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Assessment of neuroleptic-induced movement disorders in a naturalistic schizophrenia population

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ACADEMIC DISSERTATION

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To Riina and our children

Contents

Abbreviations

AIMS	Abnormal Involuntary Movement Scale
ANOVA	Analysis of variance
AUC	Area under curve
BARS	Barnes Akathisia Rating Scale
CNS	Central nervous system
D_2	Dopamine receptor, subtype 2
DDD	Defined daily dose
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
EMG	Electromyography
EP	Extrapyramidal
GABA	γ-aminobutyric acid
H	Histamine
HT	Hydroxytryptamine
ICC	Intra-class correlation coefficient
ICD-10	International Classification of Diseases and Related Health Problems, 10th revision
NIA	Neuroleptic-induced akathisia
NIMD	Neuroleptic-induced movement disorder
NIP	Neuroleptic-induced parkinsonism
NPV	Negative predictive value
PD	Parkinson's disease
PPV	Positive predictive value
PsA	Pseudoakathisia
ROC	Receiver operating characteristic
SAS	Simpson–Angus Scale
SD	Standard deviation
TD	Tardive dyskinesia
UPDRS	Unified Parkinson's Disease Rating Scale

1 List of original publications

This thesis is based on the following original publications, which are referred to in the text by Roman numerals I–IV:

I Janno S, Holi MM, Tuisku K, Wahlbeck K. Prevalence of neuroleptic-induced movement disorders in chronic schizophrenia inpatients. Am J Psychiatry 161: 160–163, 2004.

II Janno S, Holi MM, Tuisku K, Wahlbeck K. Actometry and Barnes Akathisia Rating Scale (BARS) in neuroleptic-induced akathisia. Eur Neuropsychopharmacol 15(1): 39–41, 2005.

III Janno S, Holi MM, Tuisku K, Wahlbeck K. Validity of Simpson–Angus Scale (SAS) in a naturalistic schizophrenia population. BMC Neurol 17; 5(1): 5, 2005.

IV Janno S, Holi MM, Tuisku K, Wahlbeck K. Neuroleptic-induced movement disorders in a naturalistic schizophrenia population: diagnostic value of actometric movement patterns. Psychiatry Res, (submitted).

In addition, some unpublished data have been included in this thesis.

2 Abstract

The prevalence and assessment of neuroleptic-induced movement disorders (NIMDs) in a naturalistic schizophrenia population that uses conventional neuroleptics were studied. We recruited 99 chronic schizophrenic institutionalized adult patients from a state nursing home in central Estonia. The total prevalence of NIMDs according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) was 61.6%, and 22.2% had more than one NIMD.

We explored the reliability and validity of different instruments for measuring these disorders. First, we compared DSM-IV with the established observer rating scales of Barnes Akathisia Rating Scale (BARS), Simpson–Angus Scale (SAS) (for neuroleptic-induced parkinsonism, NIP) and Abnormal Involuntary Movement Scale (AIMS) (for tardive dyskinesia), all three of which have been used for diagnosing NIMD. We found a good overlap of cases for neuroleptic-induced akathisia (NIA) and tardive dyskinesia (TD) but somewhat poorer overlap for NIP, for which we suggest raising the commonly used threshold value of 0.3 to 0.65.

Second, we compared the established observer rating scales with an objective motor measurement, namely controlled rest lower limb activity measured by actometry. Actometry supported the validity of BARS and SAS, but it could not be used alone in this naturalistic population with several co-existing NIMDs. It could not differentiate the disorders from each other. Quantitative actometry may be useful in measuring changes in NIA and NIP severity, in situations where the diagnosis has been made using another method.

Third, after the relative failure of quantitative actometry to show diagnostic power in a naturalistic population, we explored descriptive ways of analysing actometric data, and demonstrated diagnostic power pooled NIA and pseudoakathisia (PsA) in our population.

A subjective question concerning movement problems was able to discriminate NIA patients from all other subjects. Answers to this question were not selective for other NIMDs.

Chronic schizophrenia populations are common worldwide, NIMD affected two-thirds of our study population. Prevention, diagnosis and treatment of NIMDs warrant more attention, especially in countries where typical antipsychotics are frequently used. Our study supported the validity and reliability of DSM-IV diagnostic criteria for NIMD in comparison with established rating scales and actometry. SAS can be used with minor modifications for screening purposes. Controlled rest lower limb actometry was not diagnostically specific in our naturalistic population with several co-morbid NIMDs, but it may be sensitive in measuring changes in NIMDs.

3 Introduction

Schizophrenia is life-time disease that causes considerable suffering and economic burden to the individual and society, and necessitates long-term treatment, sometimes for decades (Murray & Lopez 1997, Csernansky & Schuchart 2002). The treatment of schizophrenia is based mainly on antipsychotic medication and various psychosocial treatments (Csernansky & Schuchart 2002). Traditionally, an obstacle to compliance with antipsychotic treatment has been the adverse effects, with movement disorders being particularly problematic (Csernansky & Schuchart 2002). Neuroleptic-induced movement disorders (NIMDs) have been suggested to be caused by blockade of dopamine 2 (D_2) receptors in the basal ganglia and to some extent in cortical structures (Cross et al. 1985). Nowadays, in most developed countries, atypical antipsychotics, which cause less blockade of D_2 and also affect serotonergic receptors, are being used, and as they induce less NIMDs (Liebermann et al. 2003), these disorders may have become less common. In some parts of the world, however, even conventional antipsychotics are not available (World Health Organization 2005). The prevalence of NIMDs in non-developed economies has not been thoroughly studied by contemporary instruments.

NIMD has traditionally been assessed and diagnosed by clinical evaluation and by observer rating scales. Some established observer rating scales include the Barnes Akathisia Rating Scale (BARS) for neuroleptic-induced akathisia (NIA) (Barnes 1989), the Simpson–Angus Scale (SAS) for neuroleptic-induced parkinsonism (NIP) (Simpson & Angus 1970) and the Abnormal Involuntary Movement Scale (AIMS) for tardive dyskinesia (TD) (Guy 1976). These established instruments have not so far been studied against the current diagnostic criteria of NIMD.

These scales provide only a rough assessment, and they have been suggested to be insensitive to change (Caligiuri et al. 1997, Dean et al. 2004). Motor instrumental measurement, an objective way of quantifying movement, has been postulated be more sensitive to changes, and perhaps more sensitive to find NIMD cases (Tuisku et al. 2000).

Actometry has been used in different NIMDs, as an objective measure of disordered movement, and is a promising tool for diagnosing and measuring the severity of NIA (Tuisku et al. 1999). It has not however, been used in a naturalistic setting. Moreover, it has not been properly studied in NIP or TD. Descriptive actometry has rarely been investigated in patients with several NIMDs simultaneously.

4 Review of the literature

4.1 Antipsychotic drug treatment

Antipsychotics are drugs that specifically alleviate psychotic symptoms (i.e. not just by calming or tranquilizing the patient) (Deniker 1960). The first of these drugs, chlorpromazine, started a new era in psychiatry in the last half of the twentieth century, as for the first time psychotic symptoms could be managed by a drug, and many psychotic patients no longer required physical restraint or chronic hospitalization (Denham & Carrick 1961, Davis & Casper 1977). Different classes of antipsychotic drugs, categorized according to their structure or profile of action on different neurotransmitters, exist. The blockage of dopamine receptors is a key feature common to all antipsychotics.

Antipsychotic drugs include dopamine receptor antagonists or typical (or conventional) antipsychotics (e.g. chlorpromazine, haloperidol), serotonin-dopamine antagonists or atypical antipsychotics (e.g. risperidone, clozapine) and dopamine partial agonists (e.g. aripiprazole) (Liebermann 2004).

4.1.1 History of antipsychotic treatment

Before 1950, psychiatry treated schizophrenia with non-specific biological treatments such as insulin coma, electroconvulsive therapy, narco-analysis and psychosurgery; the drugs used were opioid derivatives, barbiturates and chlorals (Healy 1996, Caldwell 1978).

Henri Laborit, a surgeon from France, tried to find a drug that acted centrally on the autonomous nerve system to prevent surgical shock and administered chlorpromazine in 1951. He identified the psychotropic properties of chlorpromazine, as his patients did not lose consciousness; instead they had a tendency to drift off and become "disinterested" in their surroundings (Caldwell 1978).

Jean Sigwald, from the Val-de-Grace Hospital in France, started treating a psychotic female patient with chlorpromazine on 28.12.1951 at doses of 25–50 mg, and the patient's hallucinations lost their threatening character (Caldwell 1978).

Delay and Deniker prepared a series of reports on using chlorpromazine for psychotic patients beginning in March 1952 (Deniker 1960). They presented their results on the effectiveness of chlorpromazine at a scientific meeting in May 1952. Usage of chlorpromazine rapidly spread over the world (Caldwell 1978). Several drugs similar to chlorpromazine were synthesized within the next few years (Caldwell 1978). In 1958 Paul Janssen synthesized haloperidol, which had relatively selective D_2 receptor actions and therefore better tolerability (Cunningham Owens 1999). The use of neuroleptics was associated with extrapyramidal side-effects so frequently that these were seen as markers of efficacy (Haase 1961). The introduction of clozapine, an antipsychotic with minimal motor adverse effects, in 1966 made this correlation questionable (Healy 1996).

Nevertheless, the clinical impact of introducing neuroleptics was dramatic, as for the first time the number of patients in chronic mental hospitals began to drop, and more and more individuals became manageable as outpatients (Davis & Casper 1977).

4.1.2 Mechanism of action

The dopamine hypothesis has been offered as an explanation for the mechanism of action of antipsychotics (Carlsson & Lindqvist 1963). The simplest formulation of the dopamine hypothesis posits that schizophrenia results from excessive dopaminergic activity that affects two of the main dopamine pathways in the brain – the mesolimbic and mesocortical pathways – producing changes in brain activity. The theory evolved from two observations. First, the potency of dopamine receptor antagonist drugs to reduce psychotic symptoms is most closely correlated with the affinity of these drugs to D_2 receptors. The mechanism of therapeutic action for dopamine receptor antagonist drugs is hypothesized to be through D_2 receptor antagonism, which prevents endogenous dopamine from activating the receptors (Carlsson & Lindqvist 1963). Second, drugs that increase dopaminergic activity, notably amphetamine, are psychotomimetic (Lieberman 1987).

Serotonin-dopamine antagonists or second-generation antipsychotics are antagonists of D_2 receptors but have a diverse range of binding activities at other receptor types (Meltzer et al 1989). Clozapine has variable affinities for several neurotransmitter receptors, including high affinity for serotonin 5-HT_{2A}, 5-HT_{2C}, 5-HT_6 and 5-HT_7, histamine H_1, and muscarinic acetylcholine receptors, but moderate or low affinity for various dopamine receptors (Meltzer et al. 1989, Tarsy et al. 2002). Atypical antipsychotics with a low EP adverse effects risk, and clozapine in particular, have relatively low affinity and occupation levels at D_2 receptors and at least moderate affinity for D_4 receptors, which are present mainly in cortical and limbic regions, with especially low prevalence in the basal ganglia (Tarsy et al. 2002). The dopamine partial agonists have partial agonist activity at both D_2 and 5-HT_{1A} receptors (Liebermann 2004).

An antipsychotic will occupy dopamine receptor sites within an hour of a patient receiving an adequate dose of the drug (Farde et al. 1992), but the full antipsychotic effect takes several weeks (Deniker 1960; Liebermann et al. 2003).

The precise mechanism of action of antipsychotics remains unclear.

4.1.3 Clinical effects

All typical neuroleptic agents have the ability to reduce positive psychotic symptoms after several weeks of treatment (Deniker 1960, Denham & Carrick 1961). Some atypical antipsychotics have been shown to alleviate a greater variety of symptoms, resulting in more complete treatment response (Davis et al. 2003). Withdrawal of neuroleptic agents causes a relapse of psychosis in patients with schizophrenia, at the rate of approximately 10% per month, so that 50% or more will have relapsed by 6 months after discontinuation of neuroleptic agents. Consequently, long-term treatment with antipsychotics is indicated in schizophrenia for at least 1–2 years after alleviation of symptoms (Davis & Casper 1977, Csernansky & Schuchart 2002).

4.1.4 Adverse effects

The most common adverse effects of typical antipsychotics are extrapyramidal effects, which are described in detail in section 4.3.

Other side-effects are due to antihistaminic (weight gain) or alpha adrenergic (cardio-

vascular side-effects – hypotonia) blocking, and anticholinergic properties (tachycardia, dry mouth, blurred vision, constipation, exacerbation of narrow angle glaucoma, urinary retention) (Malhotra et al. 1993). Metabolic changes (increase of blood glucose, glycosylated haemoglobin, cholesterol, triglycerides) are associated more strongly with atypical antipsychotics (Lieberman et al. 2003, 2005).

The most common adverse effects associated with clozapine are sedation and hypersalivation (Liebermann & Safferman 1992). Neuroleptics may decrease the seizure threshold (Woolley & Smith 2001).

Dermatological effects include skin rashes, pigmentation and photosensitivity. The most significant neuroendocrine effect of antipsychotics is hyperprolactinaemia (Malhotra et al. 1993).

Possibly fatal side-effects include malignant neuroleptic syndrome (Nagamine et al. 2005), aplastic anaemia (remoxipride) (Laidlaw et al. 1993, Philpott et al. 1993), and agranulocytosis with clozapine (Alvir et al. 1993, Idänpään–Heikkilä et al. 1997).

4.1.5 Pharmacoepidemiology

Economic resources differ between countries, resulting in different prescribing patterns.

Developed and developing economies

In 1989–1997 psychiatrists and other physicians in the United States prescribed olanzapine or risperidone 40% of cases in which antipsychotics were prescribed. The amount of typical antipsychotics over time has not changed, but prescribing of atypicals had grown (Hermann et al. 2002). In 1997, novel antipsychotics were prescribed for almost half of all psychotic patients (47%) in the United States. Prescribing practices were reported to be influenced by both facility and patient characteristics (Owen et al. 2001).

The prescribing patterns are similar in Europe. In 1998 in Italy 55% of schizophrenia patients received typical antipsychotics (Magliano et al. 2004). Typical antipsychotics accounted for 44% of all antipsychotic prescriptions in the United Kingdom in 2003 (National Health Service 2003). According to data from the Finnish National Agency for Medicines (2002, 2005), 61% of antipsychotic DDD/1000 people in 2001 and 39% in 2004 were typical antipsychotics.

Typical antipsychotics comprised 72% of all prescribed antipsychotics in six East Asian countries (China, Hong Kong, Japan, Korea, Singapore and Taiwan) in 2001 (Chong et al. 2004).

These figures show that in the developed economies a transition to use of atypical antipsychotics has occurred, and today a majority of prescriptions for schizophrenia are atypicals. The data about developing countries is extremely scarce, but the majority of prescriptions are not atypical antipsychotics and in some parts of the world even typical antipsychotics are not available (World Health Organization 2005).

Transitional economies

According to data from the Bulgarian Drug Agency, 73% of antipsychotic DDD/1000 people in 2001 were typical antipsychotics (Bulgarian Drug Agency 2005). According to the Czech Republic State Institute for Drug Control, 67% of antipsychotic DDD/1000 people in 2001

and 57% in the year 2004 were typical antipsychotics (personal communication, 2005). According to the Latvian State Medicines Pricing and Reimbursement Agency (2005), 59% of antipsychotic DDD/1000 people in 2004 were typical antipsychotics.

Estonia

According to an Estonian study conducted in 2001–2002, 12.8% of schizophrenia patients received clozapine and 10.5% new atypicals (mainly risperidone); all the others received typical antipsychotics (Jaanson 2002). Data from the Estonian Health Insurance Fund (personal communication 2005) indicate that 68% of patients with the diagnosis F20–F29 were prescribed typical antipsychotics (haloperidol, melperone, flupenthixole, chlorprotixen, zuclopenthixol) and 32% atypical antipsychotics (clozapine, olanzapine, quetiapine, amisulpiride, risperidone) in 2004. According to the Estonian State Agency of Medicines, 80% of antipsychotic DDD/1000 people in 2004 were typical antipsychotics (Eesti Ravimiamet 2005).

Taken together, these data show that in transitional economies the majority of antipsychotic drug prescriptions are still for typical antipsychotics.

4.2 Movement disorders

Movement disorders are neurological motor disturbances characterized by abnormally increased motor activity or impaired back posture or by abnormally decreased motor function, mobility or posture (Chouinard 2004).

