] The severity of acute dystonia may vary during the day and can even be completely absent for a short period of time. It has recently been reported that acute dystonias appear particularly between 12.00 noon and 11:00 p.m.[6] A possible explanation could be the circadian rhythm of a physiological system, possibly that of serum iron, since iron has been linked to the functioning of dopamine receptors, and dopaminergic transmission in the striatum is thought to play an important role in dystonia.[6] Acute dystonia often causes anxiety and/or pain.[7]

Differential diagnosis

For the diagnosis of acute neuroleptic-induced dystonia, a patient must have been exposed to dopamine blocking agents within the past few days. However, the patient may be too psychotic to give reliable information, or may have received a depot neuroleptic injection but has not interpreted it as medication.

Sometimes, antipsychotics are abused as drugs.[3,8] Occasionally, children may take antipsychotics unwittingly.[3]

Simulation and conversion

The most important differential diagnoses are simulation and conversion, although no symptom indisputably allows for a distinction to be made between a psychogenic and an organic dystonia. Psychogenic dystonia can be suspected when (a) the dystonia has a static fixed form, (b) absence of dystonia during unnoticed observation, (c) presence of other psychogenic movement disorders or nonorganic neurological features, (d) presence of several somatizations, or (e) a clear secondary (e.g. financial) gain from the disorder.[9] However, simulation or conversion are often overdiagnosed, for instance because dystonia may make rather a bizarre impression, sometimes reinforced by speech problems if the tongue or larynx is dystonic.[9-11] It is a common misconception to consider the cause as psychological when the dystonic features are exacerbated by fear and alleviated by relaxation. The severity of nearly all movement disorders is affected by stress and relaxation. Moreover, as mentioned above, a fixed form of dystonia rather suggests a psychological cause. Sometimes, the wish to have anticholinergics prescribed is a motive for simulation, but a normal dose of anticholinergics does not lead to euphoria.[12] Because it is not really possible to distinguish between psychogenic dystonia and dystonia induced by antipsychotics, it is, generally speaking, prudent to give the patient the benefit of the doubt.

Catatonia

Catatonia sometimes resembles dystonia. Catatonia is often accompanied by symptoms such as rigidity, akinesia, flexibilitas cerea, and mutism, which are not seen in acute dystonia. Moreover, in catatonia the administration of anticholinergics does not lead to a quick recovery. Finally, the relation in time with antipsychotics is missing, which is so characteristic of acute dystonia.

Temporal lobe epilepsy

Temporal epilepsy may cause bizarre behavior and bizarre movements and can therefore be confused with dystonia.

Tardive dystonia

Phenomenologically, tardive dystonia cannot be distinguished from acute dystonia.[13-15] However, tardive dystonia only appears at rather a late stage in the treatment with antipsychotics and does not improve rapidly after normal doses of anticholinergics. Occasionally, acute dystonia is mistaken for tardive dystonia.[10,16]

Causal agents, not merely antipsychotics

The agents listed in table 1 are not used as antipsychotics, but may cause

acute dystonia. Because of their frequent use, the anti-emetics are an important group. In a study using the database that registered the side-effects of metoclopramide, 455 cases of acute dystonia/dyskinetic reactions were reported. The prevalence was estimated at 28.6 per one million prescriptions. Patients in the age-range 12 to 19 were significantly more often affected (109.1/one million prescriptions).[22] Another prevalence study reports no cases of acute dystonia induced by anti-emetics, but this study concerned a group of older patients, who rarely show acute dystonia.[23]

Table 1 *Agents that are not used as antipsychotics but can cause acute dystonia*

agents	examples
anti-emetics	metoclopramide, prochlorperazine, thiethylperazine, promethazine [2-4,11]
antidepressants	SSRI's,[17] tricyclic antidepressants[18,19]
antivertigo agents	cinnarizine, flunarizine[20]
anticonvulsant drugs	carbamazepine, phenytoin[20]
antimalaric agents	chloroquine, hydroxychloroquine, amodiaquine, cycloquine[20]
others	buspirone,[20] diazepam,[20] cocaine (after use as well as after abstinence)[21]

SSRI = Selective Serotonin Reuptake Inhibitor

Hypocalcemia

Hypocalcemia may cause features resembling acute dystonia. If the treatment of the dystonia is not successful, the calcium level should be measured.[4]

Causes of an oculogyric crisis

The oculogyric crisis is the only form of acute dystonia which may also appear while the patient is receiving a stable dose of antipsychotic. Alcohol, emotional stress, fatigue and suggestion are described as provoking factors.[24]

Epidemiology: prevalence and risk factors

The prevalence of acute dystonia as a result of antipsychotics is dependent mainly on the presence or absence of risk factors. The risk of acute dystonia varies from 2 to 90%.[2-4] In table 2 the patient-related risk factors for acute dystonia are presented. High-potency antipsychotics (for instance, haloperidol, fluphenazine, pimozide cause dystonia more frequently than do low-potency antipsychotics (for instance chlorpromazine, thioridazine). The receptor-blocking ratio between dopamine and acetylcholine in the basal ganglia is probably the best hypothesis to explain the differential rates of dystonia across the types of antipsychotics; the higher the ratio of the dopamine-acetylcholine antagonism, the higher the risk of acute dystonia.[2] In

fact, low-potent antipsychotics have an intrinsic anticholinergic prophylaxis. There is a complicated inverted U-shaped curve between the risk of dystonia and the antipsychotic dose. Thus, at minimal doses and at large megadoses, the risk of dystonia is less than at moderate doses.[2]

The atypical antipsychotics are much less likely to cause acute dystonia than the typical antipsychotics. Clozapine does not cause acute dystonia. Only once was clozapine related to acute dystonia. This concerned a patient in whom the clozapine level was too high and the dystonia appeared after stopping treatment with benzodiazepine.[33] However, clozapine may cause myoclonia, which is sometimes confused with dystonia.[32] No acute dystonia has been reported with olanzapine, which resembles clozapine in its side-effects.[34] Sertindole, too, has very few extrapyramidal side effects.[35] The risk of causing acute dystonia at doses of 2 to 6 mg is lower for risperidone than for haloperidol, but over 6 mg the frequency of extrapyramidal side effects increases.[35]

Pathophysiology

It is remarkable that so far no specific pathophysiological mechanism has been found which explains acute dystonia, whereas the phenomenon has been known since antipsychotics were introduced in 1951.

