Antipsychotic induced parkinsonism in the elderly:

assessment, causes and consequences

Wilma Knol

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Antipsychotic induced parkinsonism in the elderly:
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Door antipsychotica geïnduceerd parkinsonisme bij ouderen:
beoordeling, oorzaken en gevolgen
(met een samenvatting in het Nederlands)

Proefschrift

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Wilma Knol

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Promotoren:	Prof. dr. A.F.A.M. Schobben
	Prof. dr. A.C.G. Egberts
Co-promotoren:	Dr. R.J. van Marum
	Dr. P.A.F. Jansen

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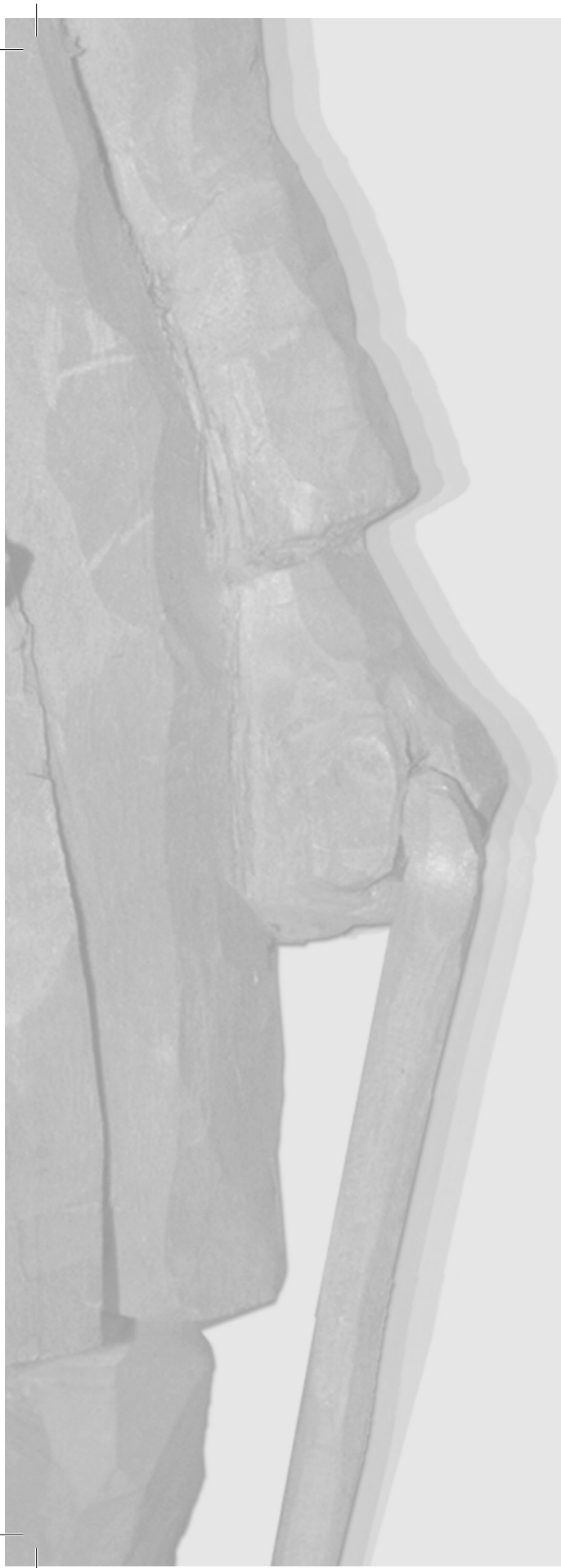


Chapter 1

General introduction

Antipsychotic induced parkinsonism in the elderly

Epidemiology

Over 15% of the population of the Netherlands is older than 65 years and a substantial increase of the aging population is expected over the next 20 years.[1] A common problem in the elderly are psychotic and behavioural symptoms. Deciphering the underlying cause of psychotic symptoms in elderly can be complex, but is necessary in order to take adequate treatment decisions. Delirium and dementia are the most common primary causes of psychotic symptoms in elderly. Delirium occurs with frequencies in the elderly population of up to 56% during hospital admission and the prevalence of behavioural problems in elderly with dementia raises above 75% in nursing homes.[2,3]

Antipsychotic drugs are widely used since their introduction in the 1950's to relieve psychotic symptoms. The reported annual prevalence of antipsychotic drug use is approximately 3.6% (36 per 1000 persons) in elderly in a general population, which is more than three times higher than in people below 65 years of age.[4] In nursing home residents the prevalence of antipsychotic drug use varies even between 12% and 52%.[6-8,13] Although widely used, scientific proof of efficacy of antipsychotics in elderly is limited. Especially the efficacy of antipsychotics in dementia, which is studied more extensively than the efficacy in delirium or schizophrenia in elderly is considered modest.[9-13]

The high use of antipsychotics in nursing homes led to federal regulations in 1987 in the US, which resulted in a small decrease in its use.[14] In the late 1990's, there was a significant shift from conventional to atypical antipsychotics given the latter's lower reported rates of extrapyramidal symptoms and better safety profile. However, in 2005 the Food and Drug Administration warned healthcare providers for an increased all-cause risk of death with atypical antipsychotics in patients with dementia.[15] The deaths seemed to be related to cardio- and cerebrovascular events or infections. However, the relation between infections, mostly pneumonia, and antipsychotics is not entirely clear. Although observational studies suggest similarly increased mortality in users of conventional antipsychotics, the concerns about safety and tolerability of atypical antipsychotics contributed to slow down the increasing trend in their use in elderly during the last decade.[4,15-18] Nowadays haloperidol is still the most frequently prescribed antipsychotic in the elderly in the Netherlands and other European countries.[4,5]

In contrast to the paucity of controlled studies on the efficacy in the elderly, numerous studies have been published about possible adverse effects of antipsychotics. Increased risk of extrapyramidal symptoms, falls and fractures, cardiac arrhythmias, cerebrovascular events, venous thrombo-embolism and metabolic abnormalities

including obesity have been reported.[19] The sensitivity to specific adverse effects changes with older age.[20-22]
Drug-induced parkinsonism (DIP), which is characterized by tremor, bradykinesia, rigidity, and postural instability is a well known adverse effect of conventional antipsychotics. Between 26% and 67% of patients using conventional antipsychotics develop DIP, although the lack of a widely accepted gold standard for diagnosis of this condition means that its incidence is possibly under- and maybe overestimated.[23-25] The interval between initiation of antipsychotics and onset of DIP is highly variable, ranging from a few days to several months.[24] DIP can be a reason for discontinuation of antipsychotic treatment or noncompliance and it may persist for several months after discontinuation of antipsychotics.[26,27] The influence of antipsychotic induced parkinsonism (AIP) on quality of life has not been investigated in elderly patients.

Elderly people are more prone to develop AIP, but there are also notable variations in occurrence of this adverse effect in elderly people. The factors that influence these variations have not been well elucidated. Better understanding of causes and consequences of antipsychotic induced parkinsonism is needed to develop effective treatment strategies tailored to the individual older patient.

Assessment
Clinical recognition rates of AIP are low (about 50%), but can be improved after specific training.[28,29] While clinicians may want to assess AIP objectively, researchers are obliged to do so. The first attempts to quantify and correlate a feature of drug induced parkinsonism were H.J. Haase's efforts to establish a 'neuroleptic threshold' using changes in handwriting.[30] The first and most widely used scale for assessment of drug-induced parkinsonism is the Simpson Angus Scale (SAS), published in 1970.[31,32] Most of the available rating scales are developed to evaluate the broader complex of extrapyramidal side effects, including parkinsonism. Combined scales have been reported to be impractical in clinical use because of their complexity, which makes them less attractive.[33]
Rating scales are designed to improve the reliability and validity of patient assessment over what might be accomplished in a standard clinical interview or physical examination. To be useful, observer-based rating scales must be reliable (i.e. have internal consistency, inter-rater reliability and test-retest reliability) and valid (i.e. accurate in representing the true event).[34] Although several rating scales have been developed for the assessment of AIP, there are only few clinimetric data available, especially about validity.[35] Given this lack of data, it is not surprising that there is limited agreement about which scale should be used in clinical practice as well as in research.