4.2.1 Classification

Movement disorders due to basal ganglia diseases are classified into different clusters by the International Classification of Diseases, 10th revision (ICD-10): the majority are classified as neurological diseases but some are classified as mental and behavioural disorders (tic disorders including Gilles de la Tourette syndrome), some as endocrinological diseases (Wilson's disease) and some as cardiological diseases (rheumatic chorea) (World Health Organization 1992). The DSM-IV define a classification for drug-induced movement disorders, which is presented in section 4.3.4.

The causes of movement disorders can be neurodegenerative, vascular, hereditary, infective, metabolic or drug-induced (Chouinard 2004, Alarcon & Gimenez-Roldan 2005).

Movement disorders can be divided into hypo- and hyperkinetic disorders (Litvan et al. 1998). The major features of akinetic-rigid syndromes are bradykinesia (small, slow movements), rigidity and tremor, often summarized as "parkinsonism" (Rice & Thompson 2001a). Hyperkinetic movements are characterized by involuntary movements and are classified according to their different patterns into syndromes of chorea, ballism, tremor, dystonia, myoclonus and tics (Rice & Thompson 2001b).

4.2.2 Epidemiology

Approximately 80% of akinetic-rigid syndromes are due to Parkinson's disease (PD) (Rice & Thompson 2001a). The prevalence of PD in Estonia is 152 per 100 000 individuals (Taba & Asser 2002). Published data indicate a PD prevalence of 108–257 per 100 000 in Europe (Campenhausen et al. 2005). Studies stating a higher prevalence include the parkinsonism syndrome; Hobson et al. (2005) found the prevalence of PD to be 105 and of parkinsonism to be 122 per 100 000. The prevalence of PD increases with age, reaching over 300 per 100 000 in the age group 60–69 years, over 400 per 100 000 in the age group 70–79 years and over 900 in the age group 80 years or older (Campenhausen et al. 2005). For another akinetic-rigid syndrome, progressive supranuclear palsy, the age-adjusted prevalence was 5 per 100 000 in Great Britain (Nath et al. 2001) and 6 per 100 000 in Japan (Kawashima et al. 2004).

The prevalence of essential tremor is 4.0% in the age group over 40 years (Dogu et al. 2003). For restless legs syndrome, the 12-month prevalence is reported to be 8.5% in a French adult population (Tison et al. 2005).

For Huntington's disease, a hyperkinetic syndrome, the prevalence is reported to be 4–8 per 100 000 individuals (Harper 1992).

The prevalence of spontaneous dyskinesias in non-psychiatric patients was 0.8% between the ages of 50 and 59 years, 6% between the ages of 60 and 69 years, and 7.8% between the ages of 70 and 79 years (Klawans & Barr 1982).

According to this data, the prevalence of movement disorders in the general population is moderately low.

4.2.3 Movement disorders associated with mental disorders

An increasing amount of neuropathology has been found underlying the psychiatric disorders classified in the DSM-IV (American Psychiatric Association 2000). At one end of the continuum, this classification includes primarily neurological diseases of an identified organic aetiology with clear neurological and neurocognitive symptoms. At the other end of the continuum are disorders considered to be primarily psychogenic or functional (Beier 1997). Between the two extremes are a large number of neuropsychiatric disorders with some neurological signs and some evidence of organic neuropathology, but in which the pathophysiological mechanisms are far from clear.

Motor abnormalities have been studied in, for example, schizophrenia, autistic disorders, and attention deficit hyperactivity disorder, all of which are considered neurodevelopmental disorders (Weinberger 1995, Taylor 1999, American Psychiatric Association 2000, Tanguay 2000).

Minor motor abnormalities, also known as "soft signs", are commonly encountered in each of these neurodevelopmental disorders (Jones & Prior 1985, Aronowitz et al. 1994, Flashman et al. 1996). While the clinical significance of neurological soft signs is uncertain, they are widely regarded as indicators of non-specific brain damage (Kennard 1960). Soft signs include involuntary movements and abnormalities in gait, balance, laterality, integrative sensomotor functions and motor coordination (Krebs et al. 2000). The term soft sign has, however, been criticized for having blurred boundaries (Sanders & Keshavan 1998). By definition, soft signs are neurological abnormalities that are not readily localizable to a specific brain region, while "hard signs", or "major neurological signs", like reflex asym-

metry, provide some indication of the underlying brain systems or regions affected (Sanders & Keshavan 1998).

Both soft and hard signs of nearly all functional domains are increased in schizophrenia, the subdomains of motor coordination and involuntary movements being the most prominent (Ismail et al. 1998). Soft signs were present in 23% of neuroleptic-naïve schizophrenia patients and in 46% of schizophrenia patients treated with neuroleptics but were absent in control group. However, neither AIMS nor SAS distinguished the neuroleptic-naïve group from the group treated with neuroleptics, which shows that the greater prevalence in the treated group was due to a medication effect (Gupta et al. 1995). At least mild parkinsonism (SAS mean score higher than 0.1) was found in 17%, spontaneous mild dyskinesia in 1% and probable akathisia in 5% of neuroleptic-naïve patients (Chatterjee et al. 1995).

4.3 Extrapyramidal adverse effects of neuroleptics

Extrapyramidal adverse effects are the various movement disorders that arise from taking antipsychotic drugs.

Four different movement disorders, i.e. NIP, NIA, acute dystonia and TD, are the most prevalent (Jenner & Marsden 1982, Wirshing 2001, Sachdev 2005).

Extrapyramidal adverse effects are among the most important reasons for non-compliance with antipsychotic treatment, as they result in subjective suffering (van Putten 1974). They cause lowering of patients' everyday function level, and social stigma (Kane et al. 1992, Krausz et al. 1999). Despite the increasing amount of atypical antipsychotics available, the extrapyramidal symptoms are still relevant in the treatment of psychosis because:

1 Globally, many patients continue to use conventional antipsychotics;
2 Even atypical antipsychotics may cause extrapyramidal symptoms (Miller et al. 1998, Tarsy et al. 2002);
3 Clinicians have a poor ability to identify NIMDs, which vary between 10% and 59% (Weiden et al. 1987, Hansen et al. 1992).

4.3.1 History

Almost immediately after introduction of neuroleptic drugs, reports have been made of extrapyramidal syndromes; NIP and NIA were reported by Steck in 1954 (Marsden & Jenner 1980), acute dystonic reactions by Delay and Deniker in 1957 (Deniker 1960) and TD which became recognized after months or years of treatment, by Sigwald in 1959 (Marsden & Jenner 1980).

The reported prevalence of parkinsonism, akathisia and dystonia has been steady for years (Ayd 1961, McCreadie et al. 1992, van Harten et al. 1996, Halliday et al. 2002). TD was not reported in the first surveys (Deniker 1960, Ayd 1961), but Faurbye used the term tardive dyskinesia for the first time and reported a prevalence of 26% in 1964 (Faurbye et al. 1964, Friedman 2004). The Nithsdale studies have shown a doubling of prevalence of TD from 1982 to 2002 (Halliday et al. 2002).

The understanding of neuroleptic-induced extrapyramidal symptoms has changed over the years. In the past, when all existing antipsychotics caused extrapyramidal syndromes,

extrapyramidal symptoms were considered a necessary step in achieving an adequate antipsychotic effect (Denham & Carrick 1961, Haase 1961). After introduction of clozapine and other second generation (atypical) antipsychotics, these symptoms were considered an adverse effect of treatment, having no relationship with clinical efficacy (Healy 1996).

4.3.2 Aetiopathogenesis

Cortical motor areas, cerebellum, basal ganglia and related subcortical nuclei, control normal movement. The classic NIMDs are mediated primarily by the impact on D_2 receptors located in the extrapyramidal system. Those agents with high D_2 receptor affinity are associated with a greater risk of developing acute and late-onset movement disorders (Agnoli et al. 1983).

Such disorders are subserved primarily by the basal ganglia (Cross et al. 1985), which modulate motor activity through complex mechanisms, ultimately balancing inhibitory and stimulating impulses through dopamine and other neurotransmitters such as serotonin (5-hydroxytryptamine [5-HT]), acetylcholine, -aminobutyric acid (GABA) and glutamate. In this context, the optimal range of D_2 blockade in drug-naïve patients may be very narrow. Kapur et al. (2000) have shown that typical antipsychotic D_2 receptor occupancy in the corpus striatum that is greater than 78% is associated with increased risk of extrapyramidal side-effects and levels of less than 65% with suboptimal efficacy. An important finding is that these levels can be achieved in first-episode patients with haloperidol doses as low as 1–5 mg per day (Kapur et al. 2000).

Neuroleptic-induced parkinsonism (NIP) is an extrapyramidal syndrome which in association with antipsychotic treatment is suggested to be caused by blockage of more than 80% of the dopamine receptors (D_2) in the nigrostriatal pathway (basal ganglia) (Farde et al. 1992). TD is proposed to be caused by development of increased sensitivity to dopamine in the nigrostriatal system as a consequence of chronic blockade by antipsychotic drugs (Klawans & Rubovits 1972, Tarsy & Baldessarini 1973). Mesocortical D_2 receptor blockade by antipsychotic drugs (Marsden 1980) and imbalance between the noradrenergic and the dopaminergic systems (Blaisdell 1994) have been suggested to cause neuroleptic-induced akathisia (NIA). The risk of developing extrapyramidal symptoms is smaller with atypical antipsychotics compared with traditional antipsychotics probably due to their relatively lower D2 receptor occupancy and commensurately higher 5-HT2 occupancy (Goldstein 2000) and their limbic selectivity (Arnt & Skarsfeldt 1998).

4.3.3 Typology

NIMDs, or extrapyramidal adverse effects, can be classified into acute and tardive syndromes on the basis of the temporal relationship with neuroleptic use (Wirshing 2001), or on their characteristics (hyperkinetic or hypokinetic, sometimes referred to as positive or negative) (Sachdev 1995). Acute NIMDs include acute dystonia, parkinsonism, akathisia and neuroleptic malignant syndrome (Sachdev 1995, Wirshing 2001). Tardive syndromes are classified by phenomenology (e.g. chorea, dystonia, tics) and can, unlike their acute counterparts, be irreversible (Wirshing 2001).

The predominant tardive syndrome is tardive dyskinesia, although several related syndromes have been described (Sachdev 2005). TD is a syndrome consisting of abnormal

involuntary movements, usually of the choreoathetoid type, sometimes stereotyped, principally affecting the mouth and face, sometimes the limbs, and occasionally the trunk (Jeste & Wyatt 1982). For research and clinical purposes, Schooler and Kane (1982) suggested the following research criteria for diagnosing TD: (1) at least 3 months of cumulative exposure to neuroleptic medication, (2) the absence of other conditions that might cause the abnormal involuntary movements, and (3) movements of mild severity (score of 2 on the AIMS) in at least two discrete body parts or movements of moderate severity (score of 3 or more) in one body area. If these criteria are fulfilled, a diagnosis of probable TD is made.

Dystonias most frequently occur during the first five days of treatment, though even a single dose of medication can induce a reaction (Ayd 1961). Acute dystonic reaction is a common adverse event characterized by involuntary muscular spasms that produce brief or sustained abnormal postures. These include oculogyric crisis, tongue protrusion, trismus, torticollis, laryngeal-pharyngeal constriction or bizarre positions of the limbs and trunk (Ayd 1961).

NIP may present with the classic triad of tremor, rigidity and bradykinesia, although only one symptom is necessary to establish the diagnosis (APA, DSM-IV). The tremor may have different manifestations and is often apparent at rest. Rigidity is commonly observed as a cogwheeling movement during passive flexion-extension of the elbow or wrists. Bradykinesia manifests as a decrease in spontaneous activity, a mask faces and a loss of accessory movements with a festinant gait (Deniker 1960). NIP is manifested mostly in upper limbs (Hassin-Baer et al. 2001). NIP is more symmetrical and involves gait and posture less commonly than PD (Hassin-Baer et al. 2001).

NIA is characterized by an unpleasant (distressing) inner restlessness, an urge to move and the presence of restless movements (Sachdev 1995, Cunningham Owens 1999). NIA typically presents with restless movements, a coarse tremor and myoclonic jerking of the feet (Braude et al. 1983, Barnes & Braude 1985) NIA has marked and often distressing subjective component. Pseudoakathisia (PsA) has only motor component of disorder (Munetz & Cornes 1982, Barnes & Braude 1985, Havaki-Kontaxaki et al. 2000).

The principal features of neuroleptic malignant syndrome are hyperthermia, muscle rigidity, alteration in consciousness and autonomic dysfunction. The syndrome is potentially fatal (Sachdev 2005).

4.3.4 Current classification

Unlike the ICD-10, DSM-IV classifies medication-induced movement disorders (APA DSM-IV) into seven categories as follows:

NIP – Parkinsonian tremor, muscular rigidity or akinesia developing within a few weeks of starting or raising the dose of a neuroleptic medication (or after reducing a medication used to treat extrapyramidal symptoms).

Neuroleptic malignant syndrome – severe muscle rigidity, elevated temperature and other related findings (e.g. diaphoresis, dysphagia, incontinence, changes in level of consciousness ranging from confusion to coma, mutism, elevated or labile blood pressure, elevated creatine phosphokinase) developing in association with the use of neuroleptic medication.

Neuroleptic-induced acute dystonia – Abnormal positioning or spasm of the muscles of the head, neck, limbs or trunk developing within a few days of starting or raising the dose of a neuroleptic medication (or after reducing a medication used to treat extrapyramidal symptoms).

Neuroleptic-induced acute akathisia – subjective complaints of restlessness accompanied by observed movements (e.g. fidgety movements of the legs, rocking from foot to foot, pacing, inability to sit or stand still) developing within a few weeks of starting or raising the dose of a neuroleptic medication (or after reducing a medication used to treat extrapyramidal symptoms).

Neuroleptic-induced TD – involuntary choreiform, athetoid or rhythmic movements (lasting at least a few weeks) of the tongue, jaw or extremities developing in association with the use of neuroleptic medication for at least a few months (may be for a shorter period in elderly persons).

Medication-induced postural tremor – fine tremor occurring during attempts to maintain a posture developing in association with the use of medication (e.g. lithium, antidepressants, valproate).

Medication-induced movement disorder not otherwise specified – this category is for medication-induced movement disorders that do not belong to any of the disorders listed above. Examples include (1) parkinsonism, acute akathisia, acute dystonia or dyskinetic movement associated with a medication other than a neuroleptic; (2) a presentation resembling neuroleptic malignant syndrome that is associated with a medication other than a neuroleptic; and (3) tardive dystonia.

4.3.5 Epidemiology of NIMD

The reported point prevalence for any NIMD in schizophrenia patient populations is 29–74% (Ayd 1961, McCreadie et al. 1992, van Harten et al. 1996, Muscettola et al. 1999, Modestin et al. 2000).

Van Harten and colleagues (1996) reported a prevalence in the higher end because they considered four NIMDs, including tardive dystonia (13%). The Nithsdale schizophrenia survey assessing three NIMDs (TD, NIP and NIA) found a point prevalence of 29% for TD, 27% for NIP, 18% for NIA, and 56% of schizophrenia patients had one or more NIMDs (McCreadie et al. 1992). After 11 years in the same region, the point prevalence of probable TD was 43%, of NIP 35% and NIA 15% for 136 patients (Halliday et al. 2002). Despite long-term use of clozapine in a Zurich hospital, 42% of inpatients suffered from at least one NIMD (Modestin et al. 2000).

Based on epidemiological data, NIMD seems to be a relevant problem in antipsychotic treatment, although the reported prevalence figures differ due to different study populations and definitions.

4.3.6 Neuroleptic-induced akathisia

NIA, one of the most distressing adverse effects of antipsychotic treatment (Halstead et al. 1994), can decrease patient compliance, increase psychotic symptoms (van Putten 1974) and provoke aggression (Stubbs et al. 2000).

NIA patients tend to experience inner restlessness, and restless legs syndrome patients tend to experience leg paresthesias as an antecedent to motor restlessness (Walters et al. 1991). Restless legs symptoms are worse in the evening, while NIA symptoms are evident in the day time (Walters et al. 1991).

Epidemiology

NIA may appear within the first few hours of antipsychotic exposure, but usually it takes days to weeks (Ayd 1961, Braude et al 1983).

The reported prevalence range for NIA is 9–35%, but the usual estimates are around 20% for patients receiving antipsychotic treatment (McCreadie et al. 1992, Halstead et al. 1994, Sachdev 1995, Van Harten et al. 1996, Cunningham Owens 1999, Muscettola et al 1999, Halliday et al 2002). A lower prevalence of NIA, 9.3%, was reported in a chronic inpatient setting (van Harten et al. 1996). A survey of 1559 in- and outpatients found an NIA prevalence 32% (Muscettola et al. 1999).