Table 2 *Patient-bound risk factors of neuroleptic-induced acute dystonia*

risk factors	comment
younger age[25]	prevalence 10-19 years ≈ 90%. 20-29 years ≈ 45% 30-39 years ≈ 35% >40 years: low
male sex	relative risk ≈ 2[2,3]
previous acute dystonia	relative risk ≈ 6[26]
recent cocaine use	relative risk ≈ 4[27,28]
affective disorders	conflicting results[29-31]
hypocalcaemic[4]	
dehydration[4]	
hypoparathyroid[4]	

According to two conflicting hypotheses the syndrome is caused either by increased or by decreased dopamine transmission.

Increase in dopamine transmission

According to the first hypothesis, the compensatory increase in dopamine release from antipsychotics overrides the dopamine receptor blockade in the nigrostriatal dopamine receptors as the antipsychotic blood and brain level decline. At this time, dopamine receptors may be transiently supersensitive or

up-regulated in response to their blockade by antipsychotics.[2]

Decrease in dopamine transmission

According to the second hypothesis the striatal dopamine function is reduced. The following data support this hypothesis (a) antipsychotics block dopamine receptors in close correlation to their clinical potency and propensity to produce acute dystonia, (b) dopamine agonists can treat acute dystonia effectively, (c) in all studies except one pretreatment with dopamine synthesis inhibitors or depleters either caused or exacerbated neuroleptic-induced dystonia.[2,35]

Treatment

The treatment of acute dystonia is usually straightforward and nearly always effective. Parenteral administration of anticholinergics (e.g. biperiden 5 mg) or antihistamines (e.g. promethazine 50 mg) is usually effective within 20 mins.[2-4] Occasionally, a second or third injection is necessary, each administered at half hour intervals. If, after the third injection, the dystonia persists, a search for other underlying medical illnesses should be undertaken.[2,4] If the patient has an oculogyric crisis which does not respond to anticholinergics, clonazepam might be beneficial.[36]

After the dystonia has disappeared, the treatment with anticholinergics should be continued for at least 24 to 48 hours to prevent recurrence. In practice, the anticholinergic is usually continued 4 to 7 days after the final increase of the antipsychotic.[4]

Intravenous administration of an anticholinergic is only necessary in cases of highly dangerous forms of acute dystonia, for instance a laryngeal stridor.

Prophylaxis

A prophylactic is usually administered by adding an anticholinergic (e.g. biperiden 2 mg, 2 to 3 times daily) to the antipsychotic. If the patient is intolerant to anticholinergics, amantadine (100 mg, 1 to 3 times daily), an anti-parkinson agent without anticholinergic properties is a possible alternative. Prophylactic treatment may give anticholinergic side-effects, in particular dry mouth, obstipation, blurred vision and sometimes memory impairment. Moreover, anticholinergics may cause a delirium in sensitive patients. It should be borne in mind that prophylaxis implies taking more tablets per day, which can be interpreted by the patient or his family in different ways, for instance as a measure of the level of seriousness of the disease.

Prophylaxis is highly effective: it reduces the risk of acute dystonia with high-potency antipsychotics by a factor of 5 to 8. The higher the risk of acute dystonia, the more effective the prophylaxis.[37]

General advice cannot be given, but it seems a good strategy to estimate the risk of acute dystonia by investigating the patient's risk factors (age, sex, past

history of acute dystonia, use of cocaine) and the antipsychotic which is being used (dose, potency, intrinsic anticholinergic activity).[2-4,25-31]

Acute dystonia is very frightening and sometimes painful.[7] When acute dystonia appears during the treatment of the first psychosis, which is a regular occurrence since the patients concerned are usually young, it may lead to poor compliance. This again greatly enhances the risk of relapse. Although it is hardly ever mentioned in treatment guidelines, it seems logical that, in the decision about prophylaxis, it should be taken into consideration whether the patient is being treated in an intramural or in an extramural setting. In the clinic a higher risk can be taken because aid is directly available. Thus anticholinergics may be prescribed more frequently for out-patients. In addicted patients the risk of abuse of the prescribed anticholinergics may be a drawback.[12] The duration of the prophylaxis is usually 7 to 14 days. After that, the anticholinergic dose should be reduced gradually, for stopping suddenly may again induce acute dystonia. Other acute extrapyramidal disorders (akathisia, parkinsonism) are usually the reason for continuing the anticholinergic beyond 14 days. The prejudice that the addition of anticholinergics may increase the risk of tardive dyskinesia is probably incorrect. Anticholinergics may aggravate an existing dyskinesia, but are not causally related to tardive dyskinesia.[38]

In conclusion: Acute dystonia is not uncommon; it is often very frightening and may seriously disturb the relationship between the doctor and the patient. Therefore, each doctor working with dopamine-blocking agents should be familiar with the prevalence, risk-factors, treatment and the prophylactics available to treat acute dystonia.

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Chapter 3.2

Cocaine as a risk factor for neuroleptic-induced acute dystonia

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Abstract

Background

A prospective study was conducted to test the hypothesis that cocaine-use is a risk factor for neuroleptic-induced acute dystonia (NIAD).

Method

The study sample consisted of a high risk group for NIAD, males between 17-45 who received high-potency neuroleptics within 24 hours of admission and did not use neuroleptics in the month prior to admission. Patients were excluded if they suffered of a neurodegenerative disorder or were exposed to anticholinergics, benzodiazepines, promethazine, carbamazepine, phenytoin, or L-dopa during the study.

During the two years of the study 29 patients entered the study, 9 cocaine-users and 20 non-users. Patients were followed for 7 days.

Results

Cocaine-using psychiatric patients developed significantly more NIAD than did non-users (relative risk 4.4, 95% CI=1.4-13.9).

Conclusion

Cocaine-use is a major risk factor for NIAD and should be added to the list of well-known risk factors. It is strongly suggested that in cocaine-using psychiatric patients who start taking neuroleptics, an anticholinergic should be added for at least seven days to prevent NIAD.