Pathophysiology

The efficacy and tolerability of antipsychotic drugs has been linked to their binding to dopamine D2 receptors.[36] Positron emission tomography (PET) studies have indicated that the therapeutic effects of antipsychotics are achieved at a blockade of 60-70% of dopamine receptors and that AIP appears when blockade of dopamine receptors is more than 80%.[37] A greater affinity of conventional antipsychotics for dopamine D2 receptors may account for their increased risk of AIP. Elderly people are prone to antipsychotic induced parkinsonism.[38] Guidelines recommend the use of low doses of antipsychotics in elderly patients and physicians follow these recommendations in daily practice. However, potential mechanisms underlying the influence of age on antipsychotic (adverse-) effects are not clear.

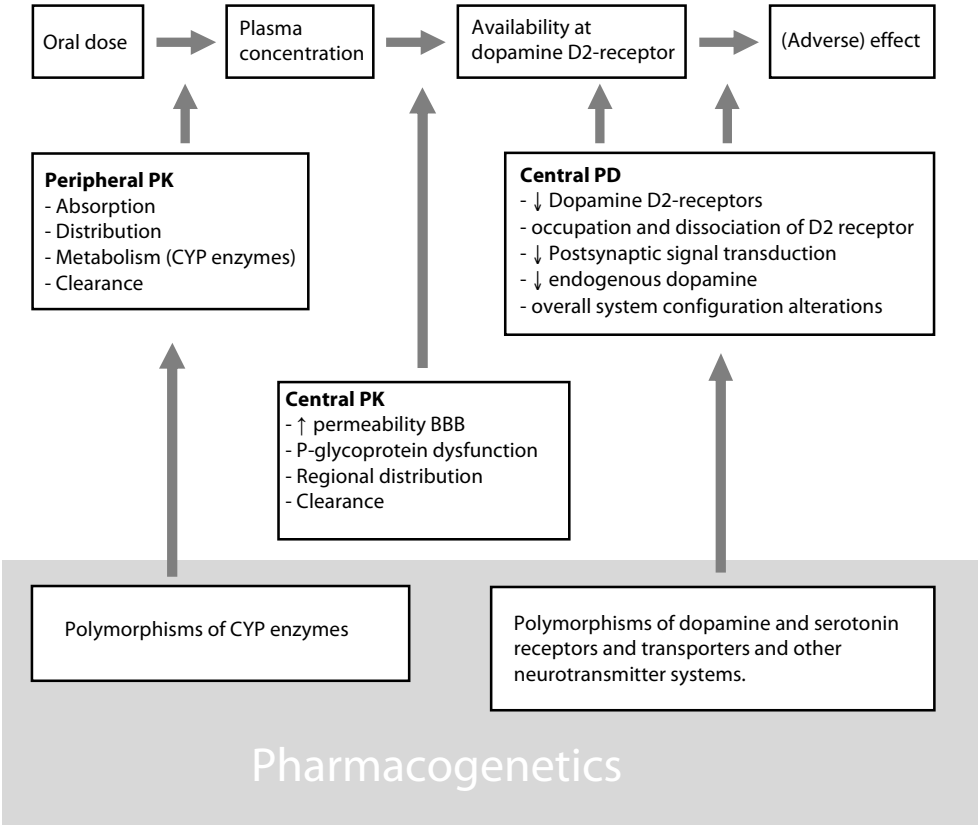
Clinical pharmacological framework

In general the pathway from the initial ingestion of an antipsychotic drug to the central (adverse) effects can be subdivided in three parts; peripheral pharmacokinetics (PK), central pharmacokinetics and central pharmaco-dynamics (PD) (figure 1). Suggested explanations for mechanisms underlying increased sensitivity and variation in sensitivity in elderly patients are either higher plasma concentrations at a given dose (peripheral PK), an increased brain access and distribution for a given plasma level (central PK), or increased sensitivity at the receptor level (central PD).[39]

Peripheral pharmacokinetics

Antipsychotics are absorbed from the gastrointestinal tract, metabolised in the liver and excreted in the urine and, via the bile in the faeces. There is a wide interindividual variation in plasma concentrations of antipsychotics and corresponding dosage levels. The cytochrome P450 (CYP) enzyme family in the liver plays a key role in the metabolism of all antipsychotics and influence of polymorphisms of CYP enzymes on the PK of antipsychotics is indisputable.[62] Although it is widely believed, an age effect on plasma concentration of antipsychotics has not been an consistent finding. Despite age-related decrease in renal and hepatic function, several studies showed that age did not have an effect on the dose/plasma concentration ratio of conventional and atypical antipsychotics, while gender, race and smoking status were contributors.[40-44] Secondly, studies that examined relationship between plasma concentration and (adverse-) effects showed contradictory results in both conventional and atypical antipsychotics.[40,45-48]
Moreover, aging is often accompanied by increased comorbidity, leading to polypharmacy and therfore more significant drug interactions.

Figure 1. Framework of potential contributors to increased antipsychotic sensitivity



Abbreviations: PK= pharmacokinetics; PD= pharmacodynamics

Central pharmacokinetics

Antipsychotics are widely distributed in the body and cross the blood-brain barrier (BBB). The BBB consists of tight junctions, loosening of these junctions would theoretically increase access of antipsychotics in the brain, but the relationship between junction integrity and aging has not been investigated. Central concentration of some antipsychotics is also regulated by P-glycoprotein (P-gp), which restricts the permeability of the BBB indirectly by pumping drugs back into the peripheral circulation.[49,50] However, haloperidol is not a P-gp substrate and literature addressing age effects on P-gp in vivo with antipsychotics in general is not available.

An age related decline in synthesis of dopamine is suggested in post-mortem studies and one PET study examining the release of dopamine in response to a challenge.[51-53]

Central pharmacodynamics

Available evidence indicates a gradual decline in the structural and functional status of the dopaminergic system with age. Postmortem studies and studies that used stereological cell-counting methods have reported that cell counts in the substantia nigra decline with age at the rate of approximately 10% per decade.[54,55] Also decline of dopamine D2 receptors with age have consistently been reported in post-mortem as well as in vivo studies.[56,57]

Dopamine receptors are coupled to guanine nucleotide binding proteins (G-proteins) that transduce signals form receptors to effectors (such as adenylate cyclase), which in turn, trigger downstream cellular response. Age related alterations in the structure of the cell membrane, in which G-proteins and adenylate cyclase are embedded could result in a reduction of signal transduction.[58] However, G-protein mediated signal transduction is not confirmed for dopamine receptors.

Finally, in the single available antipsychotic drug-binding PET study in elderly (whom received risperidone) parkinsonism was observed at D2 occupancy of 34%-79%, which is in contrast with published literature in younger patients in whom occurrence of AIP is consistently associated with occupancy levels higher than 80%.[59]

Pharmacogenetics and AIP

Pharmacogenetics is a promising and challenging field of research in antipsychotic induced parkinsonism. It focuses on the identification of genetic variants and generates the possibility to identify patients potentially at higher risk for parkinsonism as a adverse effect of antipsychotics.

Since the middle of 1990, hundreds of studies concerning pharmacogenetics and (adverse) effects of antipsychotics have been published, making it a rapidly growing research area.[62] However, research of antipsychotic induced parkinsonism has been less extensive than that of tardive dyskinesia. Furthermore different studies have been inconsistent and only few of these studies have been performed in an elderly population. Candidate gene association studies are best equipped to study genetics in drug induced parkinsonism. This type of studies can test the effect of genetic variants of a potential contributing gene (the candidate gene) in unrelated cases and controls. Most genes contain many known DNA sequence variations called single nucleotide polymorphisms (SNP's). Genetic variation may contribute to alterations of plasma concentration (peripheral PK)[60,61] or alterations within the dopaminergic system (central PD) and may contribute to individual differences in susceptibility of developing adverse effects.

Objectives of this thesis

The objectives of this thesis are A) to qualify the available rating scales for drug induced parkinsonism, B) to quantify the influence of several potential determinants that may explain variability of antipsychotic induced parkinsonism, including the role of genetic factors, and C) to investigate consequences of antipsychotic induced parkinsonism in the elderly.

Outline of this thesis

The thesis consists of three parts of research in antipsychotic induced parkinsonism in the elderly. The first part describes the assessment of antipsychotic induced parkinsonism. In chapter 2 we first review the available rating scales for drug induced parkinsonism and their clinimetric characteristics. This is used to select a rating scale for evaluation of antipsychotic induced parkinsonism in the further studies. Secondly, we asses the clinimetric characteristics of the chosen rating scale in an elderly population.