Socio-demographic variables (age, race, sex) do not appear to be significant risk factors for NIA (Braude et al. 1983, Sachdev & Kruk 1994, Sachdev 1995, Chong et al. 2003, Kim & Buyn 2003). Instead significant risk factors are drug-related, including high-potency drugs (Ayd 1961), drug dose and rapid dosage escalation (Braude et al. 1983, Sachdev & Kruk 1994).

Treatment

NIA may occur less frequently if patients are adequately informed, carefully monitored and encouraged to report adverse effects.

The recommended interventions to treat NIA are dose reduction of antipsychotic medication or switching to the drugs less likely to produce extrapyramidal symptoms (Taylor et al. 2001). When the intervention is not effective or proves impossible, either an anticholinergic drug or propranolol could be added to the treatment, but the former may be effective only in patients with comorbid drug-induced parkinsonian symptoms (Barnes & McPhillips 1999, Taylor et al. 2001). The evidence for a benefit with central action beta blocker or anticholinergics is weak (Lima et al. 2004a, 2005b). Secondary options include benzodiazepines, cyproheptadine and clonidine (Taylor et al. 2001). Low-dose mianserine has also shown some effectiveness (Poyurovsky et al. 1999), and other serotonergic drugs may prove useful in the future (Poyurovsky & Weizman 2001).

Prognosis

Braude et al. (1983) found that improvement of NIA occurred in all ten patients whose neuroleptic dose was reduced. Some patients experience withdrawal akathisia, which emerges after drug dose reduction (Barnes & Braude 1985). With maintenance antipsychotic treatment, akathisia can become a long-term problem (Barnes & Braude 1985). NIA can be uncovered by switching to atypical antipsychotics (Tuisku 2000).

4.3.7 Neuroleptic-induced parkinsonism

NIP can produce an inability to perform everyday tasks because of rigidity and disturbed movements, compromising the patient's quality of life (Cunningham Owens 1999). Rigidity and dullness of thinking, sometimes called mental parkinsonism, have been described by patients in association with NIP (Hellewell 2002). NIP differs from Parkinsonian disease by more bilateral involvement with relative symmetry, and by affecting upper limbs more often than lower limbs (Hassin-Baer et al. 2001). NIP tends to be associated with the triad

of bradykinesia, tremor and rigidity, while PD more often involves gait and posture (Hassin-Baer et al. 2001).

Epidemiology

NIP may develop within a few days of drug treatment, with 50–75% of cases appearing by one month and 90% within three months (Ayd 1961).

The point prevalence range for NIP is 15%–36% (Ayd 1961, McCreadie et al. 1992, van Harten et al. 1996, Muscettola et al. 1999, Halliday et al. 2002). Ayd (1961) using clinical impression found the point prevalence of NIP in large (3775 patients) survey to be 15%. Modestin et al (2000) reported that point prevalence of NIP using UPDRS in in-patients using typicals and clozapine was 20%. Recent studies using rating scales have found the point prevalence in chronic in-patients to be 36% with UPDRS (Van Harten et al 1996) and 29% using a modified version of SAS (Muscettola et al 1999). The Nithsdale population survey of 136 schizophrenia patients found that NIP was present as often in those receiving atypicals as in those receiving standard oral antipsychotics (29% and 27%, respectively) using SAS (Halliday et al. 2002).

Risk factors include use of higher doses of antipsychotics, high-potency typical antipsychotics, age over 40 years (corresponding to the age of onset of idiopathic Parkinsonian disease) and a basal ganglia dysfunction (Marsden & Jenner 1980, Ayd 1961). There is an individual susceptibility to the development of NIP in response to a given dose of neuroleptics (Jenner & Marsden 1982).

Treatment

The treatment strategies for NIP are reducing the dose of the neuroleptic or switching to a low-potency conventional neuroleptic or an atypical antipsychotic (Jenner & Marsden 1982, Holloman & Marder 1997, Wirshing 2001).

Anticholinergics have traditionally been used to treat parkinsonian symptoms, and they have been used prophylactically for many years (Jenner & Marsden 1982, Wirshing 2001). Anticholinergics should not, however, be given for more than three months, as longer periods are neither necessary nor effective (Jenner & Marsden 1982). Compared with other available drugs, biperiden has a slightly higher affinity for the muscarinic receptors that predominate in the central nervous system (Wirshing 2001). This means that biperiden is associated with fewer peripheral effects, although it still has the potential to cause confusion and memory disturbances (Wirshing 2001).

The dopaminergic agent amantadine has been shown in several clinical trials to be as effective as anticholinergics in treating NIP (Ananth et al. 1975). Advantages of amantadine over anticholinergics are that it may be better tolerated and that it does not adversely affect memory (Jenner & Marsden 1982).

Prognosis

Many patients respond to a reduction in neuroleptic dosage or a switch to a lower potency drug (Jenner & Marsden 1982).

The majority of patients are free of extrapyramidal signs within a few weeks of discontinuation of neuroleptic therapy, but in some cases signs may persist for weeks or months (Jenner & Marsden 1982).

4.3.8 Neuroleptic-induced tardive dyskinesia

TD is among the most serious adverse effects of long-term neuroleptic use in terms of its frequency, persistence, treatment resistance and overall impact on the well-being of patients and their caregivers (Kane et al. 1992).

Epidemiology

TD appears after many months or even years of drug treatment (Jeste et al. 1995).

The prevalence range for TD is 18–46% (Jeste & Wyatt 1981, Mukherjee et al. 1982, Koshino et al. 1992, McCreadie et al. 1992, van Harten et al. 1996, Cunningham Owens 1999, Muscettola et al. 1999). Its prevalence has doubled over the last 20 years (Halliday et al. 2002).

Ageing is the main risk factor for TD (Mukherjee et al. 1982, Barnes et al. 1983, Jeste & Caligiuri 1993, Morgenstern & Glazer 1993). Other risk factors include female gender, mood disorders, diabetes mellitus and early extrapyramidal side-effects (Chouinard et al. 1986, Jeste & Caligiuri 1993, Sachdev 2004). High rates of TD have also been reported in neuroleptic-treated individuals with mental retardation (Wirshing 2001, Sachdev 2005).

Longitudinal follow-up studies suggest that the cumulative incidence of TD increases with duration of neuroleptic treatment, at a rate of about 3–5% per year for the first several years, reaching a plateau of 20–25%. However, new cases continue to occur many years after drug initiation (Chouinard et al. 1986, Sachdev 2005).

Treatment

The primary strategy in the management of TD is preventative (Sachdev 2005). No effective treatment is available, although several drugs have been tried based on preliminary understanding of its pathophysiology (Sachdev 2005).

The treatment of TD involves careful risk-benefit analysis of the patient history of psychosis versus the disability caused by the movement disorder (Jeste and Wyatt 1982, Malhotra et al. 1993). Although neuroleptic cessation appears to be a first-line recommendation, no randomized controlled trials have been conducted to support this (McGrath & Soares-Weiser 2000). A number of pharmacological interventions proposed, including the use of non-neuroleptic catecholaminergic drugs, benzodiazepines, GABA agonists, calcium channel blockers and tocopherol (vitamin E), have subsequently been shown to be ineffective (Lyra da Silva et al. 2005, Umbrich & Soares 2003, Soares et al. 2001, Soares & McGrath 2001a, 2001b). No evidence has emerged to indicate that anticholinergic and cholinergic drugs relieve TD (Soares & McGrath 2000, Tammenmaa et al. 2004). Sometimes transition to clozapine may alleviate TD symptoms (Louza & Bassitt 2005), but at least one case of clozapine-induced TD has been reported (Ertugrul & Demir 2005).

Prognosis

For most people, TD does not become progressively worse; if it does get worse, it generally tends to show a fluctuating course with some spontaneous remissions (Sachdev 2005). In a five-year follow-up study by Bergen et al. (1989), at each examination only two-thirds of the subject pool was TD-positive. Of the patients, 24% showed a fluctuating course, 45% were TD positive at most examinations and 31% in at least one examination.

Of these patients who were consistently TD-positive, 82% showed no overall significant change in AIMS scores, 11% improved and 7% worsened (Bergen et al. 1989). Within 5–10 years, about 50% of patients demonstrate a 50% reduction in symptoms (Smith & Baldessarini 1980). The outcome is more favourable in the young and in those for whom drug treatment can be stopped (Smith & Baldessarini 1980). Improvement can be expected to continue for many years after neuroleptics have been terminated. The prognosis of withdrawal-emergent dyskinesia is more favourable, with over 75% showing improvement (Kane et al. 1992).

Jeste & Wyatt (1982) reported that TD remits in one-third of patients after three months of drug discontinuation and in 60% of patients after five years.

4.3.9 Pseudoakathisia

PsA is not classified in DSM-IV (APA 2004). This disorder has rhythmical movements, like NIA, but no subjective feeling of restlessness or distress (Munetz & Cornes 1982, Barnes & Braude 1985, Havaki-Kontaxaki et al. 2000). The overall prevalence of PsA has been reported to be 12.9% (van Harten et al. 1996), 4.8% in inpatients (Havaki-Kontaxaki et al. 2000) and 5% in outpatients (McCreadie et al. 1992). Munetz & Cornes (1982) have proposed that PsA is a progression of NIA to TD or a subtype of TD.

4.4 Measurement of neuroleptic-induced movement disorders

Methods of assessing human motor activity include systematic direct observations, self-report questionnaires, observer-based scales and instrumental measurement (Caligiuri 1994, Dale et al. 2002). Measuring movements and motor activity is common in clinical neurophysiology, neurology and sleep medicine, but it has also been utilized in psychiatry, geriatrics, orthopaedics, traumatology, physiatrics, occupational medicine and sports medicine (Tuisku 2002).

Adverse events can be monitored in several ways: awaiting spontaneous reports by the patient, inquiring generally about adverse events, systematic interview, using a checklist of symptoms, inquiring generally about health and inquiring specifically about target events (Schooler & Chengappa 2000).

In addition to the clinical evaluation, several specific rating scales have been developed to assess acute and late-developing extrapyramidal side-effects of antipsychotic medications (Schooler & Chengappa 2000). Measures (e.g. scales) are designed to improve the reliability and validity of patient assessment over what might be accomplished in a standard clinical interview (Blacker & Endicott 2000). To be useful, observer-based rating scales must be reliable (i.e. have internal consistency, interrater reliability and test-retest reliability) and valid (i.e. accurate in representing the true event) (Blacker & Endicott 2000).

All motor extrapyramidal symptoms can be measured by objective instruments. Parkinsonian symptoms have been studied more than the others, initially because of the clinical importance of primary Parkinson's disease (Caligiuri 1994). The earliest objective measure for recording finger tremor to revolving drum appeared in the literature in 1889 by Peterson (Caligiuri & Tripp 2004). The earliest documented study in which an electromechanical transducer was used to record rigidity was reported in 1959 (Webster 1959).

4.4.1 Observational measurement

Observer-based rating scales for NIMD evaluation are designed to evaluate several NIMDs simultaneously (combined rating scales) or particularly one NIMD (specific rating scales).

Combined rating scales

Some rating scales are aimed to cover several different movement disorders included in NIMD measurement. The earliest examples from the beginning of the 1970s with 31 and 4 items (Kennedy et al. 1971, van Putten 1974) had no names and were not used widely (Cunning-Owens 1999). The Smith Scale (Bell & Smith 1978) with 15 items, for instance, has not been used, according to a Medline search, in later published studies. The most widely used scales, the Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard et al. 1980) and the St. Hans Scale (Gerlach et al. 1993), with 26 and 21 items, respectively, are complex and difficult to use in day-to-day practice, but reportedly have good statistical properties (Cunningham-Owens 1999). Recently developed combined rating scales for NIMD are the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) with 8 subscales and one total item (Inada et al. 2002, 2003; Kim et al. 2002) and the Schedule for the Assessment of Drug-Induced Movement Disorders (SADIMoD) with 8 subscales (Loonen et al. 2000).

Among the combined rating scales, one self-report has been developed, the Liverpool University Neuroleptic Side-Effect Rating Scale (LUNSERS) with 51 items (Day et al. 1995), which has demonstrated reasonable convergent validity with established NIA and NIP scales (Barnes Akathisia Rating Scale and Simpson–Angus Scale) (Jung et al. 2005).

Combined scales have been reported to be impractical in clinical use because of their exhaustiveness and complexity, and their usefulness therefore limited to the research setting (Cunningham Owens 1999). However, since significant overlap exists between the different NIMDs, a combined approach may be more suitable than using specific rating scales for individual NIMDs.

Specific rating scales

Standardized rating scales have been developed for three NIMDs (NIA, NIP and TD), but not for acute dystonia, which can not be evaluated by such a formal assessment because of the wide spectrum of symptomatology, the rapid progression and the considerable disability, which does not allow cross-sectional evaluation or patient participation (Cunningham Owens 1999).

Neuroleptic-induced akathisia

For evaluation of NIA, several scales has been used, e.g. Hillside Akathisia Scale (Fleischhacker et al. 1989), Barnes Akathisia Rating Scale (BARS) (Barnes 1989) and Prince Henry Hospital Akathisia Rating Scale (Sachdev 1994), BARS being the most established. Several epidemiological and medication studies have used BARS (McCreadie et al. 1992, van Harten et al. 1996, Halliday et al. 2002).

BARS is a four-item anchored scale (Barnes 1989). The first three items assess objective and subjective characteristics of akathisia on a scale from 0 to 3. The fourth item, termed the global item, is measured on a scale from 0 to 5, with higher scores indicative of more

severe akathisia. Brief instructions are provided for raters regarding administration, but specific questions to be used in assessing subjective akathisia are not included (Barnes 1989).

The interrater reliability Cohen's kappa values have been as high as 0.738 in objective items, 0.827 in subjective awareness items, 0.901 in subjective distress and 0.955 in global clinical assessment (Barnes 1989).

The scale has been widely used in recent phase III trials of new antipsychotics (Liebermann et al. 2003). Because these medications are hypothesized to reduce akathisia in comparison with typical antipsychotics, the studies provide opportunities to assess the validity of BARS (Schooler & Chengappa 2000). First-episode psychosis patients receiving olanzapine showed a statistically significant mean reduction of 0.4 and patients receiving haloperidol showed a statistically significant mean increase of 0.3 in the BARS score compared with baseline (Liebermann et al. 2003). An earlier study used BARS for screening purposes to find NIA cases and actometry found difference in activity levels of NIA and non-NIA patients, which supports the validity of BARS (Poyurovski et al. 2000).

Neuroleptic-induced parkinsonism

The Unified Parkinson's Disease Rating Scale (UPDRS) was designed for assessment of treatment efficacy of idiopathic PD, but has also been applied for assessment of NIP (Fahn et al. 1987). Several scales have been used to evaluate NIP, e.g. Mindham Scale (Mindham et al. 1972), Scale for Targeting Abnormal Kinetic Effects (Wojcik et al. 1980) and Simpson–Angus Scale (SAS) (Simpson & Angus 1970), and modifications of the latter (Lehmann et al. 1970, Rifkin et al. 1978, Perenyi et al. 1984, Caligiuri et al. 1989).

SAS is most widely used in epidemiological and medication studies (McCreadie et al 1992, Halliday et al 2002, van Harten et al 1996, Liebermann et al 2003).

SAS contains ten items for assessing parkinsonian and related extrapyramidal side-effects, each scored from 0 to 4, with higher scores indicative of more severe symptoms (Simpson & Angus 1970). These original items are gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor and salivation. The mean score is obtained by adding all of scores and dividing by 10.

The mean interrater correlation coefficient between two raters was 0.87, with a range between 0.71 and 0.96, except for the salivation item, where it was between 0.16 and 1.0 (Simpson & Angus 1970). SAS has been criticized for its item choice (6 of 10 items concern rigidity) and the low mean interrater reliability coefficients for the gait, wrist rigidity, tremor and salivation items (Cunningham Owens 1999). The intraclass correlation coefficients (ICC) for wrist rigidity, tremor and salivation items were below 0.34 in a study conducted in elderly patients (Sweet et al. 1993).

SAS validity was obtained from a study involving two levels of haloperidol and placebo; the difference between the haloperidol group and the placebo group was statistically significant (Simpson & Angus 1970). A mean score of 0.3 was cited as the upper limit for patients without NIP or related extrapyramidal symptoms.