Introduction

Neuroleptic-induced acute dystonia (NIAD) is a common side-effect which almost always occurs within five days in patients who have just started taking neuroleptics or who have had their dosage substantially increased. The sudden onset and unpredictability of NIAD often cause fear and anxiety. Attacks can be very painful and occasionally are even life-threatening.[1] The known risk factors for NIAD are male sex, younger age, neuroleptic potency and dose, and a history of NIAD.[1] Two reports, however, have suggested that cocaine might be a risk factor too. In a laboratory study in which seven people were given cocaine and haloperidol simultaneously, six developed NIAD.[2] One retrospective study suggested that NIAD was three times more likely to occur in cocaine-users than in non-users.[3] However, the laboratory study with seven patients was small and not representative for psychiatric patients and the retrospective nature of the second study restricted the usefulness of the results.
We conducted a prospective study to test the hypothesis that cocaine is a risk factor for NIAD.

Patients and methods

The study was performed at the psychiatric hospital (Dr. D.R. Capriles Hospital) on the island of Curaçao, which is the only psychiatric hospital in the Netherlands Antilles. The characteristics of the inpatient population of this hospital at June 1, 1992 have been described elsewhere.[4] There are about 250 admissions per annum. The general policy followed by the acute-care psychiatry inpatient service for psychotic patients was to prescribe high potency neuroleptics preferably without prophylactic anticholinergics. The patients included in this study were admitted between June 1, 1993 and June 1, 1995. The study sample consisted of a high risk group for NIAD, males aged between 17-45 who received high-potency neuroleptics within 24 hours of admission and did not use neuroleptics in the month prior to admission. Patients were excluded if they suffered from a neurodegenerative disorder or were exposed to anticholinergics, benzodiazepines, promethazine, carbamazepine, phenytoin, or L-dopa during the study. Lower potency neuroleptics were excluded to decrease the possible confounding effects of the intrinsic anticholinergic activity. Data were collected on age, DSM-III-R diagnosis, mean dose and peak dose of neuroleptics (before NIAD), other medication, and the use of cocaine and cannabis. The neuroleptic dose was converted into chlorpromazine dose equivalents (CPZEQ).[5]

Cocaine-use was defined as the use of cocaine or base (a cocaine derivative) within a period of 24 hours prior to admission on the basis of either (a) evidence from urinary samples or (b) a positive answer during the admission interview to

questions about recent cocaine-use. Urinary samples were collected within 24 hours after admission and checked for cocaine and cannabis with a cut-off of 100 ng/ml for tetrahydrocannabinol-carboxylic acid and a cut-off of 300 ng/ml for benzoyl-ecgonine. The results were confirmed by chromatographic procedures.[6] The results of the urinary sample were not revealed to the attending resident doctor until the file was closed.

NIAD was defined as the sudden onset within seven days after the start of neuroleptic treatment of sustained muscle contractions, which frequently caused twisting and repetitive movements or abnormal postures but resolved rapidly after the intramuscular administration of 5 mg biperiden.[7] Nurses who were not informed about the purpose of the study were instructed to report NIAD. Diagnosis of dystonia was confirmed by the attending resident doctor. Since almost all cases of NIAD occur within five days of neuroleptic treatment, the files were closed after seven days.[1]

Chi-square tests were used to compare categorical data and an ANOVA was used to compare continuous data.[8]

Results

During the two-year study period 29 patients fulfilled the inclusion criteria and gave informed consent. The urine of four patients was not obtained within 24 hours. Of these the first two reported cocaine-use and were classified as cocaine-users; the third patient denied using cocaine and was classified as a non-user; the fourth patient was mentally retarded and was unable to give reliable information about cocaine-use. He was classified as a cocaine-user because his family reported that he had used cocaine recently.

Of the 9 cocaine-users 5 were diagnosed to be suffering from schizophrenia, 3 from mania and 1 from a cocaine-induced psychosis. Of the 20 non-users 15 were diagnosed to be suffering from schizophrenia, and 5 from mania. Cocaine-users did not differ significantly from non-users in mean age (31.2 years, SD=6.2, versus 33.9, SD=7.0, F=0.94, p=0.66), in mean daily dose (467 CPZEQ, SD=146, versus 612 CPZEQ, SD=240, F=2.77, p=0.10), and in peak neuroleptic dose (531 CPZEQ, SD=191 versus 756 CPZEQ, SD=362, F=3.06, p=0.09). Nine of the 29 patients developed NIAD. Significantly more cocaine-users developed NIAD (6 out of 9), than did non-users (3 out of 20); which yielded a relative risk of 4.4 (95% CI=1.4-13.9). The average time between the start of neuroleptics and the development of NIAD was 55.1 hours (h) (SD=28.8h range 21-100h) and there was no significant difference in the rate of onset in the cocaine-users and in the non-users (54h, SD=31 versus 58h, SD=30, F=0.03, p=0.9). The neuroleptics used were penfluridol, clopenthixol, haloperidol, flupentixol, droperidol, fluphenazine, and pimozide and no difference was found in the type of neuroleptic used by the NIAD group and the non-NIAD group. All patients except three were Afro-Caribbean.

Discussion

This prospective study shows clearly that cocaine-use is a major risk factor for neuroleptic-induced acute dystonia (relative risk 4.4) in patients suffering from a psychosis that is treated with high potency neuroleptics. The fact that cocaine is frequently used by psychiatric patients underlines the clinical importance of our finding.[9] To our knowledge this is the first prospective study that has investigated the relationship between cocaine and NIAD.

This study has some limitations. The urine of four patients was not sampled for cocaine metabolite, but these patients were included in the study. Two of these patients admitted cocaine-use, the third denied it and the fourth patient was classified as cocaine-user on the basis of information supplied by the family. Classification as a cocaine-user on the basis of a positive answer by the patient to cocaine-use can be considered as valid.[9] However, the classification in the third and fourth patient is doubtful since denial of drug use is common.[9] One could argue about the possible effect on the results if the third and fourth patient (neither developed acute dystonia) were classified subsequently as a cocaine-user or as a non-user. This gives three other outcomes which are additional to the relative risk reported in the results. All three outcomes remained significant with a relative risk varying between 3.8 (95% CI 1.2-12.1) and 5.3 (95% CI 1.7-16.1). An alternative would be to include only the 25 patients whose urine was sampled. This gives a relative risk of 4.22 (95% CI 1.3-13.8).