In the second part we study a population of elderly people during treatment with haloperidol. In chapter 3.1 we describe the prevalence of AIP and investigate the association with prescribed dose, plasma concentration, duration of use of haloperidol and AIP. In Chapter 3.2 we evaluate the association between several polymorphisms of candidate genes and AIP. The selection of these candidate genes is based on the relevance to the pharmacological action of haloperidol and results of prior association studies. We studied several polymorphisms in dopamine D2, dopamine D3, serotonin 2A, serotonin 2C, a second messenger protein (RGS2), an enzyme involved in the biosynthesis and biotransformation of endogenous neurotransmitters (COMT) and a neutrotrophin, which has an important role in promoting and modifying growth, differentiation and survival of neurons (BDNF).

In the last part we focus on consequences of antipsychotic induced parkinsonism and evaluate in chapter 4.1 quality of life in elderly patients with antipsychotic induced parkinsonism. This study uses data from the same population as in chapter 3.1 and 3.2. In chapter 4.2 we describe whether or not the use of antipsychotics is associated with the risk of pneumonia in elderly. We speculate in this study about the possible mechanism of this adverse effect of antipsychotic drugs.

In the general discussion in chapter 5 the results of our studies are placed in a broader perspective in relation to both clinical practice and research. In addition we offer considerations for clinical pratice and future research.

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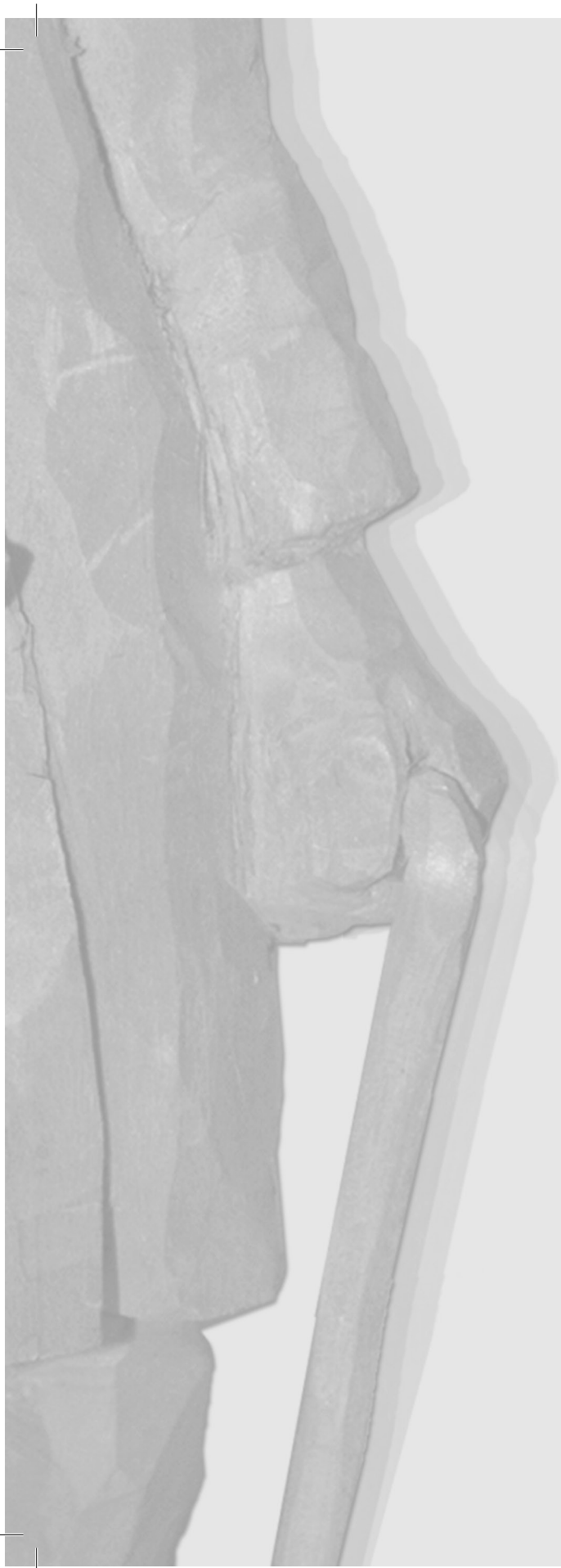

Chapter 2

Assessment

Chapter 2.1

Systematic evaluation of rating scales for drug induced parkinsonism and recommendations for future research

Wilma Knol
Carolina J.P.W. Keijsers
Paul A.F. Jansen
Rob J. van Marum

J Clin Psychopharmacol 2010; 30:57-63

Abstract

Objective
Drug induced parkinsonism (DIP) is one of the most common adverse effects of antipsychotics. The limited agreement about which rating scale should be used in clinical practice to assess DIP prompted us to review the feasibility and clinimetric qualities of the available instruments.

Methods
PubMed and EMBase databases were searched in November 2008 using the terms "parkinsonism", "scale" and "drug induced", to identify instruments used to measure DIP. Then the literature was searched for studies investigating the use and clinimetric properties of each identified instrument. Outcome measures included feasibility, validity (including appropriateness of used reference test), and reliability (internal consistency, inter-rater and intrarater).

Results
Seventeen rating scales were identified, each with a different representation of the concept of parkinsonism. The Simpson Angus Scale (SAS) was used the most, followed by the Extrapyramidal Symptom Rating Scale (ESRS). There were limited clinimetric data, especially regarding validity, available for any scale. The SAS, the Drug Induced Extrapyramidal Scale (DIEPSS), and the parkinsonism subscale of the Schedule for the Assessment of Drug-Induced Movement Disorders (SADIMoD), which is identical to the Sct. Hans Rating Scale for Extrapyramidal Syndromes (SHRS), appeared to have moderate to good reliability and acceptable validity. The time-consuming nature of the SADIMoD would make it less useful in daily practice.

Conclusion
Although various scales are used to assess DIP, few have been evaluated for validity and reliability. The SAS, SHRS, and DIEPSS seem to be the most valid, reliable, and easy-to-use instruments to evaluate DIP in clinical practice.

Introduction

Drug induced parkinsonism (DIP), which is characterized by tremor, bradykinesia, rigidity, and postural instability, affects between 26% and 67% of patients using typical antipsychotics, although the lack of a widely accepted gold standard for this condition means that its incidence may be underestimated.[1-3] DIP may have a huge impact on the quality of life of patients; indeed, DIP may be a reason why patients with schizophrenia are non-compliant with antipsychotic treatment.[4] Moreover, DIP may persist for several months after discontinuation of antipsychotics.[5] All drugs that block dopamine receptors can cause DIP. Although several rating scales have been developed for the assessment of DIP, there are few clinimetric data available, especially about validity.[6] Given this lack of data, it is not surprising that there is limited agreement about which scale should be used in clinical practice. To rectify this situation, we performed a systematic review of available instruments and assessed their clinimetric qualities and feasibility.

Methods

We considered all instruments used to measure DIP that included items on bradykinesia, rigidity and tremor.

Search strategy

The search was conducted in two stages. First, PubMed, EMBase, and movement disorders handbooks were searched to identify instruments used to measure DIP. Databases were searched for assessment scales, using the terms "parkinsonism", "scale", and "drug induced" (search conducted November 2008). Searches were not restricted to the English language. Animal studies and studies using scales that primarily assessed dyskinesia, dystonia, or akathisia were excluded. Studies using the broader outcome "drug-induced extrapyramidal symptoms" (DIEPS) including parkinsonism were included. The title and abstract of retrieved articles were screened for relevance and the reference lists were searched for other relevant articles. In the second stage, we searched the literature for studies reporting the use and clinimetric properties of each scale identified.