The scale has been widely used in recent phase III trials of new antipsychotics (Liebermann et al. 2003). Because these medications are hypothesized to have fewer extrapyramidal side-effects than typical antipsychotics, studies of these medications provide opportunities to assess the validity of SAS (Schooler & Chengappa 2000). First-episode patients receiving olanzapine showed a statistically significant mean reduction of 1.2, and

patients receiving haloperidol showed a statistically significant mean increase of 0.6 in SAS score compared with baseline (Liebermann et al. 2003).

Neuroleptic-induced tardive dyskinesia

Abnormal Involuntary Movement Scale (AIMS) (Guy 1976, Munetz & Benjamin 1988) and the Rockland (Simpson) Tardive Dyskinesia Rating Scale (Simpson et al 1979) have been mostly used for evaluation of TD. Dyskinesia Identification System: Condensed User Scale (DISCUS) was designed for developmentally based learning disabilities populations (Sprague & Kalachnik 1991).

AIMS was designed to record in detail the occurrence of dyskinesias in patients receiving neuroleptic medication (Schooler & Chengappa 2000). AIMS is by far the most established scale for rating TD (Schooler & Chengappa 2000). It has been used in several epidemiological studies (McCreadie et al. 1992, van Harten et al. 1996, Halliday et al. 2002).

The AIMS is a 12-item anchored scale (Guy 1976). Items 1–7 assess specific involuntary movements of the orofacial region, the extremities and the trunk. Items 8–10 deal with global severity, as judged by the examiner, and the patients' awareness of the movements and associated distress. Items 11 and 12 are yes–no items concerning problems with teeth and/or dentures because such problems can lead to a mistaken diagnosis of dyskinesia.

Each item is scored on a scale from 0 to 4, with higher scores indicative of more severe movements. The AIMS total score is a sum of items 1–7. Item 8 (severity of abnormal movements) can be used as an overall severity index. Specific instructions are provided for asking the patient certain questions and having him/her perform certain manoeuvres (Guy 1976). Score assignment is addressed well in an article by Munetz and Benjamin (1988).

Smith et al. (1979) assessed test–retest reliability, which range was from 0.12 to 0.75. Interrater reliability (Pearson correlation coefficients) in the same study ranged from 0.66 to 0.82 for individual body area items. The correlation for overall severity was 0.75 (Smith 1979). An interrater reliability ICC of 0.91 for the seven body areas was found when rating ten elderly patients with AIMS (Sweet et al. 1993). Satisfactory levels of test–retest consistency have been achieved for AIMS (Lane et al. 1985, Sweet et al. 1993). However, the interrater variability often exceeds intra-rater variability, this has been shown also for AIMS and SAS (Bergen et al. 1984, 1988, Tonelli et al. 2003).

In terms of content validity AIMS seems to cover the commonly observed clinical features that accompany TD (i.e. facial, oral, buccal, lingual, jaw and extremity movements) and the less common truncal movements. It does not cover rare or more severe movements, e.g. pharyngeal and respiratory movements or tardive dystonias (Schooler & Chengappa 2000). Use of a threshold, such as the Schooler and Kane criteria (1982), permits construct validity to establish a probable diagnosis of TD associated with antipsychotics (Schooler & Chengappa 2000).

AIMS has been used to assess TD in trials of the newer antipsychotic drugs (Tollefson et al 1997). The ability of new medication to produce lower AIMS scores provides evidence of the validity of the scale (Schooler & Chengappa 2000). Tollefson and colleagues (1997) compared 707 patients treated with olanzapine for a median of 237 days with patients treated with haloperidol for a median of 203 days. Using the total of AIMS items 1–7 as their dependent variable, they found that scores were reduced by an average of 0.13 scale points in the olanzapine group and increased by an average of 0.36 scale points in the haloperidol group, a statistically significant difference ($F = 9.02$, $df = 1.898$, $p = 0.003$).

Validity and reliability of rating scales

Rating scales bring reliability to psychiatric research, and thus have become a major means of psychiatric measurement. Monitoring for extrapyramidal side-effects is probably the most thoroughly developed area of adverse event measurement in psychiatry (Schooler & Chengappa 2000). Nevertheless, there are still some problems associated with observer ratings, such as variable reliability, non-linearity and poor sensitivity, which have been suggested to be overcome by instrumentation (Kane et al. 1992).

4.4.2 Instrumental measurement

Interest in using instrumental measurement in addition to clinical examination and observer-based rating scales has a long traditions. Instrumental measurement has been reported (1) to identify more EPS patients than observer-based ratings (Cortese et al. 2005), (2) to be more sensitive to subclinical motor changes, (3) to exhibit greater linearity with regard to severity (Lohr & Caligiuri 1992, Caligiuri et al. 1997, Dean et al. 2004), and (4) to need less training to achieve sufficient interrater reliability and test–retest reliability (Caligiuri et al. 1997).

Multiple methods have been used to instrumentally measure NIMDs, including electromyography (EMG), accelerometers, force and position transducers, ultrasound devices, digital movement analyses and videotape analyses (Lohr & Caligiuri 1992, Tuisku 2002).

An overview of studies in the field of instrumental measurement of NIMDs is presented in Table 1.

Methods of instrumental measurement

Human motor activity can be measured directly as gross and fine three-dimensional movements by accelerometric methods and as electric activity of motor units by EMG and its applications. EMG electrodes measure electrical signals emitted during muscle contractions.

Surface electrodes can detect activity from large superficial muscles, but more invasive needle or wire electrodes are needed to discriminate activity from smaller deep muscles. The disturbing effect of EMG electrodes on normal moving of subjects was studied in neurological child patients (Young et al. 1989), and as expected, the surface electrodes caused fewer disturbances.

Angular joint movements can be measured by electro-goniometers (e.g. strain gauges), which record the relative orientation of two bases connected by an elastic beam (Legnani et al. 2000). Position transducers show displacement and produce signals that can be mathematically differentiated to yield velocity and acceleration (Lohr & Caligiuri 1992, Caligiuri et al. 1999).

Strain gauges are also components of a force transducers, which measures muscle rigidity (Caligiuri 1994), defined as the ratio of changing muscle force to changing muscle length. A force transducer is attached to the limb of the patient, and the external force applied by the examiner to displace the patient's limb is transduced along with rotation (Caligiuri 1994). The basic technique in force transducers consists of having the patient exert pressure on a rigid beam instrumented with strain gauges. The patient is instructed to maintain a constant force under isometric conditions for a set time period (Caligiuri et al. 1991, Lohr & Caligiuri 1992).

Table 1 Studies using instrumental assessment of NIMD.

	Accelerometry	EMG	Force transducers
NIA	Braude et al. 1984 Gardos et al. 1992 Rapoport et al. 1994 Tuisku et al. 1999 Tuisku et al. 2000 Poyurovsky et al. 2000	Cunningham et al. 1996 *in polysomnography:* Lipinski et al. 1991 Walters et al.1991 Nishimatsu et al. 1997	
NIP	Collins et al. 1979 Rapoport et al. 1998 Caligiuri & Tripp 2004	Bathien et al. 1984 Rondot & Bathien 1986 May et al. 1983	May et al. 1983 Bartzokis et al. 1989 Wirshing et al 1989 Kern et al. 1991 Caligiuri et al. 1991 Caligiuri 1994 Caligiuri et al. 1999 Dean et al. 2004 Cortese et al. 2005
TD	Denney & Casey 1975 Alpert et al. 1976 Chien et al. 1977 Fann et al. 1977 Stafford & Fann 1977 Nishikawa et al. 1986 Tryon & Pologe 1987 Sprague et al. 1993 Adler et al. 1999	Jus et al. 1973 Crayton et al. 1977 Bathien et al. 1984 Rondot & Bathien 1986 Nishikawa et al. 1986 May et al. 1983 Yasufuku-Takano et al. 1995 El-Mallakh et al. 2001	May et al. 1983 Bartzokis et al. 1987 Vrtunski et al. 1989 Vrtunski et al. 1994 Wirshing et al. 1989 Wirshing et al. 1991 Caligiuri et al. 1991 Caligiuri et al. 1997 Jeste et al.1995 Adler et al. 1999 Dean et al.2004 Cortese et al. 2005

Other indirect methods of measuring motor activity are, for example, ultrasonographic movement counters (May et al. 1983, Hoff et al. 1999) digital video camera movement analysis (Nilsson et al. 1996), photodetectors (May et al. 1983, Hoff et al. 1999), posturography (Bloem et al. 1998, Lanska 2001), pedometers (Dale et al. 2002) and static charge-sensitive beds (SCSB), which record electric potential changes in the mattress of the bed induced by body movements (Alihanka & Vaahtoranta 1979, Kronholm et al. 1993).

In addition to measuring body movements and motor activity of the muscles, other dimensions of motor functions, such as central magnetic or electric potentials, corticospinal excitability and peripheral conduction velocity (Rossini & Mauguire 1990), are measured in neuropsychiatry.

Accelerometry

Actometry and actigraphy are used in the literature as synonyms for recording methods based on accelerometric sensors. Actometry (actigraphy), a direct instrumental method for measuring human motor activity both quantitatively and qualitatively, was developed from accelerometry. Accelerometric applications include both old mechanical and more modern

piezoelectric, computerized detectors, and they all react to acceleration signals produced by body movements. Accelerometers are small computerized movement detectors weighing only a few grams; they do not significantly obstruct movement, nor do they impose a significant inertial load (Lohr & Caligiuri 1992, Tuisku et al. 1999, Caligiuri & Tripp 2004).

The modulation, integration and recording of the signal are varied, as is the output of the data, in different types of accelerometric methods and their commercial applications. In activity monitors (accelerometers), the three principal modes of data collection are known as "time above threshold", "zero-crossing" and "digital integration". In the first mode, the monitor tracks the length of time that elapses from the point when acceleration exceeds a threshold value until it falls below the threshold. In the second mode, the monitor detects the number of times that acceleration crosses the zero point within a certain time period. In digital integration, the amount of acceleration is recorded and sampled at a high rate, and these values are used to calculate the average activity level within a time window (Gorny & Allen 1999, Spiro & Spiro 2001). All accelerometric monitors measure locomotor activity quantitatively, and some also allow qualitative motion analysis. The smaller the time window, the higher the time resolution of the movement (Tuisku 2002).

An increasing amount of data from accelerometric studies in psychiatry has been collected, and activity monitoring has been suggested to be a valuable research tool for clinicians in diagnosis and prediction of treatment response (Teicher 1995). The customary use of accelerometric activity monitoring is diurnal recording with a relatively long sampling window ranging between several minutes and one hour. In diurnal activity monitoring, the monitors typically are attached to the non-dominant wrist in a wristwatch manner.

However, movement disorders such as NIA manifest predominantly in the lower limbs. Gardos et al. (1992) have created an accelerometric method for quantifying lower limb activity in this disorder. Rapoport et al. (1998) reported that all 14 NIP patients had tremor in upper limbs and only three had tremor in lower limbs.

Actigraphy has proved to be useful as a sensitive, non-invasive tool for measuring the effect of antipsychotics on spontaneous motor activity (Kiang et al. 2003).

Instrumental assessment of NIA

NIA has been studied mostly by accelerometry (actometry, accelerometric applications) (Braude et al. 1984, Gardos et al. 1992, Rapoport et al. 1994, Tuisku et al. 1999, Poyurovsky et al. 2000, Tuisku et al. 2000) and by EMG (Cunningham et al. 1996), the latter being used mostly in polysomnographic studies (Lipinski et al. 1991, Walters et al. 1991, Nishimatsu et al. 1997).

Overall motor activity of eight NIA patients over a 24-hour period was measured by actometric monitor strapped to the non-dominant ankle, and NIA was found to have no relationship with nocturnal activity and did not shorten the sleep period (Gardos et al. 1992). Diurnal motor activity analysis of wrist-worn accelerometer data of 16 NIA patients and 16 non-NIA patients revealed that NIA patients had a higher level of motor activity during two day-time intervals. This could be the result of a morning dose of neuroleptics. A comparable increase at night was not evident because patients were asleep (Poyurovsky et al. 2000). Quantified movement activity measured by accelerometers on ankles and waist in standardized rest-activity (30 minutes) discriminated 10 pure NIA patients from themselves in remission and from 10 healthy controls with no overlap. Only activity of the non-dominant ankle (left ankle) was used for statistical comparison, since no signifi-

cant differences in laterality were found (Tuisku et al. 1999). This method was able to reveal akathisia in a patient who had mostly subjective complaints and hypokinesia-masked akathisia (Tuisku et al. 2000).

The toe tremor was more informative than the finger tremor in distinguishing six akathisia patients from controls by actometry. Characteristic of NIA were low-frequency (less than 4 Hz) rhythmic toe movements (Braude et al. 1984).

The movement pattern of NIA has been studied by accelerometric methods, with a monitor being placed over the body segment with the involuntary movement (mostly a leg). The qualitative analysis of actometric movement patterns (Tuisku et al. 1999, Rapoport et al. 1994) revealed characteristic patterns for NIA and PsA. In such a study 16 NIA patients manifested involuntary, intermittent, low frequency (less than 4 Hz) and rhythmic motor activity (Rapoport et al. 1994).

The movement patterns reported by accelerometric studies for NIA are consistent with those reported by EMG-derived from polysomnographic studies (Lipinski et al. 1991, Walters et al. 1991): relatively irregular but rhythmic bursts of lower limb activity of 0.5–3 Hz. An EMG study used a marker for akathisia that was 10 s in duration and less than 4 Hz in the anterior tibialis tracings to evaluate 26 subjects (16 NIA patients) (Cunningham et al. 1996).

Instrumental assessment of NIP

NIP has been studied by EMG (May et al. 1983, Bathien et al. 1984, Rondot & Bathien 1987) and by force transducers (May et al. 1983, Bartzokis et al. 1989, Wirshing et al. 1989, Kern et al. 1991, Caligiuri et al. 1991, 1994, 1999, Dean et al. 2004, Cortese et al. 2005). In addition NIP tremor has been investigated by accelerometry (Collins et al. 1979, Rapoport et al. 1998, Caligiuri & Tripp 2004).

NIP tremor occurred in the range of 5–7 Hz when recorded by EMG in a pair of antagonist muscles in studies with 8 and 12 NIP patients and was distinguishable from activity of TD (Bathien et al. 1984, Rondot & Bathien 1987).

Force and rotation transducers were useful in identifying asymmetries, measuring NIP hand tremor in the range of 4–6 Hz and rigidity in 21 patients with co-existing TD (Caligiuri et al. 1991).

Rigidity, bradykinesia and tremor were also assessed with wrist force and displacement transducer in a follow-up study with 56 older patients receiving a mean dose of 43 mg of chlorpromazine-equivalent antipsychotics, and a significant increase in parkinsonism was found (Caligiuri et al. 1999).

Accelerometry revealed that the overall NIP tremor score by SAS and finger tremor frequencies were negatively and significantly associated in 19 patients (Collins et al. 1979). PD, essential tremor and NIP tremor mean frequencies were similar for the resting tremor 6.0 Hz (SD 1.13). Tremor power (which was calculated by summing the acceleration amplitudes) had more variability, and the proportion of time that the hand movement met the criteria of tremor was 57% in NIP (Caligiuri & Tripp 2004).

Accelerometric recordings from 14 patients in frequencies between 4 and 7 Hz were helpful in differentiating neuroleptic-induced tremor from other NIMDs and psychogenic tremor, but their overall potential to distinguish neuroleptic-induced tremor from some other types of organic tremor was more limited (Rapoport et al. 1998).

Instrumental assessment of TD

TD has been studied instrumentally by EMG (Jus et al. 1973, Crayton et al. 1977, May et al. 1983, Bathien et al. 1984, Nishikawa et al. 1986, Rondot & Bathien 1987, Yasufuku-Takano et al 1995, El-Mallakh et al 2001), force transducers (May et al. 1983, Bartzokis et al. 1989, Vrtunski et al. 1989, 1994, Wirshing et al. 1989, 1991, Caligiuri et al. 1991, 1997, Jeste et al. 1995, Adler et al. 1999, Dean et al. 2004, Cortese et al. 2005), ultrasound devices (Resek et al. 1981, Bartzokis et al. 1989, Kern et al. 1991, Wirshing et al. 1991), digital image processing (Buchel et al. 1995, Nilsson et al. 1996, Stanilla et al. 1996) and accelerometers (Denney & Casey 1975, Alpert et al. 1976, Chien et al. 1977, Fann et al. 1977, Stafford & Fann 1977, Nishikawa et al. 1986, Tryon & Pologe 1987, Sprague et al. 1993, Adler et al. 1999).