It is unlikely that any other amphetamine could be responsible because on the island of Curaçao drug abuse is limited almost exclusively to cocaine (or base) and cannabis. Another possibility is that another risk factor for NIAD occurs more often in cocaine-users than in non-users. However, no difference was found between the cocaine-users and non-users with regard to the known risk-factors of NIAD such as mean age, mean neuroleptic dose, peak dose and type of neuroleptic used.

Our findings are supported by a recent animal study that has shown that cocaine targets the dopamine (DA) transporter.[10] It has been suggested that NIAD is caused when the compensatory increase in dopamine release from neuroleptic drugs overrides the DA receptor blockade as neuroleptic blood and brain levels decline.[1] At that time dopamine receptors may be transiently supersensitive in response to their blockade by the neuroleptic. When cocaine blocks the DA transporter it will cause a dramatic increase in the DA concentrations in the extracellular space.[10] Thus, it could be possible that cocaine-users may have manipulated dopamine receptors which are prone for NIAD. However, it remains hypothetical because it is impossible to make a reliable connection between cocaine metabolites in the urine and the blood levels of cocaine.

Our results strongly suggest that cocaine-using psychiatric patients who start

taking neuroleptics should be provided with some protection against NIAD. Protection can be provided by administering anticholinergics along with the neuroleptics.[1]

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Summary and concluding remarks

This thesis concerns extrapyramidal syndromes (EPS) and is divided into three parts because each part has its own study design. The focus of part 1 is on the epidemiology of the EPS tardive dyskinesia, tardive dystonia, parkinsonism, and akathisia. Part 2 focuses on tardive dystonia. It starts with a review of this syndrome and then reports the results of a clinical trial with clozapine. Part 3 opens with a review of acute dystonia and then the results are given of a prospective study that investigated whether the use of cocaine is a risk factor for neuroleptic induced acute dystonia.

Part 1

The introduction describes the history of these EPS and discusses why in DSM IV these syndromes form a separate category of 'medication-induced movement disorders'. Furthermore, the background for each research question of this thesis is discussed.

Chapter 1.1 provides a review of the phenomenology and differential diagnosis of tardive dyskinesia, parkinsonism and akathisia. Tardive dystonia and acute dystonia are reviewed extensively in chapter 2.1 and 3.1, respectively.

Chapter 1.2 describes the results of a prevalence study of EPS that was conducted among all psychiatric inpatients of the Netherlands Antilles (N=194; mean age 53.1). The Netherlands Antilles are very suitable for epidemiological research as it is a well-defined catchment area with only one psychiatric hospital and a health care system based on western principles. In this mainly chronic population, the prevalence of tardive dystonia, tardive dyskinesia, parkinsonism and akathisia was measured using the Fahn-Marsden rating scale, the Abnormal Involuntary Movement Scale, the Unified Parkinson Disease Rating Scale and the Barnes Akathisia Rating Scale respectively. The prevalence numbers were as follows: for tardive dystonia 13.4%, tardive dyskinesia 39.7%, parkinsonism 36.1%, akathisia 9.3%, and pseudoakathisia 12.9%.

Conclusions: The prevalence of tardive dystonia was higher than reported in most other studies and EPS are very common in this predominantly Negroid population, in which three out of four patients suffer from one or more EPS.

Chapter 1.3 describes both the strength of the inter-relationships of EPS and the prevalence of combinations of EPS. The inter-relationships between the EPS were analyzed by means of logistic regression. The adjusted odds ratios between the various EPS revealed strong connections between the hyperkinetic syndromes (tardive dyskinesia, tardive dystonia and akathisia). Parkinsonism was found to be inversely related to tardive dyskinesia and to tardive dystonia.
Almost 30% of the patients suffered from two or more EPS. The highest prevalence rates of combinations were: tardive dyskinesia combined with

parkinsonism 12.9%, tardive dyskinesia combined with tardive dystonia 9.8%, and tardive dyskinesia combined with akathisia 5.2%.

Conclusions: Our findings show a strong positive correlation between hyperkinetic forms of EPS. Furthermore, chronic psychiatric inpatients regularly suffer from combinations of EPS. Different treatment strategies are suggested for various combinations of EPS.

In ***chapter 1.4*** it is hypothesized that there is an association between three lifetime medication variables (cumulative amount of neuroleptics, number of interruptions in treatment with neuroleptics, cumulative amount of anticholinergics) and the occurrence and/or severity of tardive dyskinesia. Of all the psychiatric inpatients, the ones selected where those who used antipsychotics at the time of the study and for whom lifetime medication data were available (N=133, mean age 51.5 years). Of the three lifetime medication variables, only the number of neuroleptic interruptions was significantly related to tardive dyskinesia (adjusted OR 1.3, 95% CI 1.07-1.62). If the number of neuroleptic interruptions is dichotomized into less than or equal to two and more than two the resulting adjusted OR is 3.3 (95% CI 1.27-8.49).

Conclusion: Our finding supports the schizophrenia protocol that recommends long-term neuroleptic treatment rather than targeted or intermittent neuroleptic treatment. More than two interruptions increase the risk of tardive dyskinesia more than threefold.

Part 2

Chapter 2.1 provides an overview of the phenomenology, epidemiology and treatment of tardive dystonia. Tardive dystonia is one of the EPS that starts after long-term use of dopamine receptor antagonists. The diagnosis is based on the presence of chronic dystonia, which is defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures. Furthermore, the patient must develop dystonia either during or within 3 months of a course of antipsychotic treatment and other causes such as Wilson's disease, acute dystonia or a conversion reaction must be ruled out.

Tardive dystonia occurs in about 5% of patients on long-term antipsychotic treatment. Some probable risk factors for tardive dystonia are younger age, male, and the presence of tardive dyskinesia.