Methods of review

Although rating scales should provide a conceptual explanation of what they measure, there is no consensus on the ideal construct of a rating scale for measuring DIP. For this reason we decided to describe the construct of each selected rating scale without using specific criteria. We adapted the method of McDowell and Newell for presenting the quality of scales.[7] Two reviewers (WK, CK) independently judged the quality of the

identified publications, using a checklist to evaluate sample characteristics, used reference standard, appropriateness of statistical analysis, and clinimetric characteristics, namely, reliability (internal consistency, inter-rater reliability, intrarater reliability), and validity (content validity, criterion validity, and construct validity). There is no general agreement about how to interpret the different indices of correlation and degrees of agreement. Few studies declare what level of correlation is demonstrating adequate validity or reliability. We used the following cut-off points for different correlations and degrees of agreement for validity and reliability: the Spearman's coefficient ρ, Pearson's coefficient ρ, Kendall's coefficient W or T with values of 0.7 and lower were considered poor, whereas values over 0.7 were considered moderate to good. [8] The values for kappa (k), weighted kappa (k_w), and intraclass correlation (ICC) were interpreted using the criteria proposed by Landis and Koch (< 0.20 slight agreement, 0.21 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 good agreement and 0.81 to 1.0 very good agreement).[9] A value for Cronbach's α lower than 0.70 was considered poor, whereas values of 0.71 to 0.90 were considered moderate to good.[10] If, however, α is too high (α>0.90), then some items may be redundant.[8] The trade-off between sensitivity and specificity was evaluated using a receiver operating characteristics (ROC) curves. The area under the ROC curve (AUC) values between 0.5 and 0.7 indicate a poor accuracy, values between 0.7 and 0.9 indicate a test useful for some purposes, whereas values over 0.9 indicate a high accuracy.[11] A paired t-test giving p>0.05 (non significant result) indicates that there is no evidence of systematic difference between the results of two assessments. Factor analysis is commonly used to study the internal structure of a scale that contains separate components, each reflecting a different aspect of the measured domain.[12] Preferably, unrelated items should not belong to the same factor; however, the multidimensional nature of DIEPS means that it is not useful to use a cut-off point for correlation among different factors.

The feasibility of the rating scales was determined by evaluating the availability of instruction material on how to examine patients and how to score items, how user-friendly the scale is to use and score, and the time the assessment takes.

Results

Of 1109 relevant articles retrieved, 291 mentioned 16 rating scales. An additional scale was identified from the reference lists. Thirteen of these rating scales were used in 149 studies of DIP, namely, the Simpson Angus Scale (SAS), the Unified Parkinson Disease Rating Scale (UPDRS), the Extrapyramidal Symptoms Rating Scale (ESRS), Hoehn and Yahr (H&Y), the Diagnostic and Statistic Manual of Mental Disorders IV (DSM IV), the Webster rating scale (Webster), the Mindham's rating scale (Mindham), the Smith trims rating scale (Smith-trims), Cornell University Rating Scale (Cornell URS), the Columbia University Rating Scale (CURS), the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS), the Sct. Hans Rating Scale for Extrapyramidal Syndromes (SHRS), and the Udvalg for Kliniske Undersøgelse (UKU). The remaining four rating scales were used in 147 studies of DIEPS, namely, the Schedule for the Assessment of Drug-Induced Movement Disorders (SADIMoD), the Drug Induced ExtraPyramidal Symptoms Scale (DIEPSS), the Maryland Psychiatric Research Center Scale (MPRC), and the Yale Extrapyramidal Symptom Scale (YESS).

Application of rating scales

We identified 144 and 778 studies that described the use of rating scales for DIP and DIEPS, respectively. We did not identify any studies describing the use of the SADIMoD and the YESS (table 1).

In clinical studies, the SAS was used the most often to assess DIP, followed by the ESRS. The UPDRS, H&Y, Webster rating scale, and Cornell URS were used to assess 7, 6, 5, and 1 times, respectively. These scales were primarily designed to assess the severity of symptoms of Parkinson's disease and not to assess DIP. The DSM IV was also not designed to assess parkinsonism. Most of the other rating scales were designed to assess extrapyramidal symptoms and contained a subscale for parkinsonism (e.g. the ESRS, the UKU, the DIEPSS, the LUNSERS, the MPRC, the SADIMoD, the SHRS, and the YESS). The only rating scales exclusively designed for DIP were the SAS and the Mindham.

Clinimetric characteristics

We identified 7 studies that described the clinimetric characteristics of the DIP-specific rating scales (SAS and Mindham) and 15 studies that described the clinimetric characteristics of the 8 other rating scales for evaluating DIEPS including DIP (ESRS, UKU, DIEPSS, LUNSERS, MPRC, SADIMoD, SHRS, YESS). No validation studies were identified for the remaining 7 rating scales: Cornell URS, Columbia URS, DSM IV, H&Y, Smith-trims, UPDRS, and Webster. The characteristics of the 10 validated scales are given later (table 2 and 3).

Table 1. Application and Validation studies

Name scale	Embase	Pubmed	No scale in article	Application studies				Validation studies		
	N	N	N	DIP	DIEPS	PD	Other	DIP	DIEPS	Other
Cornell URS	1	4	4	1	0	0	0	0	0	0
Columbia URS	28	34	0	0	3	52	3	0	0	4
DIEPSS	18	17	0	0	27	0	4	0	*1	3
DSM IV	72	95	4	4	2	0	154	0	0	3
ESRS	102	99	0	9	180	0	9	0	**1	2
Hoehn & Yahr	126	116	0	6	0	221	15	0	0	0
LUNSERS	9	8	0	0	7	0	2	0	4	4
Mindham	56	61	111	4	0	0	0	2	0	0
MPRC	38	116	150	0	2	0	0	0	1	1
SADIMoD	4	4	0	0	0	0	1	0	2	5
SAS	268	276	0	106	415	0	8	5	2	8
Smith-Trims	14	18	30	2	0	0	0	0	0	0
SHRS	87	74	137	0	17	0	3	0	1	3
UKU	62	63	0	0	111	0	6	0	***2	6
UPDRS	377	350	0	7	14	668	28	0	0	10
Webster	30	27	0	5	0	42	7	0	0	3
YESS	28	29	55	0	0	0	0	0	1	1
Total	**2711**		**491**	**144**	**778**	**983**	**240**	**7**	**15**	**53**

* Inada 2003: Comparison of prevalence and incidence of DIP in Japanese and Caucasian schizophrenic population with respectively DIEPSS and SAS (no appropriate validity study, excluded).[13]

** Chouinard G. 2005.[14] refers to 3 studies: all not available, excluded:[15-17]

*** In 2 studies LUNSERS was compared with the UKU to evaluate construct validity, those 2 studies were not counted in the number of validity studies for the UKU [18;19]

Description and clinimetric characteristics of the scales for DIP and DIEPS

1. Drug-Induced ExtraPyramidal Symptoms Scale (DIEPSS)

The DIEPSS was developed in 1994 to assess extrapyramidal side effects and consists of 9 items, 5 for parkinsonism, and 1 each for akathisia, dystonia, dyskinesia, and severity. Items are scored on a 5-point scale. A manual for the scale was developed in 1996.[39] An abstract reported good inter-rater reliability,[40] and one study showed the DIEPSS to have good to very good inter-rater and intrarater reliability for individual items and total score, when the instrument is used by trained assessors. The correlation between parkinsonism items is acceptable, and these items show high agreement with the SAS. ROC analysis showed that a total sum score of 5 for the parkinsonism items is optimal for measuring DIP with high accuracy. A 4-factor solution accounts for approximately 80% of the variance. The first factor consists of gait, bradykinesia, and rigidity (28% of total variance), the second factor consists of sialorrhea and tremor (19.3%), the third factor consists of dystonia and dyskinesia (17.6%), and the fourth factor consists of akathisia (14.8%).[21]

2. Extrapyramidal Symptom Rating Scale (ESRS)

The scale was developed by Chouinard and Ross-Chouinard and was first used in clinical trials in 1976. The scale consists of eight items: a questionnaire, examination scales for parkinsonism, dystonia, and dyskinesia, and subscales for global impression of severity of tardive dyskinesia, parkinsonism, dystonia, and akathisia. A manual was made in 2005. The assessment takes 15 minutes.[14] In a review article, Chouinard described the characteristics of the scale extensively and reported on some clinimetric characteristics, evaluated by the people who developed the scale.[14] Chouinard mentioned a good inter-rater reliability in patients with schizophrenia or idiopathic Parkinson's disease.[16] The agreement between the ESRS and AIMS for dyskinesia is high, but validity data for the other subscales including parkinsonism are lacking.[41] A major disadvantage of the ESRS is its complexity. For example, scoring the rigidity of each limb and tremors in as many as eight body areas (at the same time noting the amplitude) makes the instrument difficult to use in daily practice.[20]

3. Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS)

The LUNSERS is a self-administered rating scale for assessing and quantifying adverse events during antipsychotic treatment. The instrument is based on the UKU and was developed by Day et al. (1995). Forty-one side effects, covering extrapyramidal, anticholinergic, autonomic, psychic, allergic, hormonal, and other miscellaneous side effects, are scored on a 5-point scale. The scale also includes 10 Red Herrings, symptoms that are not known as antipsychotic side effects. A high score on these items suggests

that reporting is unreliable and that the patient has a high level of general symptomatology. The test takes 5 to 20 minutes to complete.[18] Two studies showed the scale to have a good internal consistency.[18,22] One study showed good intrarater reliability on total score over a week.[18] Two studies reported an acceptable correlation between the total score and the UKU.[18,19] The correlation between individual items ranges from ρ=0.11 to 0.88; the variation in correlation could be due to the small number of participants and difficulties completing the self-report assessment with unusual words.[18,19] One study reported a poor, but statistically significant, correlation between the extrapyramidal symptoms and Parkinson subscales of LUNSERS and SAS.[21]

4. The Mindham Rating Scale (Mindham)

Mindham described this rating scale in 1976.[24] The scale consists of five clusters of items scored on a 4-point scale (0-3) for evaluation of face expression, rigidity, tremor, steadiness of gait, and global assessment of physical state. A sixth cluster for the global evaluation of akathisia was added by Bersani et al in 1990.[42] We were not able to find a manual or description how to interpret scale scores. Two small studies showed that, during treatment with fluphenazine decanoate for 6 months, the pattern of parkinsonism symptoms measured with the Mindham scale was comparable with performance on tests such as the grooved-peg-board test and the impulse counter test.[23,24] Mindham et al stated that clinical assessment with the Mindham scale distinguished more clearly between drug treatments than performance tests (Grooved-peg-board and impulse counter test).[24]

5. Maryland Psychiatric Research Center Scale (MPRC)

The MPRC was developed in 1985 and is based on the Smith scale, which is primarily intended for rating tardive dyskinesia.[25,43] The MPRC provides a finer discrimination of anatomic area and severity. It consists of 13 dyskinesia and 15 parkinsonian ratings and a global rating for dyskinesia, parkinsonism, and akathisia, scored on an 8-point scale (0-7). The scale is considered appropriate for use by non-physicians. Since assessment of tardive dyskinesia is beyond the goal of this article, only the scale's clinimetric characteristics concerning DIP were evaluated. In a study of the clinimetric characteristics of the scale when used for patients with DIEPS including parkinsonism, the internal consistency of the parkinsonian items was found to be moderate, and the inter-rater reliability for total parkinsonian score to be very good and for individual items acceptable to very good.[25] The intrarater reliability for the global parkinsonian score and the parkinsonian items lip tremor, masked facies, resting arm tremor, and diminished arm swing was good.[25] The other parkinsonian items were not sufficiently present to calculate intrarater reliability. No validity data are available for evaluation of parkinsonism.

6. Schedule for the Assessment of Drug-Induced Movement Disorders (SADIMoD)

The SADIMoD was developed by Loonen in 1994 and the most recent English version was published in 2000.[44] The assessment of drug-induced movement disorders is based on the Sct. Hans Rating Scale for Extrapyramidal Syndromes (SHRS), the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Scale (BAS), and Fahn-Marsen Dystonia Movement Scale with the addition of three new subscales for the assessment of tremor, ataxia, and global assessment of relevant psychiatric syndromes. The SADIMoD consists of a standard examination, recorded on videotape to allowing later scoring of movement disorders. The scale contains several subscales: dyskinesia (7 items), dystonia (9 items), parkinsonism (8 items), akathisia (2 items), tremor (3 items), ataxia (5 items), and psychiatric symptoms (sedation, depression, psychosis, and anxiety) (4 items). Items are scored on a 5-point scale. Each subscale has a total score and a global impression score (0-4), with the latter offering the assessor the possibility to express his/her opinion concerning the true character of the observed movement disorder. A manual with video instruction is available. It takes about 30 minutes to complete the SADIMoD. The clinimetric characteristics of the SADIMoD have been well studied by Loonen et al. The internal consistency for the SADIMoD subscales is good, and the intrarater and inter-rater reliability are moderate to good. The parkinsonism subscale of the SADIMoD has a moderate but highly significant correlation with the SAS,[26,27] demonstrating the scale's concurrent validity. A major disadvantage of the SADIMoD is its complexity, which makes it time consuming to use, especially by inexperienced raters.

7. Simpson Angus Scale (SAS)

The SAS was developed in 1970. The scale consists of 10 items measuring gait (hypokinesia; 1 item), rigidity (6 items), and glabella tap, tremor, and salivation (1 item each). Items are scored on a 5-point scale (0-4). The scale was developed for the assessment of parkinsonism and related extrapyramidal adverse effects.[33] The total score is the sum of the separate items divided by 10, with a total score higher than 0.3 being indicative of parkinsonism. On the basis of ROC analysis, Janno et al suggested a cut-off value of 0.65, whereby specificity could be doubled without losing sensitivity (sensitivity of 1.0 and specificity of 0.62).[30] Hawley and colleagues published an instruction guide in 2003.[45] In 1980 the original SAS scale was modified to avoid the need for an examination table. Leg pendulousness was omitted and head dropping was changed to head rotation. However, the authors never published any material on this modified version and both published studies and clinical trials in Europe use the first version. The total assessment takes about 10 minutes.[29] Seven studies have assessed the scale's clinimetric characteristics. The internal consistency is good.[30,32,34] Although evaluated in different ways, the inter-rater reliability for total score appears to be good,[28,29,32-34] whereas data

are discrepant for the items tremor and salivation. We found a low weighted kappa for the item salivation, which could be explained by a limited range of scores rather than modest agreement.[32] With acceptance of one point difference on an item, we found 87 till 100 % of agreement between raters on all 10 items. Sweet at al found very low inter-rater reliability for the item tremor.[29] Three studies evaluated the validity of the SAS,[29,30,32] but two of these studies used an inappropriate reference test.[29,30] Janno et al based the diagnosis of neuroleptic induced parkinsonism (NIP) on DSM-IV criteria, but these criteria are not validated for NIP, and Sweet et al used the assessment by the author of the study as criterion standard, which represents information about reliability and not about validity. We chose the SADIMoD as reference test, based on its established reliability and validity. The SAS showed an acceptable correlation with the parkinsonism subscale of the SADIMoD.[32]

A disadvantage of the scale is that some items are difficult to score, such as the head drop item. Questions have risen whether the SAS properly evaluates the different aspects of parkinsonism. For example, 6 items measure rigidity whereas only 1 item measures bradykinesia. The items glabella tap and salivation seem not to discriminate between patients with and without DIP.[6,27]

8. The Sct. Hans Rating Scale for Extrapyramidal Syndromes (SHRS)

The SHRS is a multidimensional scale developed by Gerlach to quantify the severity of extrapyramidal symptoms (final version published in 1979). The scale consists of four categories scored on a 7-point rating scale (0-6): parkinsonism (8 items), dyskinesia (8 body areas, active and passive scored), and a global score for parkinsonism, hyperkinesia, dystonia and akathisia (for both psychic and motor akathisia). The internal consistency of the parkinsonism category is good. The inter-rater and intrarater reliability are good to excellent, with the highest reliability being observed with experienced raters.[35] Training in SHRS administration seems to be necessary or at least useful, but no training guide is available.[26,35] It is not clear how subscores and total scores should be interpreted. The parkinsonism scale and total AIMS score showed divergent validity, probably because the scales measure different domains of extrapyramidal symptoms.[35] There are insufficient data on the parkinsonism items to assess the scale's validity.