The first EMG study, with more than 20 TD patients, revealed several patterns and registered facial movements not visible in clinical observation (Jus et al. 1973).

Caligiuri group has done extensive TD research with force and position transducers. Force instability was used as an additional measurement to quantify hand and jaw dyskinesia in a study of TD risk factors (Jeste et al. 1995). Force transducers are highly reliable across multiple study sites – the overall ICC from 45 patients was 0.995 (Caligiuri et al. 1997).

The accelerometer gave an abnormal movement frequency in one case of TD, 3.75 Hz, by spectral analysis measured between the fingers but not in the mouth (Denney & Casey 1975). Fann et al. (1977) described a method to record the acceleration profiles in TD with triaxial accelerometers on the wrist, ankles and chin. Patients were measured in a laboratory while at rest and while performing alternating paced arm movements between predefined targets. Results using these methods were not, however, reported (Fann et al 1977). Chien et al. (1977) described a significant correlation between AIMS score and accelerometry for 9 patients with oral TD who completed the study out of the original 15 patients. An accelerometric study of 10 patients with TD and 8 controls revealed that TD patients had a lower peak for dyskinetic arm movements, and all patients were correctly classified as to the presence or absence of TD (Tryon & Pologe 1987).

Bathien et al. (1984) described measuring by EMG sitting-position activity bursts of 20 ms or more. Three consecutive 20-s epochs were analysed. The movement pattern was described as one of three types of irregular bursts below 3 Hz: type I 1–3 Hz, type II <1 Hz, type III great variability. The mean frequency of neuroleptic-induced tremor was 4.5 ± 1.1 Hz and the mean length 0.06 ± 0.01 s. TD was classified into three types: types I and II were regular, with mean frequency of 1.6 ± 0.5 and 0.5 ± 0.2 Hz and a duration of 0.27 ± 0.06 and 1.27 ± 0.35 s, respectively, type III had great variability, but was irregular, with a frequency 0–3 Hz (Bathien et al. 1984). Almost all TD patients (15/16) had abnormal activity in their limbs (Bathien et al. 1984, Rondot & Bathien 1987).

Reliability of instrumental measurement

Reliability, or consistency, between measurements made under uniform conditions is a necessary attribute for any assessment tool (Caligiuri et al. 1997).

Laboratory studies have demonstrated relatively high test–retest reliability using instrumental techniques. Isometric force procedures have yielded intra-patient reliability coefficients of 0.85 (Caligiuri & Lohr 1990). Procedures that count movements, such as position sensors (Trzepacz and Webb 1987) or ultrasonic techniques (Resek et al. 1981, Bartzokis

et al. 1989) are highly reliable, with test–retest correlation coefficients greater than 0.90. Gattaz & Buchel (1993) reported an intra-subject reliability coefficient of 0.84, using an automated digital video image processing system that evaluated oral movements. In a multicentre ($n = 9$) study using force transducers to evaluate TD, an ICC 0.995 was found for all patients across sites (Caligiuri et al. 1997).

Truncal accelerometry has shown high absolute test–retest repeatability in healthy subjects – for walking tests ICC ranged from 0.79 to 0.94 for the three axes (Moe Nilsson 1998).

Digital movement analysis of orofacial TD gave internal reliability (by test–retest) correlation coefficients of 0.8–0.99, and the lowest coefficients particularly in Parkinsonian frequencies (3–6 Hz) were 0.8 and 0.84. In TD frequency bands, the lowest coefficient was 0.94 (Nilsson et al. 1996).

Digital movement analysis validity was estimated by correlation with AIMS; Pearson r coefficients were between 0.54 and 0.73 (Nilsson et al. 1996).

The accelerometric recordings demonstrated in all cases of akathisia a constant and regular wave form, frequency (below 4 Hz) and amplitude. Actometric findings were reproducible, i.e. similar patterns appeared in several recordings of the same patient during the abnormal movements (Rapoport et al. 1994). Specificity and sensitivity of instrumental measurement

An EMG study used a marker for akathisia that was 10 s duration and less than 4 Hz in the anterior tibialis tracings to evaluate 26 subjects (16 NIA patients); this method yielded a sensitivity of 69% and a specificity 70% in detecting NIA (Cunningham et al. 1996).

Quantitative accelerometry had a trend towards positive correlation with the BARS global score ($r = 0.56$, $p < 0.06$), and NIA patients had a higher overall level of activity than patients without NIA ($p < 0.01$) (Poyurovsky et al. 2000). Actometric findings had no overlap in differentiating selected NIA patients from non-NIA patients (Tuisku 1999).

A study of wrist rigidity in 29 patients revealed that an objective rigidity score, representing the degree to which motor activity increases muscular stiffness, correlated highly with clinical ratings of parkinsonian rigidity and demonstrated 89% specificity and 82% sensitivity (Caligiuri 1994).

5 Aims of the study

NIMD in a chronic naturalistic schizophrenia inpatient population in Estonia was examined. The prevalence of NIMD was estimated using different measuring methods, including clinical rating scales and actometric measurement. Detailed aims of the study were as follows:

I To assess the prevalence of NIMD in an Estonian naturalistic institutionalized schizophrenia inpatient population by using various diagnostic criteria.

II To evaluate the usefulness of a standardized actometric method (controlled rest activity measurement) and BARS in a clinical sample of unselected schizophrenia inpatients by comparing them with regard to case identification and severity measurement of NIA.

III To evaluate the internal consistency of SAS and improve convergence between DSM-IV and SAS-based NIP case finding, and to determine how the SAS measures objective motor symptoms verified by actometry.

IV To determine actometric patterns of NIMDs and PsA.

V To evaluate the usefulness of a single self-rated question in the diagnosis of NIMDs and PsA.

6 Subjects and Methods

6.1 Subjects

The subjects were 99 chronic schizophrenic institutionalized adult patients from a state nursing home in central Estonia. This typical Estonian nursing home had 354 inhabitants, 172 of whom were diagnosed with schizophrenia or schizoaffective disorder. Reasons for institutionalization were mostly a low level of functioning and a poor support network, the latter of which is important in Estonia as the social welfare system is weak.

Inclusion criteria were a DSM-IV diagnosis of schizophrenia or schizoaffective disorder (American Psychiatric Association 2000), stable antipsychotic medication (for at least one month) and an age of 18–65 years. Diagnosis was made using a semi-structured interview according to DSM-IV criteria for schizophrenia or schizoaffective disorder by a psychiatrist (S.J.) and available medical records. Of the schizophrenia patients, 68 failed to meet inclusion criteria: 63 due to old age and 5 due to not using antipsychotic medication. Exclusion criteria were severe somatic and neurological illness. One patient was excluded because of rheumatoid arthritis. In addition, there were 4 refusals.

After a complete description of the study to subjects, written informed consent was obtained. The Ethics Review Committee on Human Research of the University of Tartu approved the study protocol. Data were collected from 29.10.2001 to 27.03.2002.

6.2 Methods

6.2.1 Clinical evaluation

A psychiatrist (S.J.) assessed all subjects to identify any of three NIMDs (NIA, NIP or TD) in accordance with DSM-IV. In this study, NIMD is defined as occurrence of at least one of the three DSM-IV neuroleptic-induced syndromes. Furthermore pseudoakathisia was diagnosed using existing criteria (Barnes and Braude 1985, Rapoport et al. 1994).

The temporal connection between a NIMD and PsA with neuroleptic medication was established retrospectively by interview and medical records.

The psychiatrist (S.J.) observed all patients' for abnormal movements in the sitting and standing position.

The psychiatrist (S.J.) posed one subjective question to all patients concerning problems with movement: "Do you have troubles with movements, and if so, does it disturb you?" The answer was allocated to one of four categories:

a) No.
b) Yes, but it does not disturb me.
c) Yes, and it disturbs me.
d) Yes, and it is very difficult to cope with.

The psychiatrist (S.J.) evaluated postural tremor in patients' outstretched hands. Rigidity was evaluated in upper limbs in the standing position. Rigidity in legs was evaluated with

patients sitting on a table. Rigidity in the neck was evaluated in a lying position on a couch. Gait and posture were evaluated when the patient walked in the corridor or in evaluation room.

6.2.2 Assessment scales

The Barnes Akathisia Rating Scale (BARS) (Barnes 1989) was used for assessment of clinical akathisia (and pseudoakathisia), the Simpson–Angus Scale (SAS) (Simpson & Angus 1970) for NIP, and the Abnormal Involuntary Movement Scale (AIMS) (Guy 1976) for TD to estimate prevalence and severity. For case finding, the threshold value for NIA was a BARS total score of 2 or more (scale range 0–5), and for NIP, SAS mean global score of 0.3 or more (scale range 0–4). TD cases were defined by AIMS according to the Schooler–Kane criteria, which require at least moderate dyskinetic movements in one body area or mild dyskinetic movements in two body areas (Schooler & Kane 1982).

6.2.3 Actometry

Ambulatory activity monitors of type PAM3 (IM-Systems, Baltimore, USA) were used to record subjects' motor activity attached to both ankles. The mode of data collection in PAM3 is based on digital integration. These actometric monitors contain triaxial piezoelectric accelerometer sensors that react to acceleration rates above 0.1 g. The recorded acceleration signal is sampled as an activity count at a rate of 40 Hz, and the values for each sample are used to calculate the average activity counts within a chosen time window, generally 0.1 s. The time window is sufficiently small to allow analysis of movements within the range of EP movement disorders. With the 0.1 s time window, a 1 g acceleration equals approximately 106 activity counts. The movement index for a chosen time period is the sum of average activity counts for each time window included in this period (Tuisku 2002).

6.2.4 Controlled rest activity

Thirty minutes seems to be the maximum time that akathisia patients are able to maintain the sitting position (Rapoport et al. 1994) and it is long enough for motor symptoms to manifest (Barnes 1989). Moreover, it is the usual length of a clinical interview, effective in keeping the patient's attention focused on the discussion. The patient is not instructed to sit still during the interview to allow spontaneous, natural movements. However, it is customary for a co-operative patient to remain seated in a medical interview even in the presence of an urge to stand up and walk (Tuisku 2002). Most often, patients who are able and willing to give informed consent are also sufficiently co-operative to follow this type of procedure (Tuisku 2002).

Controlled rest activity is recorded in a standardized setting, in which the subject is observed in a clinical assessment room. The solid, standard chair for subjects' is equipped with a support for the back and hands, is located two metres from the interviewer, the clinician. The conversation with the subject is characterized by a low-stress, neutral atmosphere created by open questions and adhering to themes voluntarily discussed by the subject.

The interview opens with questions about the overall health record, including somatic, neurological and psychiatric history of symptoms, possible treatments, previous examinations and routine health check-ups. Next, questions about the subject's activity rhythms are posed concerning daily activity, sleeping and physical training habits. Each subject is asked about possible movement disorder or hyperactivity symptoms. The subject is also encouraged to talk about eating, drinking and smoking habits. Naturally, the subjects are aware of the actometric recording and the monitors attached to their bodies, but the idea of the interview is to focus their attention away from the monitors and from their own movements to allow as naturalistic a setting as possible while maintaining a standardized and controlled situation (Tuisku 2002).

Controlled rest-activity of lower limbs (the average of right- and left-ankle activity) is the main outcome parameter (Studies II and III, and unpublished data). The non-dominant side is typically chosen for actometric recording (Nagels et al. 1996), as we did in Study IV, using the data of left ankle movements. Purposeful movements, which can mask more pathological movement patterns, are lateralized to the dominant side by definition (Springer & Deutch 1993). In actometry, both a qualitative and a small quantitative difference are present between the dominant and non-dominant upper limb activities (Nagels et al. 1996). However, data may be lost in unilateral analysis of motor activity, and definition of motor dominance can vary (Tuisku 2002).

Absolute movement indices are reported for controlled rest because it is a fixed time period of 30 min (Tuisku 2002). Actometric movement index for 30 min of controlled rest activity was missing for one male patient due to non-cooperation. For this patient, we used the data for 20 min of controlled rest activity for descriptive analysis of movement patterns (Study IV).

6.2.5 Actometric evaluation of patterns of NIMD

Experienced raters of actometric data can evaluate raw actometric patterns quickly and intuitively (by the "picture" on the computer screen). We, however, wanted to develop a method that could be used by inexperienced raters. Five neuropsychiatrists developed consensus-based rating instructions and a data-collection form. Data extraction was taught during two hours to two raters blind to the clinical diagnoses of subjects and patterns of movement disorders.

At the pilot stage of training, data for 8 subjects outside the study with different NIMD patterns as well as for 2 normal subjects were used. After achieving an appropriate level of interrater reliability (ICC = 0.44–1.0, mean 0.82), the two raters evaluated all subjects' actometric activity recordings. After the pilot stage of raters' training, the data extraction form was slightly modified (we added a second and a third dominant frequency).

Raters assessed the raw data for the existence of activity periods, the number of activity periods (activity for at least 10 s), the existence of rhythmic activity, the three most dominant frequencies and the highest acceleration peaks in activity periods (over 10 s). In the case of discrepant assessments, a consensus meeting, where raters reached a consensus for the frequencies of activity periods of 27 patients, was held after calculating interrater reliability.

Blindly extracted data by raters were evaluated to identify patterns for particular NIMDs, according to the DSM-IV diagnosis of NIMDs and the pseudoakathisia diagnosis (Barnes

Table 2 Interrater reliability coefficients for 99 inpatients with schizophrenia: kappa for categorical and intraclass correlation coefficients (ICC) for continuous measures.

	kappa
Presence of activity periods	0.905*
Presence of rhythmic activity	0.786*
	ICC (95% CI)
Number of activity periods	0.967 (0.951–0.978)*
Dominant frequency	0.739 (0.624–0.822)*
Second most prevalent frequency	0.787 (0.672–0.864)*
Third most prevalent frequency	0.789 (0.672–0.867)*
Minimal frequency	0.351 (0.149–0.525)#
Maximal frequency	0.831 (0.750–0.887)*
Highest value of acceleration peaks	0.841 (0.768–0.893)*

* $p < 0.001$ # $p = 0.001$

and Braude 1985, Rapoport et al. 1994). We analysed the data for possible movement patterns of NIMDs and PsA. Answers to the subjective question were correlated with movement disorders diagnoses.

Raters achieved excellent interrater reliability in almost all parameters of movement patterns of actometric recordings, except in defining the minimal frequency of movement patterns. Interrater reliability coefficients are presented in Table 2.

6.2.6 Statistical analysis

In the first study, we estimated the prevalence of NIMD using different approaches; a clinical diagnosis according to DSM-IV and standardized rating scales for movement disorders (AIMS, BARS, SAS) were applied.

Student's independent sample t-tests and chi-square tests were used to compare subjects with and without NIMDs.

The correlation between the lower limb actometric activity index (mean activity of right and left ankles) and the BARS global score was analysed by Spearman correlation coefficients in Study II. Differences between the NIA and the non-NIA patient median values in these variables were analysed by the Mann–Whitney two-tailed U-test. The performances of the two instruments in NIA case identification were evaluated by receiver operating characteristics (ROC) analyses (Murphy et al 1987). Validity coefficients (specificity and sensitivity) for different thresholds were calculated, and the cut-off points were defined by optimal trade-off between sensitivity and specificity.

Cronbach's alpha was calculated to evaluate the internal consistency of SAS in Study III. The correlations between lower limb activity (the mean of right- and left-ankle movement indices) and individual item scores and mean SAS scores were analysed. Differences

between the NIP and non-NIP, as well as between the NIMD and the non-NIMD groups, in the SAS mean score and lower limb activity were examined. The performance of SAS mean score and individual item scores in case identification was evaluated by ROC analyses against the DSM-IV NIP diagnosis. Validity coefficients (specificity, sensitivity, positive and negative predictive value [PPV and NPV, respectively]) for different mean SAS score thresholds were calculated. To explore the discriminatory power of individual single SAS items' we performed ROC analyses for each item separately. We also explored the effect on the validity coefficients of merging the six rigidity items of SAS into a single item to de-emphasize the influence of rigidity on the mean SAS score. The Spearman test was used for correlation analysis and the Mann–Whitney two-tailed U-test for comparisons between two groups because of the non-normal distribution of the data.

The correlation between the lower limb actometric activity index (mean activity of right and left ankles) and the AIMS global score, was analysed by the Spearman correlation test (unpublished data). Performances of the two instruments in TD case identification were evaluated by ROC analyses (Murphy et al. 1987). The area under the curve in ROC analyses range from 0.5 (no case-finding power) to 1.0 (optimal case-finding power). Validity coefficients (specificity and sensitivity) for different thresholds were calculated, and the cut-off points were defined by optimal trade-off between sensitivity and specificity.