The treatment of tardive dystonia starts with an evaluation of the need for using the causative drug. If antipsychotics have to be continued, a switch to an atypical antipsychotic may be helpful. However, since these agents can only be taken orally they may affect the compliance of medication-taking in patients who were previously on depot antipsychotics.

If the dystonia is relatively localized, an effective but not well-known treatment possibility is to use botulinum toxin. If tardive dystonia is more extensive, either dopamine depleting drugs or high dosages of anticholinergics can be tried.

Chapter 2.2 describes the results of an open clinical trial (N=7) that measured

the course of severe tardive dystonia in chronic psychiatric patients after the discontinuation of neuroleptics and the subsequent use of clozapine.
The dystonia was regularly assessed using the Fahn-Marsden Rating Scale. The eventual concomitant tardive dyskinesia was assessed using the Abnormal Involuntary Movement Scale. The mean follow-up was 103 weeks.
The results for the tardive dystonia: four patients recovered totally, two improved considerably and one did not recover.
The results for the concomitant tardive dyskinesia: five of the seven patients also had dyskinesia, one patient had a total and three a partly remission. One patient worsened and one patient developed dyskinesia.

Conclusion: It is suggested that treatment with clozapine should be considered for patients who have tardive dystonia and have to continue antipsychotic treatment.

Part 3

Chapter 3.1 provides a review of neuroleptic-induced acute dystonia (NIAD) and is intended as a guide for the clinician. A description is given of the clinical features, differential diagnosis, epidemiology, pathophysiology, treatment and the advantages and disadvantages of prophylaxis.
The risk of NIAD increases when one or more of the following factors are present: young age, male sex, use of cocaine, past history of NIAD and a normal dosage of a high-potency neuroleptic. In most cases, NIAD appears after the start of treatment with a dopamine blocking agent or after the dose has been increased. It is often overlooked that when dopamine blocking agents are used not as antipsychotics but, for instance, as anti-emetics, they may also cause NIAD. Anticholinergics are highly effective in both the treatment and prevention of NIAD. In any case it is advisable to administer a prophylactic to patients at risk.

Chapter 3.2 gives the results of a prospective study that tested the hypothesis that cocaine-use is a risk factor for NIAD.

The study sample consisted of a high risk group for NIAD, males between 17-45 who received high-potency neuroleptics within 24 hours of admission and did not use neuroleptics in the month prior to admission. Patients were excluded if they suffered of a neurodegenerative disorder or were exposed to anticholinergics, benzodiazepines, promethazine, carbamazepine, phenytoin, or L-dopa during the study. During the two years of the study 29 patients entered the study, 9 cocaine-users and 20 non-users. Patients were followed for 7 days. Cocaine-using psychiatric patients developed significantly more NIAD than did non-users (relative risk 4.4, 95% CI=1.4-13.9).

Conclusions: Cocaine-use is a major risk factor for NIAD and should be added to the list of well-known risk factors. It is strongly suggested that in cocaine-using psychiatric patients who start taking neuroleptics, an anticholinergic should be added for at least seven days to prevent NIAD.

Samenvatting en conclusies

Extrapiramidale syndromen (EPS) geassocieerd met antipsychotica zijn het onderwerp van dit proefschrift. In de introductie van dit proefschrift wordt ingegaan op de historie van deze syndromen en de redenen waarom in de DSM-IV een aparte categorie is opgenomen van "bewegingsstoornissen door medicamenten teweeggebracht". Het creëren van deze categorie is gebaseerd op de aanname dat EPS sterk samenhangen met antipsychotica. Deze aanname is voor dit proefschrift van groot belang: alle onderzoeksvragen zijn daarop gebaseerd. De argumentatie achter deze aanname wordt besproken in de introductie.

Dit proefschrift is verdeeld in drie delen, daar het drie verschillende studies betreft. Het eerste gedeelte (part 1) beschrijft de epidemiologie van tardieve dyskinesie, parkinsonisme, acathisie en tardieve dystonie. Het tweede gedeelte (part 2) betreft een literatuuronderzoek naar tardieve dystonie en een onderzoek naar de behandeling daarvan. Het derde gedeelte (part 3) bevat een literatuuronderzoek naar acute dystonie en een onderzoek naar de vraag of cocaïne een risicofactor is voor door antipsychotica geïnduceerde acute dystonie.

De drie studies werden uitgevoerd op de Nederlandse Antillen. De Nederlandse Antillen zijn om een aantal redenen erg geschikt voor epidemiologisch onderzoek: het zijn eilanden en het is dus een scherp omschreven gebied, er is maar één psychiatrisch ziekenhuis waar alle intramurale chronisch psychiatrische patiënten verblijven en waar meestal al hun zorg plaatsheeft, en er bestaan goede populatiegegevens vanwege een volkstelling in 1992, het jaar van de studie.

Part 1

Hoofdstuk 1.1 beschrijft de karakteristieken en de differentiaaldiagnose van parkinsonisme, acathisie en tardieve dyskinesie. Tardieve dystonie wordt uitgebreid beschreven in hoofdstuk 2.1.

Parkinsonisme is een akinetisch rigide syndroom met als kernsymptomen rusttremor, rigiditeit, bradykinesie (akinesie) en houdingsinstabiliteit.

Acathisie betekent letterlijk: onvermogen om te zitten. Het wordt omschreven als het aanwezig zijn zowel van subjectieve klachten van rusteloosheid alsook van objectieve bewegingen, vooral zichtbaar in het telkens bewegen van de benen.

Tardieve dyskinesie kenmerkt zich vooral door onwillekeurige choreatische (vloeiend continue) bewegingen van de tong, lippen, kaak en/of het gezicht. Regelmatig worden ook choreatische bewegingen van de ledematen, met name de vingers en de tenen, en soms de romp gezien.