9. Udvalg for Kliniske Undersøgelse (UKU)

The UKU and its manual were developed by Lingjaerde et al in 1981 and updated in 1987 for the assessment of drug induced neurological adverse effects. The UKU is a rating scale consisting of 48 items scored on a 4-point scale (0-3) in four categories: psychic (10 items), neurological (8 items including 3 parkinsonism items), autonomic (11 items), and other side effects (19 items). In addition, both patient and physician score

the extent to which adverse effects interfere with activities of daily living. The UKU is intended for use by a trained investigator and takes 30–60 minutes to complete, which means that the UKU is not suitable for use in daily practice.[18] In an extensive description of the scale, Lingjaerde et al referred to 3 small not published clinimetric studies carried out in Scandinavia.[36] The results for inter-rater reliability are divergent: slight to very good agreement for the item rigidity, fair to very good agreement for hyperkinesia, and moderate to very good agreement for tremor.[36] Data about intrarater reliability and internal consistency are lacking. As mentioned before, 2 studies showed an acceptable correlation on total score with the LUNSERS.[18,19] Validity data for parkinsonism items are lacking. A patient self-rating version of the UKU - with transformation of items into descriptions of symptoms - was presented in 2001[37]. The correlation between patient-rated versus clinician-rated adverse effects regarding parkinsonism items is low, only the item tremor shows significant correlation.[37]

10. Yale Extrapyramidal Symptom Scale (YESS)

The YESS was developed by Mazure et al (1995) as a short, easy-to-use assessment scale for extrapyramidal symptoms. The scale consists of three parts: parkinsonism (rigidity, gait, arm sway, facial expression, and tremor), akathisia (objective and subjective), and dystonia, scored on a 5-point scale (0-4). The literature does not mention how long it takes to administer the test or whether training material is available. One study has evaluated the scale's clinimetric characteristics but internal consistency and intrarater reliability were not evaluated. The inter-rater reliability is good (k_w=0.60–0.80). Construct validity was assessed by comparing each parkinsonian item with corresponding items from Webster's scale. Although there was a good correlation with the parkinsonism items of Webster's scale,[38] the latter is a Parkinson's disease rating scale that is not validated for DIP and for this reason a questionable reference test.

Table 2. Metric characteristics of rating scales

		Characteristic			Reliability			Validity	
			Patients	Raters	Extern		Intern		
Name	**Study**	**Population**	**N**	**N**	**Intrarater**	**Inter-rater**			**Reference test**
DIEPSS	Kim 2002[20]	Schizophrenic IP	182	2	N=42 ICC 0.60-0.91	N=40 ICC 0.76-0.96	N=100 Cronbach's α 0.78	N=100 Concurrent validity Spearman's ρ : 0.92 (p<0.001) ROC analysis Cut-off score 5 sens 0.89 spec 0.92	SAS
ESRS	Chouinard 1980[16]	Schizophrenic OP IP				N=89 ICC 0.8-0.97 N= 64 ICC 0.88-0.97			
LUNSERS	Day 1995[18]	Schizophrenic OP	50/10	1/2	N=50 Pearson's ρ Item = 0.579 (0.264-0.834) Total: 0.811		N=50 Cronbach's α 0.89	Concurrent validity Pearson's ρ : Item: 0.605 (0.115-0.884) Total: 0.828 N=10 ROC analysis Cut-off score 26 sens 0.7 spec 0.75	UKU
	Lambert 2003[19]	Schizophrenic or affective IP and OP	29	1				Concurrent validity Spearman's ρ : Item: 0.11-0.70 Item in low RH: 0.16-0.84 Total : 0.48 Total in low RH: 0.58	UKU
	Jung 2005[21]	Schizophrenic or affective	83	1				LUNSERS PAR Pearson's ρ: 0.31 (p<0.05) LUNSERS EPS Pearson's ρ : 0.28 (p< 0.01) Shakiness item 81% correctly classified DIP	SAS BARS
	Yilmaz 2006[22]	Antipsychotic drug users	117	1	ρ = 0.81, p<0.02		Cronbach's α 0.89		

Mindham	Lamb 1976[23]	Schizophrenic IP	6	1				"comparable pattern "	Peg board Impulse counter
	Mindham 1976[24]	Schizophrenic IP	16	1				"comparable pattern"	Peg board Impulse counter
MPRC	Cassedy 1997[25]	Patients referred for drug induced movement disorders	1107	10 physicians, 2 nurses 4 social workers	N=32 ICC Total park score: 0.83 Global park score: 0.65	N=24 ICC Item: 0.41-0.89 Total: 0.90	N=1107 Cronbach's α 0.73		
SADIMoD	Loonen 2000[26] 2001[27]	Psychiatric IP with movement disorders	31	6 teams	Spearman's cor. coeff. Overall 0.38-0.88 Park 0.69	Kendall W 0.462-0.715, Park 0.643	Cronbach's α 0.75-0.94	Park subscale Spearman's ρ: Park 0.48 p<0.01 Park (global) 0.42 p<0.05	SAS
SAS	Lejoyeux 1993[28] *French version*	Psychotic schizophrenic IP	15	2		Student t-test 0.632 (NS)			
	Sweet 1993[29]	Geriatric IP	30	3		N=10 ICC Item: 0.15-0.90 Total: 0.79		ICC: 0.63-0.90	Author R.A.S
	Janno 2005[30]	Schizophrenic IP	99	1			Cronbach's α 0.79	Cut off 0.65 Sens 1.00, Spec 0.62	DSM IV by experienced rater
	Sanchez 2005[31]	Antipsychotic drug users	103	1			Cronbach's α 0.92 Interitem covariance Glabellar sign: 0.55 Other items 0.68-0.84		

		Characteristic			Reliability			Validity	
			Patients	Raters	Extern		Intern		
Name	**Study**	**Population**	**N**	**N**	**Intrarater**	**Inter-rater**			**Reference test**
	Knol 2009[32]	Geriatric IP (geriatric, psychiatric ward and nursing home)	15	3		Total: K_w 0.72 Item*: k_w 0.63-0.75 73 - 100 % ICC 0.88-0.93	Cronbach's α 0.83	Spearman's ρ : 0.66 with p<0.01	SADIMoD parkinsonism subscale
	Simpson and Angus 1970[33]	Psychotic IP	14	2		Correlation coeff Total score 0.87 Item 0.52-0.87			
	Calvo-Gomez 2006[34] *Validation of Spanish version*	Psychiatric IP	86		N=15 Pearson's ρ 0.86 Concordia de Lin 0.85 ICC 0.82	N=15 Total score Pearson's r 0.80 Concordia de Lin 0.80 ICC 0.81	Cronbach's α 0.92	Factor analysis: glabella tap no contribution towards total variability	SAS English version and ESRS
SHRS	Gerlach 1993[35]	Schizophrenic IP	30	7 [2 exp(a), 2 less exp(b), 3 inexperienced raters(c)]	Park. Score: Spearman's ρ a: 0.92-0.98 b: 0.88-0.94 c: 0.77-0.93	Park. items: ICC a: 0.92-0.98 b: 0.91-0.97 c: 0.75-0.81 Total group: 0.85-0.89	Park. items: Cronbach's α 0.82	Park. Items Spearman's ρ: -0.4 (divergent validity)	Total AIMS
UKU	Linjaerde 1987**[36] :								
	Lambert 2003[19]	*See LUNSERS*							

Danish study 1981	Schizophrenic or other Psychotic IP	6	5	ICC Neurol. Side Effects (SE) 0.40 p<0.05 hyperkinesia 0.28 p<0.01 tremor 0.60 p< 0.001		
Swedish study 1982	Schizophrenic or other Psychotic IP	5	6	ICC Neurol. SE 0.67 p< 0.001 Rigidity 0.88 p< 0.001 hyperkinesia 0.44 p< 0.001 tremor 0.73 p< <0.001		
Norwegian study*** 1982	Schizophrenic or other Psychotic IP	5	4	ICC Neurol. SE 0.83 p< 0.001 Rigidity 0.20 (ns) hyperkinesia 0.85 p < 0.001 tremor 0.89 p< 0.001		
Lindstrom, 2001[37]	Schizophrenic patients	63	1		UKU-SERS clin Spearman's ρ: Total score 0.46 p<0.01 Neurol. SE 0.09 (ns) Rigidity 0.13 (ns) Hyperkinesia 0.07 (ns) Tremor 0.39 p<0.01	UKU-SERS pat