The interrater reliability in Study IV was measured by kappa coefficients for categorical values and ICC (intra-class correlation coefficients) for continuous values to validate a new rating instrument lacking a "golden standard" (two-way ANOVA mixed model was used to calculate ICC in order to estimate the reliability of a single rating) (Fleiss 1981). One-way ANOVA was performed to determine whether a significant ability to discriminate different qualities of movement patterns exists. Differences between movement disorders (NIA, NIP, TD and PsA) and non-movement disorders groups in frequencies of activity periods were analysed by Mann–Whitney two-tailed U-test for continuous variables (frequency, number of periods). Chi-square test was used for dichotomous variables (presence of activity periods, rhythmic activity). Fisher's exact test for calculating significance was used, if needed. The performances of qualities of movement patterns in case identification were evaluated by ROC analyses.

Chi-square test was used for assessment of the self-rated question. The screening ability of the self-rated question for different NIMDs and PsA was evaluated by ROC analysis.

The software used in all analyses was SPSS version 12.0 (SPSS Inc. Chicago, IL, USA).

7 Results

7.1 Participants

Of the 99 participants, 45 were male (45.5%) and 54 female (54.5%). Their mean age was 49.7 years (SD = 9.5). The mean documented length of continuous treatment in the hospital or nursing home was 13.6 years (SD = 9.0). Seventy-nine patients (79.8%) were receiving conventional antipsychotics and 20 (20.2%) clozapine (one was receiving clozapine combined with sulpiride). Sixteen patients (16.2%) were receiving combinations of typical antipsychotics (either predominantly low-dose [n = 10] or predominantly high-dose [n = 6] neuroleptic regimens), and 63 (63.6%) were receiving monotherapy (haloperidol: n = 29; zuclopenthixol: n = 28; perphenazine, chlorpromazine, or thioridazine: n = 6). No new atypical antipsychotics were used. The mean daily chlorpromazine equivalent dose (Bazire 2000) was 328 mg (SD = 221). Seven patients (7.1%) received benzodiazepines, 13 (13.1%) tricyclic antidepressants, 15 (15.2%) anticonvulsants and one (1.1%) lithium. Fourteen patients (14.2%) received the anticholinergic drug trihexyphenidyl. Seventy-one patients (71.7%) had paranoid, 7 (7.1%) disorganized, 9 (9.1%) catatonic, 2 (2.0%) residual, and 5 (5.1%) simple schizophrenia, and a further 5 (5.1%) had a schizoaffective disorder. Cognitive level of patients varied, with only one patient fulfilling the criteria for dementia.

Sixty-four patients (64.7%) were smokers.

7.2 Prevalence of NIMD with various diagnostic criteria (Study I)

The point prevalence of any NIMD according to DSM-IV criteria was 61.6%; 31.3% had NIA, 23.2% had NIP, and 32.3% had TD (see Figure 1 for co-morbidity).

The prevalence of NIMDs in the patients receiving clozapine was significantly lower than in those receiving conventional antipsychotics (35.0% versus 68.4%) ($\chi^2 = 7.51$, df = 1, p = 0.006). The mean age of those with a NIMD (51.5 years [SD = 8.5]) was significantly higher than that of patients with no NIMD (46.9 years [SD = 10.4]) (t = –2.28, df = 97, p = 0.026). Among the NIMD categories, a significant difference in mean age was found only in the NIP group (53.7 years [SD = 7.3] versus 48.5 years [SD = 9.8]; t = –2.77, df = 97, p = 0.008). Chi-square tests revealed no differences between patients with a NIMD and those without with respect to sex, smoking status and use of antidepressants, anticonvulsants, benzodiazepines or anticholinergic drugs. Student's independent sample t-tests also revealed no differences in length of institutionalization or antipsychotic dosage in chlorpromazine equivalents between patients with and those without a NIMD.

The prevalence of NIA according to global score on the Barnes scale was 27.3% (27 patients), which was 92% consistent with the prevalence according to DSM-IV criteria (i.e., of 99 patients classified as having or not having akathisia per the Barnes scale, the DSM-IV criteria similarly identified 91; sensitivity = 93% [N = 25 of 27 similarly classified as having akathisia], specificity = 92% [N = 66 of 72 similarly classified as not having akathisia]). The prevalence of NIP according to mean score on the SAS was 72.7% (72 patients), which was 50.5% consistent with the prevalence according to DSM-IV criteria (i.e., of 99 patients

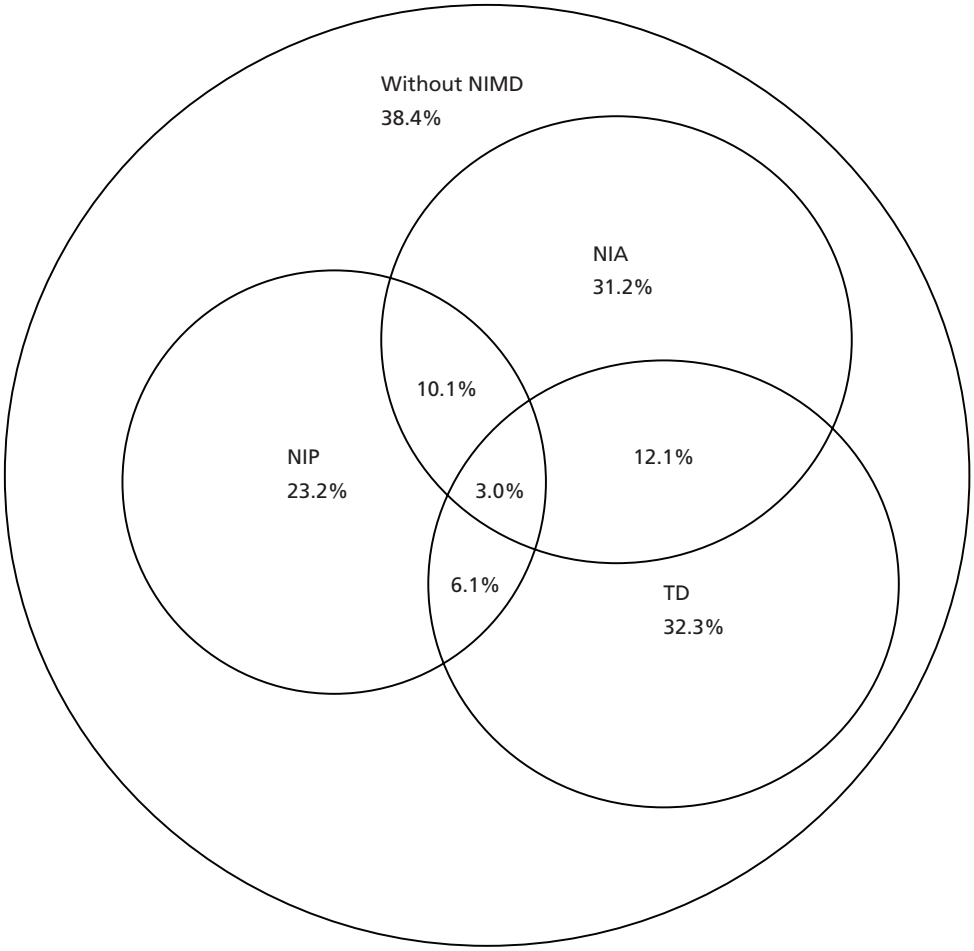

Figure 1 Prevalence of NIMD (NIA, NIP and TD) in a sample of 99 Estonian chronic schizophrenia patients treated with conventional antipsychotics or clozapine was 61.6%

classified as having or not having parkinsonism per the SAS, the DSM-IV criteria similarly identified 50; sensitivity = 32% [N = 23 of 72 similarly classified as having parkinsonism], specificity = 100% [N = 27 of 27 similarly classified as not having parkinsonism]). The prevalence of TD according to the Schooler–Kane criteria for the AIMS was 31.3% (31 patients), which was 99.0% consistent with the prevalence according to DSM-IV criteria (i.e., of 99 patients classified as having or not having TD per the AIMS, the DSM-IV criteria similarly identified 98; sensitivity = 100% [N = 31 of 31 similarly classified as having TD], specificity = 99% [N = 67 of 68 similarly classified as not having TD]).

7.3 Evaluation of BARS and actometry (Study II)

The BARS global score did not correlate significantly with the lower limb activity index in either the total population ($r = 0.189$, $p = 0.063$) or the NIA subgroup ($r = 0.159$, $p = 0.393$). After controlling for the effect of presence or absence of NIP and/or TD DSM-IV diagnoses (post-hoc analysis of co-variance), a significant correlation between BARS global score and the lower limb movement index was found ($r = 0.265$, $p = 0.009$). The median BARS global score for NIA patients was significantly higher than that of non-NIA patients (2 and 0, respectively, $U = –8.20$, $p < 0.001$). The median lower limb movement index for NIA patients was also significantly higher than that of non-NIA patients (19870 and 10119, respectively, $U = –2.82$, $p = 0.005$).

In ROC analysis, AUC for BARS global score was 0.971 (95% CI = 0.945–0.998), and for lower limb activity index 0.683 (95% CI = 0.578–0.787).

The validity coefficients and the optimal cut-off points of the methods are presented in Table 3.

Table 3 Validity coefficients and optimal cut-off points (**bold** text) of the Barnes Akathisia Rating Scale (BARS) global score, and the lower limb activity index measured by actometry during a 30-minute controlled rest in a clinical population of 98 chronic schizophrenia patients.

BARS global score	Cut-off	**< 1**	< 2	< 3		
	Sensitivity	**1.00**	0.81	0.48		
	Specificity	**0.78**	0.97	1		
	PPV	0.67	0.93	1		
	NPV	1	0.92	0.81		
Lower limb activity index	Cut-off	< 6000	< 8000	< 10 000	**< 12 000**	< 14 000
	Sensitivity	0.90	0.87	0.81	**0.77**	0.74
	Specificity	0.41	0.47	0.49	**0.57**	0.57
	PPV	0.45	0.43	0.42	**0.45**	0.43
	NPV	0.87	0.89	0.84	**0.85**	0.81

7.4 Evaluation of SAS and actometry (Study III)

Only 10 of the 23 patients with NIP presented as pure NIP without co-morbidity of other motor disorders. Among patients with NIP, 10 had co-morbid NIA and 6 TD; three of the patients had all three. The SAS mean score correlated significantly with age in our population ($r = 0.203$, $p = 0.044$).

Table 4 Mean scores of Simpson–Angus Scale (SAS) items in the neuroleptic-induced parkinsonism (NIP) group and the non-NIP group.

SAS item	NIP group Mean (SD)	Non-NIP group Mean (SD)	U	p
Gait	1.04 (0.93)	0.38 (0.52)	501	<0.001
Arm dropping	1.43 (0.73)	0.59 (0.62)	368	<0.001
Shoulder shaking	1.09 (0.60)	0.33 (0.47)	326	<0.001
Elbow rigidity	1.83 (0.58)	0.47 (0.55)	127	<0.001
Wrist rigidity	0.91 (0.85)	0.16 (0.40)	437	<0.001
Leg pendulousness	0.91 (0.85)	0.28 (0.45)	476	<0.001
Head dropping	1.48 (0.85)	0.66 (0.83)	442	<0.001
Glabella tap	1.09 (1.04)	0.86 (1.07)	755	0.286
Tremor	1.78 (1.13)	1.14 (0.92)	603	0.018
Salivation	0.83 (0.78)	0.71 (0.58)	818	0.603
Mean of SAS items	1.24 (0.44)	0.56 (0.33)	138	<0.001

7.4.1 Convergence of SAS and actometry to DSM-IV NIP diagnosis

The SAS mean score of DSM-IV NIP patients (1.24, SD = 0.44) was significantly higher from that (0.56, SD = 0.33) of non-NIP patients ($U = -6.90$, $p < 0.001$). The mean scores of each single SAS item are presented in Table 4.

The mean scores of the "glabella tap" and "salivation" items for NIP patients were not significantly higher than those for non-NIP patients. The SAS mean score for NIMD patients was significantly higher from that for non-NIMD patients ($U = -5.77$, $p < 0.001$). The internal consistency of SAS measured by Cronbach's alpha was 0.79. Tremor was rated at least "2" – tremor of hand or arm occurring spasmodically – for 54.5% of NIP patients.

Actometric data was missing for one male patient due to non-cooperation. The median lower limb movement index for NIP patients was not significantly higher than that for non-NIP patients ($U = -0.46$, $p = 0.643$). The median lower limb activity for NIMD patients was significantly higher from that for non-NIMD patients ($U = -2.66$, $p = 0.008$).

7.4.2 Convergence of SAS to quantitative actometry

The SAS mean score did not correlate significantly with actometric lower limb activity in either the whole population ($r = 0.04$, $p = 0.717$), the NIP group ($r = -0.29$, $p = 0.192$), the pure NIP subgroup ($r = -0.21$, $p = 0.587$) or the NIP subgroup with tremor ($r = -0.16$, $p = 0.612$).

Not even after a post-hoc analysis of co-variance in the whole population, where the effect of NIA (BARS global score) and TD (AIMS severity score) were controlled for, could any

significant correlation between the SAS mean score and the lower limb movement index be found (r = 0.07, p = 0.494).

The tremor item of the SAS correlated significantly with the lower limb movement index in the whole population (r = 0.25, p = 0.013) but not in the NIP population (r = 0.26, p = 0.248) or in the pure NIP subgroup (r = 0.51, p = 0.160).

No correlation was evidenced between the hypokinesia item of the SAS and the lower limb movement index in the whole population (r = –0.07, p = 0.513) in either the NIP population (r = –0.24, p = 0.290) or the pure NIP subgroup (r = –0.37, p = 0.797).

No correlation was found between the mean of rigidity items of the SAS and the lower limb movement index in the whole actometry sample (r = –0.12, p = 0.256) in either the NIP population (r = –0.37, p = 0.090) or the pure NIP subgroup (r = –0.30, p = 0.426).

7.4.3 NIP case finding by SAS

The ROC curve for diagnostic performance of the SAS mean score is presented in Figure 2. Area under the curve (AUC) for the SAS mean score was 0.92 (95% CI = 0.87–0.97). AUC of the ROC curve for the SAS elbow rigidity item was 0.93 (95% CI = 0.86–1.0). AUC for the other items was less than 0.82. The validity coefficients of the SAS mean score are presented in Table 5.

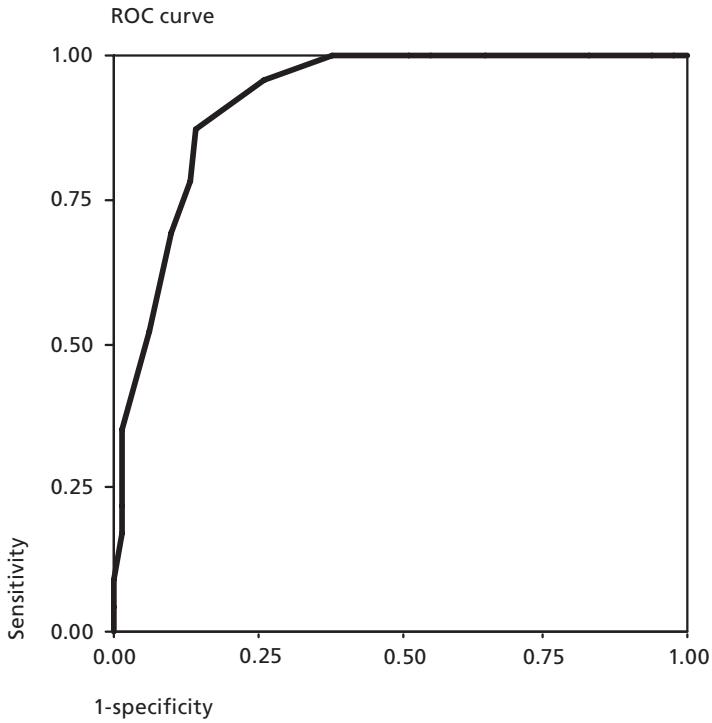

Figure 2 Receiver Operating Characteristic (ROC) curve for the mean SAS mean score against the DSM-IV diagnosis of neuroleptic-induced parkinsonism (NIP).

Table 5 Validity coefficients of the Simpson–Angus Scale (SAS) mean score at different cut-off values. The optimal cut-off point range is presented in **bold** text.