Hoofdstuk 1.2 beschrijft de prevalentie van EPS bij de totale populatie opgenomen psychiatrische patiënten van de Nederlandse Antillen die langer dan drie maanden antipsychotica hebben gebruikt (N=194, gemiddelde leeftijd 53.1 jaar, 72.7% man). Geclassificeerd volgens de DSM-III-R-classificatie leed driekwart aan schizofrenie.
In deze voornamelijk chronische populatie werd de prevalentie van tardieve dyskinesie, parkinsonisme, acathisie en tardieve dystonie gemeten met respectievelijk de Abnormal Involuntary Movement Scale, the Unified Parkinson Disease Rating Scale, de Barnes Akathisia Rating Scale en de Fahn-Marsden Rating Scale.

De prevalentiecijfers van tardieve dyskinesie, parkinsonisme, acathisie en tardieve dystonie waren respectievelijk 39.7%, 36.1%, 9.3% en 13.4%. Patiënten met tardieve dyskinesie bleken significant ouder dan patiënten zonder tardieve dyskinesie.

Conclusies: de prevalentie van EPS in deze Afro-Caribische populatie van chronisch psychiatrische patiënten was hoger dan in veel andere studies; drie van de vier patiënten heeft één of meer EPS. Verder was de prevalentie van tardieve dystonie hoger dan in de meeste andere studies. Dit is van belang aangezien patiënten dikwijls veel hinder hebben van tardieve dystonie en omdat dit syndroom vaak wordt gemist of als psychogeen wordt geïnterpreteerd.

In ***hoofdstuk 1.3*** wordt het onderlinge verband tussen de verschillende EPS alsmede de prevalenties van combinaties van EPS beschreven. Lijdt een patiënt aan één extrapiramidaal syndroom, dan is de behandeling - indien voorhanden - vaak eenduidig. De behandeling is vaak complexer als een patiënt een combinatie van EPS heeft. Behandelen van het ene extrapiramidale syndroom kan een verslechtering geven van een van de andere extrapiramidale syndromen. De onderlinge relaties tussen EPS werden geanalyseerd door middel van logistische regressieanalyse. De gecorrigeerde odds ratio's tussen de verschillende vormen van EPS lieten een sterk verband zien tussen de hyperkinetische vormen van EPS (tardieve dyskinesie, acathisie en tardieve dystonie).
Bijna 30% van de patiënten leed aan twee of meer EPS. De hoogste prevalenties van combinaties van EPS waren: tardieve dyskinesie gecombineerd met parkinsonisme 12.9%, tardieve dyskinesie gecombineerd met tardieve dystonie 9.8%, en tardieve dyskinesie gecombineerd met acathisie 5.2%.

Conclusies: onze bevindingen laten een sterke positieve correlatie zien tussen de hyperkinetische vormen van EPS. Verder blijkt dat chronisch psychiatrische patiënten regelmatig lijden aan combinaties van EPS. Een aantal verschillende behandelstrategieën voor combinaties van EPS worden besproken.

Hoofdstuk 1.4 beschrijft het verband tussen de aanwezigheid en/of de ernst van tardieve dyskinesie en de drie lifetime medicatievariabelen: cumulatieve hoeveelheid van antipsychotica, aantal onderbrekingen in de antipsychoticageschiedenis en cumulatieve hoeveelheid van anticholinergica.

Uit de populatie werden 133 patiënten (gemiddelde leeftijd 51.5) geselecteerd op basis van twee criteria: gebruik van antipsychotica ten tijde van het onderzoek en voldoende valide gegevens over lifetime medicatiedata.

Van de drie lifetime medicatievariabelen bleek alleen het aantal onderbrekingen in de neurolepticageschiedenis significant samen te hangen met de kans op tardieve dyskinesie (gecorrigeerde odds ratio 1.3, 95% betrouwbaarheidsinterval 1.07-1.62). Als het aantal onderbrekingen in de antipsychoticageschiedenis werd gedichotomiseerd in twee of minder versus drie of meer dan werd de odds ratio 3.3 (95% betrouwbaarheidsinterval 1.27-8.49).

Deze bevinding ondersteunt het schizofrenieprotocol, dat adviseert om langdurig aaneengesloten antipsychotica te geven in plaats van de behandeling regelmatig te onderbreken. Meer dan twee onderbrekingen geeft een driemaal zo hoge kans op tardieve dyskinesie.

Part 2

Hoofdstuk 2.1 geeft een literatuuroverzicht van de karakteristieken, epidemiologie en behandeling van (door antipsychotica geïnduceerde) tardieve dystonie. Tardieve dystonie ontstaat na langdurig gebruik van dopamine-antagonisten. De diagnose is gebaseerd op de aanwezigheid van langdurig aanhoudende dystone bewegingen. Dystonie is daarbij gedefinieerd als een syndroom van aanhoudende spiercontracties met vaak torderende en repetitieve bewegingen of abnormale houdingen als resultaat. Verder heeft de patiënt de dystonie ontwikkeld gedurende de behandeling met antipsychotica of ten laatste binnen drie maanden na het staken van de behandeling. Daarnaast moeten andere oorzaken van de dystonie worden uitgesloten, zoals de ziekte van Wilson, acute dystonie en een conversiesyndroom. Uit dertien prevalentiestudies bleek de gemiddelde prevalentie van tardieve dystonie bij patiënten die langdurig antipsychotica kregen ongeveer 5%. Risicofactoren zijn onvoldoende onderzocht, maar er zijn aanwijzingen dat jonge leeftijd, mannelijk geslacht en de aanwezigheid van tardieve dyskinesie risicofactoren zijn.

De behandeling van tardieve dystonie begint met de evaluatie van de noodzaak van het gebruik van antipsychotica. Als de antipsychotica moeten worden gecontinueerd, dan valt een atypisch neurolepticum te overwegen. Echter, atypische neuroleptica bestaan alleen in orale vorm. Dit kan van invloed zijn op de therapietrouw van patiënten die voordien antipsychotica in depotvorm kregen.

Als de tardieve dystonie niet te uitgebreid is, vormt botuline-toxine een effectieve, maar weinig bekende behandeloptie. Als de tardieve dystonie uitgebreid is, kunnen stoffen als tetrabenazine of hoge doseringen anticholinergica worden gegeven.