		Characteristic			Reliability			Validity	
			Patients	Raters	Extern		Intern		
Name	**Study**	**Population**	**N**	**N**	**Intrarater**	**Inter-rater**			**Reference test**
	Day 1995[18]	*See LUNSERS*							
YESS	Mazure 1995[38]	Schizophrenic IP	41	2		Park. items k_w: 0.65- 0.80		Spearman's ρ : 0.74-0.91	Webster

* with exception of salivation

** data extracted from Linjaerde 1987[36]. Original data not available

*** improved version of the scale

Abbreviations: IP=inpatients; OP=outpatients; RH=Red Herrings; SE=Side Effect; SERS=Side Effect Rating Scale

Table 3. Feasibility of rating scales

Rating scale	Total items	DIP items	Manual available	Scoring *	Interpretation **	Duration (min)
DIEPSS	9	5	Y ***	clear	clear	?
ESRS			Y	clear / complex	unclear	15
Questionaire	7					
Examination	34	16				
Global impression	4					
LUNSERS			N	clear / complex	unclear	5-20
Self rating	51	4				
Mindham	9	9	N	clear	unclear	?
MPRC	31	16	N	unclear / complex	TD clear / DIP unclear	?
SADIMoD			Y	clear / complex	unclear	30
Examination	34	8				
Global impression	5	1				
Psychic symptoms	4					
SAS	10	10	Y	clear	clear	10
SHRS			N	clear	unclear	?
Examination	16	8				
Global impression	5	1				
UKU			Y	clear/ complex	unclear	30
Single items	48	3				
Global assessment (patient and physician)	2x2					
YESS	8	5	N	clear	unclear	?

* clear, description of rating per item; unclear, no description of rating per item; complex, > 30 items

** clear, cut off score available; unclear, no cut off score available

*** Japanese, English manual in press (T. Inada, written communication)

Discussion

In a systematic review of available literature, we identified 17 different rating scales used for the assessment of DIP. The most frequently used scale is the SAS, followed by the ESRS, UPDSR, H&Y, Webster, DSM IV, and Mindham. Although widely used to assess DIP, these rating scales have seldom been adequately evaluated for validity and reliability. The SAS and the Mindham are the only rating scales that have been validated exclusively for DIP in 5 and 2 studies, respectively. Indeed, the identified rating scales can be divided into three groups: scales validated for DIP (SAS, Mindham), scales validated for DIEPS including DIP (SAS, ESRS, UKU, DIEPSS, LUNSERS, MPRC, SADIMoD, SHRS, YESS), and scales validated for symptoms of Parkinson's disease (UPDRS, Webster and Columbia URS).

Although there is general agreement on the clinical definition of parkinsonism, there is no consensus on which instrument should be used to assess DIP. The currently available rating scales to measure DIP have certain advantages and limitations, with differences in scoring, the expertise needed to administer the scale, and the time need to complete it. Because scales should be based on a good conceptual approach, a scale measuring DIP should include items on bradykinesia, rigidity, tremor, and postural instability, the latter being especially relevant for older individuals. The rating scale should also be broad enough for the intended application, assessing neither too many nor too few items. It should be feasible and easy to administer by different trained healthcare professionals and have a clear system for scoring items and interpreting results. Lastly, and most important, evidence for reliability and validity should be available. Unfortunately, none of the scales identified satisfied these requirements completely.

The DIEPSS, YESS, Mindham, SHRS, and SADIMoD parkinsonism subscale have a good construct for parkinsonism. But although the SADIMoD had the best evidence for reliability and validity, its complexity does not make it ideal for use in daily practice. The SHRS has good reliability, but validity data are lacking; however, the results of the clinimetric evaluation of the SADIMoD by van Loonen et al could be used because the parkinsonism subscale of the SADIMoD is identical to the parkinsonism part of the SHRS. The instruction video of van Loonen could also be used for the SHRS.[44] A disadvantage of the SHRS is the lack of clarity about the interpretation of subscores and total scores. The DIEPPS is mainly used in Japan and showed good reliability and validity in a Korean study. Although the original version and the Japanese guide for this scale were not available to us, Kim and Inada refer to this guide when they describe clear cut-off points for parkinsonism and easily performance.[13,20] Translation of this guide into English and confirmation of its clinimetric characteristics in a non-Asian population could make this instrument interesting for use in daily practice in Western countries. The YESS was designed to be brief and easy-to-administer instrument, but there is no information about how long it takes to complete and about the availability of training material. With

the exception of inter-rater reliability, which is good, reliability and validity have been inadequately evaluated, so we cannot make recommendations about this scale. The Mindham scale also cannot be recommended, mainly because of the lack of adequate clinimetric data, the lack of an instruction guide, and the lack of information about how scores should be interpreted.

The SAS is used the most often to evaluate DIP. The scale is easy to administer by trained healthcare professionals and a guide is available. With exception of the items tremor and salivation, we found evidence that the SAS has moderate to good reliability and acceptable validity. Although the SAS emphasizes rigidity, there was an acceptable correlation between the SAS and the SADIMoD, which consists of 4 bradykinesia items and 1 rigidity item, thereby confirming that variation in items does not necessarily influence the concept. Validation studies for the ESRS, MPRC and the self-rating scales LUNSERS and UKU are lacking or an inappropriate reference test for parkinsonism was used. Moreover, these scales are complex and time consuming to administer and thus cannot be recommended.[46]

In summary, none of the scales identified in this systematic review fulfill all the criteria of an appropriate rating scale for DIP. The SAS and SHRS are valid and easy-to-use instruments to evaluate DIP; however, it can be questioned whether the two scales actually measures all aspects of parkinsonism. The acceptable correlation between these two rating scales indicates that variation in these rating scales does not influence the concept of parkinsonism. If the DIEPSS were to become available in English and its clinimetric characteristics confirmed in a Western population, we would recommend it as rating scale for DIP. The construct and performance of the Mindham scale makes it attractive but the scale needs to be properly evaluated before it can be recommended.

Thus further research is needed to develop an optimized instrument for evaluating DIP that can be used in daily clinical practice and which has clear instructions on how to examine the patient, how to score movement disorders, and how to interpret scores.

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Chapter 2.2

Validity and reliability of the Simpson Angus Scale (SAS) in drug induced parkinsonism in the elderly

Wilma Knol
Carolina J.P.W. Keijsers
Paul A.F. Jansen
Svetlana V. Belitser
Alfred F.A.M. Schobben
Toine C.G. Egberts
Rob J. van Marum

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Abstract

Background
Quantification of drug induced parkinsonism (DIP) for study purposes is difficult. The most often used Simpson Angus Scale (SAS) lacks proper clinimetric evaluation. The newer Schedule for Assessment of Drug-Induced Movement Disorders (SADIMoD) shows good clinimetric characteristics, but has not been used in published clinical studies, probably due to complexity of the scale.

Objectives
To evaluate internal consistency and inter-rater reliability of the SAS and the correlation of the SAS with the parkinsonism subscale of the SADIMoD in elderly.

Method
Fifteen elderly diagnosed with DIP were recruited. The patients were three times assessed with the SAS by three independent investigators. The resident also performed the SADIMoD. Internal consistency was measured by Cronbach's α-coefficient, inter-rater variability was examined with weighted kappa values and percentage of agreement and correlation to SADIMoD by Spearman's correlation coefficient.

Results
SAS demonstrated good internal consistency reliability (Cronbach's α coefficient 0.83). Inter-rater reliability for sum score was good. For individual items slight agreement on the item salivation and moderate to very good agreement on remaining items calculated by weighted kappa values was reached. We found 87 till 100% agreement on the individual items with acceptance of one point difference between raters. The SAS demonstrated acceptable correlation with the SADIMoD parkinsonism subscale scores (Spearman's rho=0.66; $p<0.01$).

Conclusion
The SAS appears to be a valid and by different instructed health care professionals easy to perform research tool to evaluate DIP.