SAS mean cut-off	0.25	0.35	0.45	0.55	**0.65**	**0.75**	**0.85**	0.95	1.05	1.15
Sensitivity	1.0	1.0	1.0	1.0	**1.0**	**0.96**	**0.87**	0.78	0.70	0.52
Specificity	0.17	0.36	0.45	0.49	**0.62**	**0.74**	**0.86**	0.86	0.89	0.93
Positive predictive value	0.27	0.32	0.35	0.37	**0.44**	**0.96**	**0.65**	0.64	0.67	0.71
Negative predictive value	1.0	1.0	1.0	1.0	**1.0**	**0.98**	**0.96**	0.93	0.91	0.87

Table 6 Area under the ROC curve of Simpson–Angus Scale (SAS) parameters against the DSM-IV diagnosis of neuroleptic-induced parkinsonism.

SAS item	Area under the ROC curve	95% Confidence intervals
Gait	0.71	0.589–0.838
Arm dropping	0.79	0.690–0.889
Shoulder shaking	0.81	0.719–0.908
Elbow rigidity	0.93	0.855–1.000
Wrist rigidity	0.75	0.619–0.881
Leg pendulousness	0.73	0.603–0.853
Head dropping	0.75	0.636–0.858
Glabella tap	0.57	0.436–0.700
Tremor	0.66	0.530–0.781
Salivation	0.53	0.385–0.679
Mean of rigidity items	0.92	0.869–0.977
Mean of mean rigidity items and other SAS items	0.80	0.701–0.888
Mean of SAS items	0.92	0.869–0.973

The ROC-curve for screening performance of the SAS mean with a single averaged rigidity item was clearly inferior to the original SAS mean curve with an AUC of 0.80 (95% CI = 0.70–0.89).

Performances of the individual SAS items for NIP case finding are shown in Table 6.

As the SAS elbow rigidity item had a case-finding power similar to the SAS mean score,

we calculated an optimal cut-off point for this item. A cut-off threshold of 1.5 with a sensitivity of 0.83 and specificity of 0.97, was superior to cut-off threshold of 0.5 with sensitivity of 0.96 and a specificity of 0.55.

7.5 Evaluation of AIMS and quantitative actometry in measuring TD

Quantitative actometry failed to distinguish TD patients from non-TD patients.

The AIMS global score did not correlate significantly with the lower limb movement index in either the total population ($r = 0.13$, $p = 0.19$) or the TD subgroup ($r = 0.37$, $p = 0.03$), or in TD subgroup without co-morbidity with (NIA, NIP and PsA) ($r = 0.09$, $p = 0.81$). AUC for the AIMS total score was 0.96 (95% CI = 0.92–1.01), and for the lower limb movement index 0.57 (95% CI = 0.45–0.69). Validity coefficients are presented in Table 7.

Table 7 Validity coefficients of the Abnormal Involuntary Movement Scale (AIMS) total score and the lower limb movement index at different cut-off values. The optimal cut-off point range is presented in **bold** text.

AIMS mean cut-off	0.5	1.5	**2.5**	3.5
Sensitivity	1.000	1.000	**0.969**	0.688
Specificity	0.761	0.836	**0.940**	0.985
PPV	0.667	0.744	**0.886**	0.957
NPV	1.000	1.000	**0.984**	0.868
Lower limb activity	2000	**4000**	**6000**	8000
Sensitivity	0.938	**0.875**	**0.750**	0.688
Specificity	0.075	**0.269**	**0.343**	0.373
PPV	0.326	**0.364**	**0.353**	0.344
NPV	0.714	**0.818**	**0.742**	0.714

7.6 Patterns of NIMD in actometry (Study IV)

Prevalence of PsA was 19.2%. The comorbidity with NIMD is shown on Figure 3.

Pooled NIMD and PsA patients had more activity periods in actometric recordings than patients without NIMD and PsA.

More than 95% of NIA and PsA patients showed rhythmic activity in actometric recordings. NIMD, particularly PsA and NIA, patients had higher frequencies in rhythmic activity than patients without NIMD and PsA. NIMD or PsA, except TD, patients had higher median

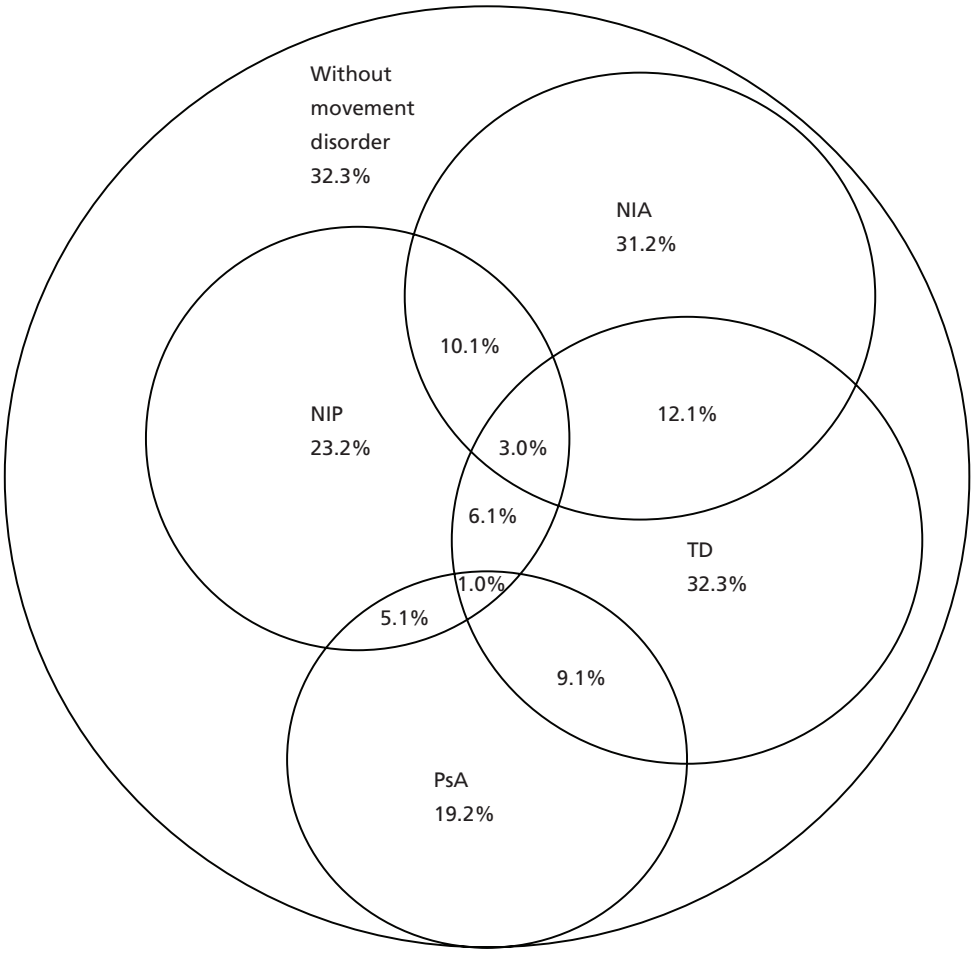

Figure 3 Comorbidity of PsA and NIMD in sample of 99 Estonian chronic schizophrenia inpatients treated with conventional antipsychotics or clozapine.

acceleration peaks in rhythmic activity recordings than non-movement disorder group patients. Results for each group are presented in Table 8.

The number of activity periods, presence of rhythmic activity, maximal frequency and highest values of acceleration peaks differentiated the subgroups of NIMDs and PsA. The other parameters of movement patterns showed no ability to discriminate between movement disorder groups by one-way ANOVA.

The PsA group differed mostly from the non-movement disorder group with regard to median number of activity periods and frequencies. The ability of the presence of activity periods and rhythmic activity to discriminate between NIMD categories is presented in Table 9.

Data were limited to patients who showed rhythmic activity. The differences in the median number of activity periods and frequencies were greatest between the PsA and

Table 8 Neuroleptic-induced movement disorder (NIMD) patterns for 99 inpatients with schizophrenia.

	Presence of activity periods n %	Median number of activity periods IQ	Presence of rhythmic activity n %	Median dominant frequency Hz IQ	Median of second frequency Hz IQ	Median of third frequency Hz IQ	Median of minimal frequency Hz IQ	Median of maximal frequency Hz IQ	Median highest value of acceleration peaks IQ
non-movement disorder n = 32	25 78%	2 1.00–7.63	24 75%	0.50 0.40–0.59	0.43 0.40–0.61	0.55 0.48–0.78	0.33 0.30–0.45	0.65 0.50–0.98	106 57–193
NIA n = 31	31 100%	13 5.00–22.00	30 97%	0.58 0.40–1.01	0.60 0.45–0.80	0.70 0.49–1.01	0.38 0.30–0.45	1.15 0.74–2.18	177 81–226
NIP n = 23	20 87%	8 1.00–14.50	16 70%	0.75 0.50–0.95	0.73 0.54–1.11	0.93 0.60–1.09	0.40 0.35–0.49	1.05 0.65–2.26	216 140–250
TD n = 32	30 94%	9.75 3.00–16.75	29 91%	0.55 0.40–0.80	0.55 0.45–0.93	0.65 0.46–0.95	0.40 0.30–0.45	0.95 0.63–2.03	125 75–206
PsA n = 19	18 95%	16 10.50–25.50	18 95%	0.80 0.50–1.53	0.80 0.49–1.00	0.60 0.49–1.04	0.40 0.30–0.43	1.15 0.75–2.58	127 79–208
All patients n = 99	88 89%	8 2.00–17.50	83 84%	0.55 0.40–0.80	0.55 0.40–0.80	0.65 0.50–0.98	0.35 0.30–0.45	0.90 0.60–1.45	129 80–213

Table 9 Presence of activity periods and rhythmical activity in differentiating neuroleptic-induced movement disorders for 99 in-patients with schizophrenia.

		Presence of activity periods	Presence of rhythmic activity
Non-movement disorders vs. NIMD and PsA	Pearson chi-square p	5.547 0.035	2.726 0.099
NIA vs. non-NIA	Pearson chi-square p	5.642 0.016	5.574 0.019
NIP vs. non-NIP	Pearson chi-square p	0.113 0.714	4.505 0.034
TD vs. non-TD	Pearson chi-square p	1.131 0.495	1.607 0.254
PsA vs. non-PsA	Pearson chi-square p	0.814 0.685	2.061 0.151
Pooled NIA and PsA vs. no akathisia	Pearson chi-square p	8.491 0.004	11.027 0.001

non-NIMD groups. The results of actometric patterns of NIMD and non-movement disorder groups are presented in Table 10.

The medians of the highest acceleration peaks (biggest digital integration of acceleration) in activity periods showed a trend to differ ($U = 444$, $p = 0.053$) between the NIP (216) and non-NIP (119) groups. No significant differences were found between other groups.

The differences in medians of the highest acceleration peaks between selected particular NIMD and non-movement disorder groups are presented in Table 10. Median values of third most prevalent frequency and minimal frequency were not significantly different between diagnostic categories.

To evaluate screening properties of actometry against DSM-IV and PsA diagnostic criteria, we used ROC analysis. The area under the ROC curve (AUC) of the lower limb activity index was 0.80 for PsA. The AUC was 0.84 for actometric activity count of pooled NIA and PsA.

7.7 Usefulness of self-rated question in screening NIMDs

Answers to the subjective question on movement problems were different between the pooled NIMDs and PsA group and patients without NIMD or PsA (Pearson chi-square 8.209, $p = 0.004$). The ROC curve for the subjective question screening performance in NIA is presented in Figure 4.

ROC analysis of the subjective question screening abilities showed an AUC value of 0.67 for pooled NIMDs and PsA, 0.87 for NIA, 0.52 for NIP, 0.46 for TD and 0.25 for PsA.

Table 10 Diagnostic group differences in actometric patterns of particular neuroleptic-induced movement disorders for 99 inpatients with schizophrenia.

	Number of activity periods	Dominant frequency	Second frequency	Maximal frequency	Median highest acceleration peak
NIA median	13	0.58	0.60	1.15	177
non-movement disorder median	2	0.50	0.43	0.65	106
Mann-Whitney U	207	262	153	177	277
p	<0.001	0.084	0.017	0.001	0.040
NIP median	8	0.75	0.73	1.05	216
non-movement disorder median	2	0.50	0.43	0.65	106
Mann-Whitney U	282	127	58	143	145
p	0.140	0.040	0.009	0.106	0.023
TD median	9.75	0.55	0.55	0.95	127
non-movement disorder median	2	0.50	0.43	0.65	106
Mann-Whitney U	294	267	163	209	305
p	0.003	0.145	0.030	0.013	0.110
PsA median	16	0.8	0.8	1.15	144
non-movement disorder median	2	0.50	0.43	0.65	106
Mann-Whitney U	87	103	82	92	156
p	<0.001	0.004	0.011	0.002	0.042
NIA and PsA median	15.75	0.68	0.60	1.15	155
non-movement disorder median	2	0.50	0.43	0.65	106
Mann-Whitney U	641	364	235	269	433
p	0.003	0.011	0.006	<0.001	0.017

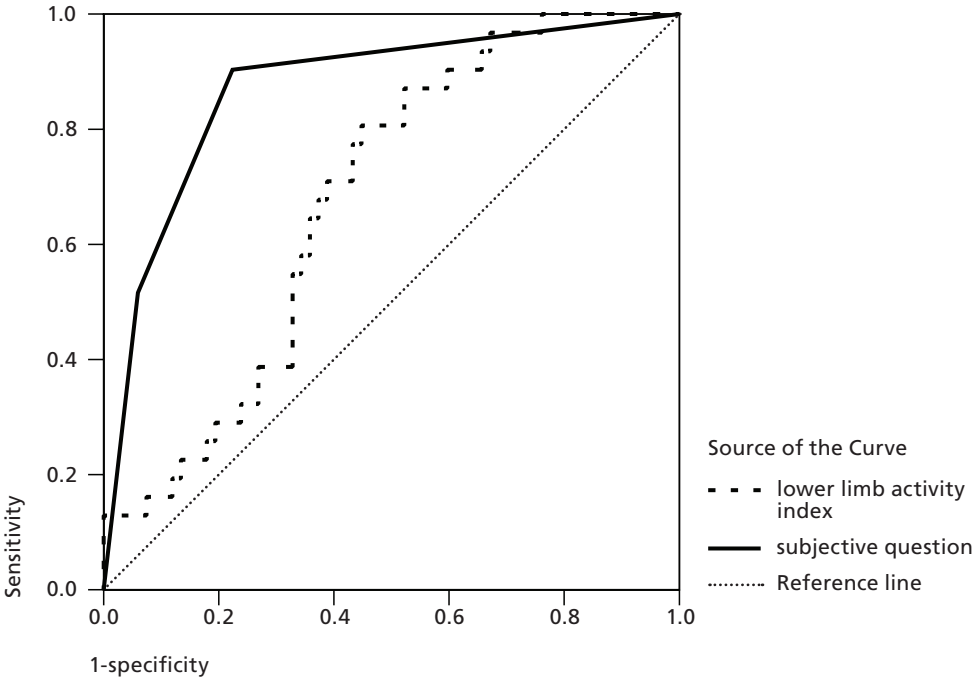

Figure 4 Receiver Operating Characteristic (ROC) curve for answers to subjective question and lower limb activity index against DSM-IV defined Neuroleptic-Induced Akathisia (NIA).

8 Discussion

We studied the prevalence of NIMDs in a naturalistic, globally relevant, schizophrenia inpatient sample that uses conventional neuroleptics and clozapine. We also explored the reliability and validity of different ways of measuring NIMDs. First, we compared the current diagnostic criteria (DSM-IV) with the most established observer rating scales (BARS, SAS, AIMS), which are also used in diagnosing these disorders. We found a good overlap in NIA and TD diagnostics, but somewhat poorer overlap in NIP, for which we suggested raising the commonly used threshold value. Second, we compared the established observer rating scales to objective motor measurement, the controlled rest lower limb activity measured by actometry. Although quantitative actometry could not differentiate the disorders from each other, it did support the validity of BARS and NIP. However, it did not prove to be a sufficiently valid instrument for use alone in a naturalistic population with co-morbid NIMDs. Still, actometry may be useful in measuring changes in NIA and NIP in situations where diagnoses have been made with another method. Third, after the failure of quantitative actometry to show diagnostic power, we explored more qualitative ways of analysing actometric data and demonstrated some diagnostic power in the case of pooled NIA and PsA data in our population.

8.1 Prevalence of NIMD

We found that nearly two-thirds of patients suffered from a NIMD despite relatively low antipsychotic doses and the use of anticholinergics. The clinical practice in the study population was first to lower the antipsychotic dose and then, if necessary, to add anticholinergics.