Hoofdstuk 2.2. beschrijft een open klinische trial (N=7) naar het verloop van

ernstige tardieve dystonie bij chronisch psychiatrische patiënten die na het staken van de klassieke antipsychotica met clozapine begonnen. De dystonie werd gemeten met de Fahn-Marsden Rating Scale. Een eventuele aanwezige tardieve dyskinesie werd gemeten met de Abnormal Involuntary Movement Scale. Patiënten werden gemiddeld 103 weken gevolgd.
Van de zeven patiënten met tardieve dystonie herstelden vier volledig, vertoonden twee een behoorlijke verbetering en herstelde één patiënt niet.
Vijf van de zeven patiënten hadden tevens tardieve dyskinesie. Van deze vijf patiënten had één een volledige en drie een gedeeltelijke remissie. Één patiënt vertoonde een verergering van de tardieve dyskinesie en één patiënt ontwikkelde een tardieve dyskinesie tijdens de studie. Deze resultaten suggereren dat clozapine een goede behandeloptie is bij patiënten die antipsychotica nodig hebben en die lijden aan tardieve dystonie.

Part 3

Hoofdstuk 3.1 geeft een literatuuroverzicht van acute dystonie. Achtereenvolgens komen aan de orde: het klinisch beeld, de differentiaaldiagnose, de epidemiologie, de pathofysiologie, de behandeling en de voor- en nadelen van een profylaxe.
De kans op acute dystonie wordt vergroot door de aanwezigheid van de volgende factoren: lage leeftijd, mannelijk geslacht, cocaïnegebruik, een voorgeschiedenis van acute dystonie en een hoogpotent neurolepticum in normale dosering. Acute dystonie treedt vrijwel altijd op na het beginnen met een dopamine blokkerend middel of na het verhogen van de dosis. Vaak is niet bekend dat dopamine blokkerende middelen die niet gebruikt worden als antipsychotica maar als bijvoorbeeld anti-emetica ook acute dystonie kunnen veroorzaken. Anticholinergica zijn uiterst effectief bij zowel de behandeling als de preventie van acute dystonie. Geadviseerd wordt om in ieder geval een profylaxe te geven aan patiënten in de risicogroepen.

Hoofdstuk 3.2 beschrijft een prospectieve studie waarin de hypothese wordt getoetst of cocaïnegebruik een risicofactor is voor het ontwikkelen van door antipsychotica geïnduceerde acute dystonie. De onderzochte populatie bestond uit patiënten met een hoge kans op acute dystonie: mannen tussen de 17 en 45 jaar die hoogpotente antipsychotica kregen binnen 24 uur na opname en die geen antipsychotica hadden gebruikt in de maand voor opname. Patiënten werden uitgesloten als ze leden aan een neurodegeneratieve aandoening of als ze anticholinergica, benzodiazepinen, promethazine, carbamazepine, diphantoïne of L-dopa kregen tijdens de studie. In een periode van twee jaar werden 29 patiënten geïncludeerd, 9 cocaïnegebruikers en 20 niet-gebruikers. Tot zeven dagen na opname werd onderzocht of een dystonie optrad.
Cocaïnegebruik was gedefinieerd als het gebruik van cocaïne of base (een cocaïne-derivaat) binnen 24 uur voor opname op basis van een positieve uitslag

van de urinetest en/of het tijdens het opnamegesprek erkennen van recent gebruik. De uitslag van de urinetest werd pas bekend nadat het onderzoek was afgesloten.
Door antipsychotica geïnduceerde acute dystonie was gedefinieerd als een plotseling ontstaan van dystonie van een of meerdere spiergroepen binnen zeven dagen na het starten van de antipsychotica, welke verdwijnt na een intramusculaire injectie met anticholinergica. Patiënten die recentelijk cocaïne hadden gebruikt, bleken significant vaker een door antipsychotica geïnduceerde acute dystonie te ontwikkelen dan niet-gebruikers (relatief risico 4.4). Het is onwaarschijnlijk dat een andere drug verantwoordelijk was voor het gevonden effect, daar op de Nederlandse Antillen vrijwel alleen cannabis en cocaïne worden gebruikt als drugs.

Conclusie: recent cocaïnegebruik is een risicofactor voor een door antipsychotica geïnduceerde acute dystonie en moet worden toegevoegd aan de lijst van bekende risicofactoren. Het wordt dringend aangeraden om bij patiënten die cocaïne gebruiken en die ingesteld worden op hoogpotente antipsychotica een anticholinergicum toe te voegen voor de duur van tenminste zeven dagen ter voorkoming van acute dystonie.

Dankwoord

Kort na aankomst op Curaçao zag ik een patiënt met een afwijking die ik nog nooit eerder gezien had. Hij liep met zijn gezicht naar de hemel en de rug als een hoepel maximaal achterover gebogen. Al meer dan een jaar leed hij aan deze extreme vorm van tardieve dystonie. Na overleg met het Academisch Ziekenhuis Utrecht besloten Glenn Matroos en ik om deze patiënt clozapine te geven. Binnen een aantal maanden herstelde hij volledig en was bij ons de belangstelling voor extrapiramidale stoornissen gewekt.

Een jaar later ontstond het plan om van alle patiënten in het psychiatrisch ziekenhuis de extrapiramidale stoornissen in kaart te brengen. Het was Wijbrand Hoek die mij ervan wist te overtuigen dat een epidemiologisch onderzoek op Curaçao meerwaarde heeft vanwege de natuurlijke begrenzing en de aanwezigheid van maar één psychiatrisch ziekenhuis. Wijbrand accepteerde het co-promotorschap en daarmee kreeg onze al jaren bestaande vriendschap een nieuwe dimensie. Ik heb veel geleerd van zijn redeneervermogen en zijn inzicht in de methodologie van onderzoek.

Glenn Matroos, psychiater en geneesheer-directeur van de Dr. D.R. Capriles kliniek is vanaf het eerste moment de medeonderzoeker. Hij heeft een onuitputtelijke optimisme en een uitstekend vermogen om ingewikkelde concepten kritisch te beschouwen. Mede door zijn loyaliteit en vriendschap is dit proefschrift tot stand gekomen. Het onderzoek loopt nog steeds door, jaarlijks vervolgen we de patiënten uit de kliniek.