To our knowledge, this is the first prevalence study to use DSM-IV criteria for identification of NIMDs and one of a few studies identifying the three NIMDs simultaneously. Since the mean antipsychotic dose in the study population was relatively low, we suggest that the prevalence of NIMDs is probably higher at the more commonly recommended antipsychotic doses.

We found a NIA DSM-IV prevalence of 31%. Previously reported NIA rates measured with BARS (Barnes 1989) are 9–11% in inpatients (van Harten et al. 1996, Modestin et al. 2000) and 15–18% in communities (McCreadie et al. 1992, Halliday et al. 2002). In long-term inpatients, 24% (Halstead et al. 1994) and in depot clinic outpatients 32%, are reported to have akathisia (Barnes & Braude 1985), which agrees with our finding that long-term patients have high prevalence of akathisia assessed with either DSM-IV or BARS.

We observed a NIP DSM-IV prevalence of 23%. Previously reported NIP prevalence rates measured by clinical impression (mild akinesia not included) are 15% (Ayd 1961) or with SAS 19% in large in- and outpatient surveys (Muscettola et al. 1999), and by UPDRS 20% in inpatients concomitantly using clozapine (Modestin et al. 2000). Higher rates (27–35%) are reported in surveys conducted in restricted areas using SAS (McCreadie at al. 1992, Halliday et al. 2002) and in inpatients (36%) using UPDRS (Van Harten et al. 1996), which are much lower than our estimate using the SAS instrument (73%), but are consistent with our estimate using DSM-IV criteria (23%) in long-term patients also receiving clozapine. One reason for the high NIP prevalence measured by SAS in our study could be our long-term

patients had more rigidity, which was emphasized in SAS measurement. Muscettola et al. (1999) used slightly modified SAS with less rigidity items.

We found a TD DSM-IV prevalence of 32%. Previously reported TD prevalence rates are 29–32% in in- and outpatients (McCreadie et al. 1992, Mukherjee et al. 1982, Koshino et al. 1992) and 40–43% in long-term patients (Van Harten et al. 1996, Halliday et al. 2002), which agree with our estimate of 32% in long-term patients with a mean age of 50 years.

The prevalence rates of NIMDs defined by DSM-IV criteria and those obtained by rating scales were similar for NIA and TD but very different for parkinsonism. This could be due to the different focuses of DSM-IV and SAS criteria.

Despite the relatively low current antipsychotic dosage in our study, the prevalence of EPS was similar to that in previous studies. Thus the longer continuous treatment with antipsychotics, the potency of the antipsychotics and the older age of our patients made the prevalence here higher than in previous studies. Another important factor is that these chronic institutionalized patients had received much higher dosages of antipsychotics in the past.

8.2 Validity of BARS

BARS has been suggested to need objective validation by movement measurement (Barnes 1989). Objective validation by actometry is possible only for the objective BARS item. In our study, the convergence between actometry and BARS (the correlation and the ability to discriminate between NIA and non-NIA groups) provides some objective support for the validity of BARS. This methodological study was the first to compare BARS and actometric lower limb controlled rest activity in NIA in a large naturalistic population with different NIMDs. While both BARS and actometric lower limb controlled rest activity measures differentiated the NIA group from the non-NIA group, BARS proved to be superior. Although an earlier report (Tuisku et al. 1999) suggests discriminant validity for quantitative actometry between pure NIA and non-NIA subjects, we were unable to distinguish NIA patients from the naturalistic sample. Tuisku et al. (1999) excluded NIP patients and used healthy people as controls. In our study, the confounding effect of other NIMDs with hyperactivity (PsA, parkinsonian tremor and TD) and possible subclinical forms of NIMD in patients prevented us from reaching a similar level of discriminant validity.

Actometric lower limb activity and the BARS global score correlated weakly but significantly. The correlation became statistically significant only after excluding or controlling for other NIMDs. The instruments measure somewhat different constructs; actometry records only movements, while BARS includes subjective experience in its score.

8.3 Validity of SAS

According to ROC analysis, SAS had good case-finding properties, converging with the DSM-IV NIP diagnosis. In our population, the commonly used cut-off threshold of SAS mean score 0.3 was inappropriate: according to our results, the optimal cut-off point should be between 0.65 and 0.95, depending on the emphasis in the trade-off between sensitivity

and specificity. We therefore suggest that the cut-off value for screening of NIP should be 0.65, whereby specificity is doubled without losing any sensitivity. For diagnostic purposes a combination of high specificity and high positive predictive value (PPV) is reached at cut-off of 0.75 (Naarding et al. 2002).

The internal consistency of SAS was satisfactory, which suggests at least moderate reliability of the scale and is consistent with an earlier report (Loonen et al. 2000). We compared SAS with DSM-IV to assess the former's discriminant validity and to evaluate its ability to detect NIP cases.

The comparison with objective movement assessment aimed to estimate the concurrent validity of SAS in NIMD diagnosing. As expected, the SAS had discriminant validity for a clinical diagnosis of NIP. The SAS mean score discriminated NIMD patients well from those without NIMD, and more specifically, also NIP patients from other patients. Actometry discriminated NIMD patients from non-NIMD patients, but did not identify DSM-IV NIP patients. To investigate criticism about the overrepresentation of rigidity items (Cunningham Owens 1999, Loonen et al. 2000), we averaged the six rigidity items to form one item. This procedure worsened the NIP case detection capacity of SAS. Using the single elbow rigidity item for case detection yielded the same (or slightly better) case detection capacity than the SAS mean score. This finding supports the use of elbow rigidity testing when assessing parkinsonism in everyday practice, as the cut-off value of 0.5 has a good sensitivity and specificity for DSM-IV NIP. Rating "0" means "normal" and "1" means "slight stiffness and resistance".

In conclusion, SAS seems to be a reliable and valid instrument. It performs similarly to DSM-IV in NIP case detection. The optimal SAS mean score cut-off value in a naturalistic population of neuroleptic-treated schizophrenia patients is, however, higher than the commonly used 0.3. We suggest that the new cut-off value for screening of NIP could be 0.65, whereby specificity is doubled without losing sensitivity. Pooling the SAS rigidity items did not improve the performance of the scale.

8.4 Lower limb controlled rest actometry in NIMD

We failed to detect subclinical movement disorders because we used DSM-IV (American Psychiatric Association 2000) and PsA (Rapoport et al. 1984, Barnes & Braude 1985) diagnostic criteria as the golden standards. Differences between Parkinsonian disease subclinical resting tremor from controls in terms of amplitude fluctuation, frequency dispersion, harmonic index and proportional power in 4.4–6 Hz have, however, been reported by Beuter et al. (2005) using laser system measuring displacement.

8.4.1 Comparison of quantitative actometry and BARS

Both measures differentiated NIA from non-NIA group, but BARS proved to be superior to actometry in finding NIA cases. Although an earlier report has suggested discriminant validity for quantitative actometry between pure NIA and non-NIA subjects (Tuisku et al. 1999), we were unable to accurately identify NIA patients in the naturalistic sample. This may be due to the confounding effect of other NIMDs (PsA, parkinsonian tremor and TD) manifesting with hyperactivity. With cut-off 12000 the sensitivity of actometry was 0.9 in

finding akathisia cases. Asking about subjective symptoms (e.g., BARS awareness item) is still needed to rule out other NIMDs in a naturalistic population. Minor changes may be difficult to detect with BARS as compared with actometry. Quantitative lower limb activity index has proved to be a sensitive follow-up tool (Tuisku et al. 2002).

The convergence between actometry and BARS provides some objective support for the validity of BARS.

8.4.2 Comparison of quantitative actometry and SAS

We found that neither SAS mean score nor hypokinesia observed during the SAS gait item correlated with actometric lower limb activity. There are a few explanations for this: Firstly, actometry measures only the productive motor dimension of parkinsonian symptoms, while SAS also takes into account rigidity, gait, salivation and glabella tap, with a clear emphasis on rigidity. The lack of correlation with actometric findings in the NIP subgroup indicates that tremor may not be the core feature of NIP. This is also supported by the small AUC for the SAS tremor item. Our finding is consistent with previous studies, which have reported tremor in 60% (Ayd 1961) and 44% (Hassin-Baer et al. 2001) of NIP patients. Secondly, we used lower limb actometry, although the clinical assessment by SAS and DSM-IV considers predominantly upper limbs. NIP may be more symptomatic in the upper limbs (Hassin-Baer et al. 2001), and upper limb disturbances may have influenced our SAS and DSM-IV assessments more than lower limb disturbances. Our findings indicate that lower limb actometry is not suitable for diagnosing NIP. Thirdly, diurnal naturalistic actometry may have more power than controlled rest activity window in detecting hypokinesia.

8.4.3 Descriptive actometry in different NIMDs

Actometry in NIA and PsA

Our findings of actometric patterns of NIMDs and PsA agree with those of a previous accelerometric study (Rapoport et al. 1994), reporting no differences between clinical observations and accelerometric recordings of NIA and PsA.

Sachdev (1995a) has proposed that PsA is not a subtype of NIA. Differences in median values of actometric count for the PsA group and the non-movement disorder group in our study validates the diagnosis of PsA. These patients have higher frequency movements than other patients, but are unaware of them (according to answers to our subjective question). They have difficulties in noticing their disturbance, which clearly distinguishes this disorder from NIA.

Actometry in NIP

The parkinsonian tremor shows rhythmic activity in accelerometric recordings, discriminating NIP patients from non-movement disorder patients. NIP patients had higher peaks of accelerations in activity periods than non-NIP patients. Comparing the NIP group with the non-movement disorder group made this finding more significant. In our descriptive analysis, the frequencies of rhythmic activity in NIP were much lower (median below 1 Hz) than previously reported (above 4 Hz) (Bathien et al. 1984, Rapoport et al. 1998, Caligiuri

and Tripp 2004). One explanation may be that other NIMDs and PsA confound the results. Another possible explanation is that by measuring lower limb activity in the sitting position we could not detect high-frequency NIP tremor. The latter is characteristic for upper limbs – all fourteen NIP patients had tremor in the upper limbs and three had tremor in accelerometric recordings of the lower limbs (Rapoport 1998), and another accelerometric study also measured tremor from the upper limbs (Caligiuri and Tripp 2004). There may have been a high-frequency tremor (close to 10 Hz) in our sample that we were not able to detect with our method due to limitations in the time window of our actometers.

Actometry in TD

Recording of movements of the ankle gave little information for detecting TD, despite the movement pattern of TD having more activity periods, more rhythmic activity, and slightly higher frequencies than non-movement disorder patterns. This is explained by TD affecting other body segments than ankles, mostly the orofacial region and sometimes the legs. Another explanation could be that the non-movement disorder group included subclinical NIMD patients, who went undetected using DSM-IV criteria for NIMD. The second explanation is supported by the following findings: (1) up to 75% of non-movement disorder group patients by DSM-IV or PsA criteria showed rhythmic activity that might be related to movement disorders, seldom normal activity during rest; and (2) non-movement disorder patients had less activity periods in recordings, but when they had them, the frequencies were quite similar to those of NIMD (mostly TD) patients.

8.5 Subjective question

Almost all NIA patients have reported subjective complaints of movement problems in the lower limbs in previous studies (Braude et al. 1983, Sachdev & Kruk 1994). The subjective question on movement problems in our study was able to distinguish NIA patients from all other subjects. Answers to this question were highly selective for NIA cases, but not for other NIMDs or PsA.

8.6 Methodological issues

A strength of our study is the naturalistic non-selected inpatient sample. The sample was gathered from the largest nursing home in Estonia; approximately 13% of all institutionalized psychiatric patients in Estonia are treated there. The sample is representative of schizophrenia and schizoaffective patients in the nursing home since 91% of all patients with these diagnoses aged 18–65 years participated. Medication of the sample represents typical medication available in state institutions for schizophrenia patients in Estonia (Jaanson 2002). We can therefore generalize our results to other chronic schizophrenia inpatients, treated with mostly typical antipsychotics.

We achieved excellent interrater reliability in descriptive evaluation of actometric data with a relatively short training of inexperienced raters with no previous actometric rating skills (Study IV).

We used 30-min controlled rest activity recorded with actometry because Tuisku et al. (1999) reported significant differences in controlled rest activity of NIA patients compared with controls. A longer recording time (14.5 hours) did not show significant differences between these groups (Tuisku et al. 1999) and would be impractical in our study design.

We used several assessment methods for NIMDs simultaneously, which allowed us to compare the diagnostic criteria of rating scales and an objective assessment method, actometry.

The main limitations of this study are connected to the nature of NIMD: (1) co-occurrence of spontaneous movement disorders, commonly detected in schizophrenia populations (Chatterjee et al. 1995), could not be excluded, and (2) the DSM-IV diagnoses of NIMDs in this study, as in clinical settings in general, are partially based on retrospective information.

The co-morbid movement disorders that exist in this real-life sample may have partially overlapping characteristics. The differentiating ability of actometry was not high for individual NIMDs.

Another limitation of the study is that for practical reasons the clinical diagnosis of NIMD or PsA, the ratings for scales and the subjective question was all assessed by the same clinician, which could result in judgement bias. Furthermore, as there was only one rater for the scales, a cross-scale contamination might have occurred.

DSM-IV was used as the standard in this study; however, little data are available on the validity of the NIMD criteria of DSM-IV. A better golden standard would probably have been an expert-consensus diagnosis. Another limitation here was that subclinical movement disorders went undetected since we used DSM-IV (American Psychiatric Association 2000) and PsA (Rapoport et al. 1984, Barnes and Braude 1985) diagnostic criteria as a gold standard.

This study was limited to a few aspects of the utility/validity of SAS: internal consistency, convergence to DSM-IV NIP diagnosis and convergence to objectively measured motor activity. Many aspects of the scale's reliability (e.g. test-retest and interrater reliability) and validity (e.g. construct) were not evaluated. With age, the prevalence of spontaneous NIMDs is known to rise. While our material did not allow a thorough examination of the issue, age did correlate with SAS mean score.

The limitation of actometric data collection was the recording of only ankle activity; recordings from the wrist and legs could give more information, especially in case of NIP, which is manifested more in the upper limbs (Hassin-Baer et al. 2001).

9 Conclusions and future considerations

9.1 Conclusions

Chronic schizophrenia populations, similar to our study population, are common worldwide. NIMD affected two-thirds of our study population. Prevention, diagnosis and treatment of NIMDs warrant more attention, especially in countries, where typical antipsychotics are frequently used. Our study supported the validity and reliability of DSM-IV diagnostic criteria for NIMD in comparison with established rating scales and actometry. BARS and SAS are valid instruments in diagnosing NIA and NIP, respectively. However, commonly applied SAS threshold for diagnosing NIP should be raised from 0.3 to 0.65. Controlled rest lower limb actometry did not achieve sufficient specificity in our population with several co-morbid NIMDs and PsA, but it may be sensitive in measuring changes in NIMDs or PsA. The subjective question on movement disturbances was highly specific and cost-effective in detecting NIA, but not other NIMDs or PsA.

9.2 Clinical implications

Nearly two-thirds of institutionalized schizophrenia patients were shown to suffer from adverse effects of conventional antipsychotics. Since the costs of switching to atypical antipsychotics are too high for many countries, other ways of coping with NIMDs must be explored, such as lowering antipsychotic dosage and using clozapine or anticholinergics.

Our subjective question was specific for NIA cases, but not for other NIMDs or PsA, probably because of the subjective component of NIA. Posing such a subjective question is a cost-effective way of screening for NIA. Careful questioning of patients is useful method of diagnosing NIA in clinical setting. The use of elbow rigidity testing has good sensitivity and specificity for DSM-IV NIP. Actometry does not offered any advantages in diagnosing TD in comparison with structured clinical observation using AIMS.

9.3 Implications for research

Actometric lower limb recording and analysis are moderately time-consuming but useful for differentiating pooled NIA and PsA patients from other patients in a non-selected populations, but do not discriminating between these two subgroups. Exact recording of a patient's present state is an advantage of actometry. Because our study was cross-sectional, we were unable to show changes in movement activity index or patterns after changes in risk factors (e.g. dosage, antipsychotic type and time course). Future research should concentrate on whether actometry is sensitive to change, especially in comparison with rating scales. The first studies have been done already (Adler et al. 1999, Tuisku et al. 1999).

The epidemiology of NIMDs and PsA should be studied in a naturalistic schizophrenia population using mostly atypical antipsychotics to estimate their prevalence and incidence.

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