Tijdens de Corsendonck-cursus werd het onderzoeksprotocol door Peter Moleman en Anton Loonen van nuttige adviezen voorzien, waarna het naar de promotoren ging. Het eerste contact had plaats met Jan van Ree, die het onderzoeksprotocol op essentiële punten bijstelde. René Kahn zou kort daarna hoogleraar worden in Utrecht en hij speelde vervolgens de grootste rol als promotor. René leerde me te differentiëren tussen wat van belang was en vooral wat niet. Hiervoor heeft hij een feilloos gevoel. Zijn snelle en efficiënte wijze van werken is een voorbeeld voor me.

Daan Kamphuis, toenmalig neuroloog op Curaçao, met veel kennis van bewegingsstoornissen bracht het onderzoek inhoudelijk op een hoger plan. Hij, Glenn en ikzelf besloten om meer kennis van de extrapiramidale stoornissen op te doen bij ‘the godfather van de movement disorders’, professor Stanley Fahn. We liepen een week stage in het Dystonia Clinical Research Center te New York, wat ons inzicht in bewegingsstoornissen vergrootte en onze onderlinge band versterkte.

De patiënten wil ik bedanken voor hun medewerking en voor die gulle Antilliaanse lach waarmee we vaak begroet werden als we met onze testjes aankwamen, het was soms ontroerend.

De rol van de verpleging bleek van onschatbare waarde: de verpleegkundigen

zorgden ervoor dat het onderzoek vlot verliep en dat de gehele populatie van de Dr. D.R. Capriles kliniek onderzocht kon worden.

Petra Koopmans leerde me de geheimen van de statistiek begrijpen. Elke donderdagavond kwam ze bij ons thuis en was ze een echte schooljuf voor me. Haar rol werd later overgenomen door Maarten Koeter, die met zijn enthousiasme en multivariate wijze van denken de analyses op een hoger niveau bracht.

Veel dank zijn we ook verschuldigd aan de NASKHO, die het belang van het onderzoek onderstreepte met een subsidie.

De co-assistenten Houkje Kooy, Martine Koorenvaar en Raju Peters hielpen bij het essentiële statusonderzoek.

De data-invoer en de administratie werden verzorgd door achtereenvolgens Astrid Brussen, Jeanine Boot, Marjon Thuis en Marjolein de Vugt, die behalve behulpzaam ook gezellig waren.

Jan van Trier en Ernst Horwitz waren als enthousiaste AGIO's de medeonderzoekers van de cocaïnestudie.

Sheila McNab reviseerde mijn Engels en schreef dan op Britse wijze, "The next step is for you to look through the suggestions I 've made and decide what to accept or reject". Er werd weinig 'gereject'.

PC Welterhof, de Raad van Bestuur, de afdeling Automatisering en al mijn collega's bedank ik voor de geboden steun en de gelegenheid om deze promotie af te ronden. Frieda Muller zorgde ervoor dat ik niet hopeloos werd van alle correspondentie.

Ineke van Harten, mijn zus, bedank ik voor de voorplaat, die goed past bij de boodschap van dit proefschrift.

De paranimfen Henk Jan van Harten, mijn broer, en Glenn Matroos hebben erg geholpen om de promotie op de rails te krijgen.

Sofie, mijn partner, grapte vaak over mijn elektronische byside als ze me weer achter de pc zag zitten. Haar humor, gezelligheid en loyaliteit hielpen me om deze klus te klaren.

Tot slot een woord over Curaçao. Heel regelmatig missen Sofie en ik de sfeer van de Antillen, de ontspannen houding van de mensen, de hartelijkheid, de ruige natuur en de prachtige koralen. In Curaçao zingen ze 'Atardi Korsow ta bunita', wat aangeeft dat het eiland op zijn mooist is vlak voor de zon ondergaat. Zo zuiver en voelbaar als de avond zijn ook de spreekwoorden van Curaçao. 'Komedo di webu, no sa loke sanka di galinja ta sinti' oftewel 'Iemand die een ei opeet, weet niet wat de kip heeft doorstaan' geeft prachtig weer hoeveel arbeid achter dit proefschrift schuilgaat. Korsow, danki pa tur kos i te aworo (Curaçao, bedankt voor alles en tot ziens).

Curriculum Vitae

Pieter Nicolaas van Harten werd geboren in 1956 te Rotterdam. In 1974 behaalde hij het Atheneum-B-diploma aan het Carolus Clusius College in Zwolle. Hij volgde zijn studie geneeskunde in Groningen en liep zijn co-schappen in het St. Elisabeth Hospitaal te Curaçao (artsexamen 1982).

Aansluitend werkte hij twee jaar bij de Stichting Nieuw Hoog Hullen te Eelde, waar hij zijn keuzestage verslavingszorg liep. In het APZ Dennenoord te Zuidlaren werkte hij anderhalf jaar; hij volgde daar de stage inrichtingspsychiatrie.

Van 1986 tot 1989 specialiseerde hij zich in de psychiatrie in het Academisch Ziekenhuis te Groningen (hoofdopleiders: prof. dr. R. Giel en prof. dr. R.J. van den Bosch) en bij de RIAGG Groningen.

Van 1984 tot 1987 volgde hij een avondopleiding psychoanalytische psychotherapie.

In 1990 ging hij naar Curaçao; hij werkte daar vijf jaar als psychiater in de Dr. David Ricardo Capriles kliniek. De laatste twee jaar was hij hoofd van de polikliniek, die hij in zijn nieuwe vorm hielp opzetten. Hij was daarnaast psychiatrisch consulent voor St. Maarten en had een nulaanstelling als docent bij de Rijksuniversiteit Groningen. Hij had een aantal nevenfuncties, zoals psychiatrisch consulent bij een kliniek voor dubbelgehandicapte patiënten, voorzitter en medeoprichter van de stichting MEPUC (Medisch Publiceren Curaçao) en voorzitter van de onderwijscommissie voor geneeskunde.

Sinds maart 1995 is hij werkzaam als A-opleider in PC Welterhof te Heerlen.

Hij is getrouwd met Sofia Kneppers, ze hebben samen drie zoons: Daan, Pieter en Bennie.

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