Introduction

One of the drawbacks of antipsychotic drug (APD) use is the induction of parkinsonism. This drug induced parkinsonism (DIP) is characterised by tremor, bradykinesia, rigidity and postural instability[1]. In the elderly, 30-70% treated with antipsychotics develop DIP,[2,3] which is often not recognised in clinical practice.[4]

The Simpson Angus Scale (SAS) is the rating scale most frequently used in clinical studies, although limited clinimetric data - in particular concerning validity - on this instrument have been published.[5-10] An important limitation of the only published evaluation study is the used reference test.[9] The NIP diagnose was based on DSM-IV criteria, although these criteria are not validated for NIP. Other suggested disadvantages of the SAS are: unclear instructions for the assessment, difficulty in scoring the items head dropping and gait and focussing mainly on rigidity, leaving other aspects of parkinsonism (e.g. tremor, bradykinesia) underascertained.[8,11]

The difficulty in studying the validity of DIP measuring instruments is the lack of a reference test.[1,2] The Schedule for Assessment of Drug-Induced Movement Disorders (SADIMoD) is the instrument most extensively evaluated for clinimetric characteristics and shows good evidence for validity and reliability.[8,11] Unfortunately, it has not been used in published clinical studies yet.

In this study we evaluate internal consistency and inter-rater reliability of the SAS performed by different health care professionals and calculate the correlation of the SAS with the parkinsonism subscale of the SADIMoD in elderly.

Methods

Participants

In the period April until June 2006, all patients aged 60 and older admitted to the department of Old Age Psychiatry of Altrecht, a mental health care center in the region of Utrecht and a psychiatric department of nursing home Rosendael in Utrecht were consecutively screened by their psychiatrist or nursing home physician. These physicians were asked to diagnose DIP based on the clinical assessment (i.e. without using instruments) of tremor, muscular rigidity, bradykinesia and/or postural instability developing after starting or raising the dose of drugs known for causing extrapyramidal side effects. When the psychiatrist or nursing home physician observed at least two of these signs, DIP was diagnosed and the patient was included for the study. In total 15 patients were diagnosed as having DIP. All 15 participants or legal representatives gave written informed consent. This study is part of our research project "Antipsychotic induced parkinsonism in the elderly" which is approved by the Dutch Central Committee on Research involving Human Subjects.

Data collection

In each patient the SAS was assessed and repeated after one and two weeks by three independent investigators; one geriatrician, one physiotherapist and one resident in geriatric medicine. This time period of one week was chosen to prevent recall effects. All investigators had previously received training by an instruction guide and instruction video.[13]

During the assessment the primary investigator (geriatrician) gave all verbal instructions to the patients. All raters observed the assessment of all items and carried out the necessary examination individually (all items with exception of gait, arm dropping and glabella tap). All raters viewed and scored this assessment at the same time. They were blinded for the scores of each other. The resident also evaluated drug induced movement disorders by means of the SADIMoD on the same day as the first assessment of the SAS. Even though we only wanted to use the parkinsonism subscale it was necessary to perform the complete SADIMoD and videotape the patient to complete the score form. The resident underwent training by studying the SADIMoD manual, the prescribed examination materials and an instruction video. The instruction video contains background information on the SADIMoD and some typical movement disorders and examples of examinations with corresponding scores of three patients.

Rating Scales

Simpson Angus Scale

The Simpson Angus Scale was developed in 1970 for the assessment of DIP and related extrapyramidal side effects. The scale consists of 10 items, one item measuring gait (hypokinesia), six items measuring rigidity and three items measuring glabella tap, tremor and salivation, respectively. Each item has to be scored on a 5-pointsscale (0-4). The total score is the sum of the separate items divided by ten. A total score over 0.3 indicates extrapyramidal symptoms. Hawley and colleagues published an instruction guide in 2003.[13] In 1980 the original Simpson Angus scale has been modified to avoid the need for an examination table. The leg pendulousness has been omitted and head dropping has been changed in head rotation. As the authors never published any material on this modified version and both published studies and running clinical trials in Europe use the first version, we evaluated the original version. The total assessment takes about 10 minutes.

The Schedule for the Assessment of Drug-Induced Movement Disorders (SADIMoD)

The SADIMoD was developed in 1994 for the assessment of drug induced movement disorders, based on the Sct. Hans Rating Scale for Extrapyramidal Syndromes (SHRS), the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Scale (BAS), Fahn-Marsen Dystonia Movement Scale with addition of three new subscales for the

assessment of tremor, ataxia and global assessment of relevant psychiatric syndromes. The SADIMoD consists of a standard examination, recorded on videotape to be able to score different items of movement disorders afterwards and complete the rating form. The scale contains several subscales: dyskinesia (7 items), dystonia (9 items), parkinsonism (8 items), akathisia (2 items), tremor (3 items), ataxia (5 items) and psychiatric symptoms (sedation, depression, psychosis and anxiety) (4 items). Each item has to be scored on a 5-point scale. Every subscale has a total score and a global impression score (0-4) by the assessor. With this global score the examiner can also express his/her opinion concerning the true character of the observed movement disorder. A manual with video instruction is available. It takes about 30 minutes to complete the SADIMoD.

Data analysis

Internal consistency

Internal consistency measures whether the individual items that compose the scale are related to each other. The internal consistency of the SAS is expressed by the Cronbach α-coefficient.[14] This coefficient tests the sufficiency with which one item can substitute for the other. A Cronbach coefficient of 0.70 or higher is considered acceptable.[15] In order to evaluate correlation of individual items with overall score on the scale we also calculated values for Corrected Item-Total Correlation and the Alpha if Item Deleted, a value of the overall alpha if a certain item is not included in the calculation. A value for corrected item-total correlation less than about 0.3 means that the particular item does not correlate very well with the overall score on the scale.

Inter-rater reliability

The inter-rater reliability is the agreement between multiple assessments made by two or more raters. A weighted kappa with quadratic weights (k_w) was calculated with 95% confidence intervals (CI) for each item of the SAS and the total score. Total scores above the cut off of 0.3 were equally divided in categories (0-0.3, 0.4-1.2, 1.3-2.2, 2.3-3.1 and 3.2-4.0). The kappa statistic estimates the proportion of agreement among observers after chance agreement (the proportion of agreement expected if the observer's rating were completely random) has been removed. A K_w adds different weights to disagreement according to the magnitude of discrepancy in ordinal data.[16] We interpreted kappa values, by using criteria proposed by Landis and Koch[17] < 0.20 slight agreement, 0.21 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 good agreement and 0.81 to 1.0 very good agreement. We also evaluated inter-rater reliability with intra-class correlation coefficient (ICC). The ICC is a parametric measure

assessing rating reliability by comparing the variability between subjects to the total variability.[18] The values of the ICC range between 0 and 1, with a higher value indicating that less variance is due to other factors such as differences between observers. The ICC was calculated as a two-way mixed effects model with absolute agreement.[19] The scores of the resident and the physiotherapist were compared to the scores of the geriatrician. Multiple-rater kappa was calculated as average of all pairwise kappa's.[20] For each calculation only the first SAS ratings were used.

Concurrent validity

Concurrent validity is a form of criterion-referenced validity. It measures the degree to which the scores on a test are related to the scores on another, already established, test administered at the same time. Validity is expected between scales that measure the same clinical symptoms. Spearman correlation coefficient and associated two-tailed p value were calculated for the SAS and the parkinsonism assessing sub-scale of the SADIMoD. The degree of agreement is expressed in rho, which can take any value from -1 to +1. A high coefficient correlates with good concurrent validity, although a clear, generally accepted cut-off value lacks. This analysis was performed on the first ratings only.

All data were screened for irregularities before analysis. The missing data were included as such in subsequent analyses. Analyses were performed with SPSS for Windows, version 12.0 and S-Plus, version 6.12 and R with library 'irr'.

Results

Patient Characteristics

Of the 15 recruited patients 11 (73%) were females. Age ranged from 67 to 91 years, with a mean age of 77.6 years. Ten patients (68%) used conventional antipsychotics, four patients used atypical antipsychotics (27%) and one patient (6.7%) used a SSRI. The mean scores of each single SAS item are presented in Table 1.

Table 1. Mean scores of Simpson Angus Scale (SAS) items by three different raters with standard deviation (SD)

SAS item	Geriatrician		Physiotherapist		Resident	
	mean	SD	mean	SD	mean	SD
Gait	1.86	1.3	2.40	1.55	1.73	1.03
Arm dropping	1.13	1.19	1.20	1.21	1.00	0.845
Shoulder shaking	0.40	0.91	0.60	0.91	1.13	0.83
Elbow rigidity	1.33	0.98	1.27	0.96	1.53	0.83
Wrist rigidity	1.33	1.23	0.93	1.22	1.73	0.96
Leg pendulousness	1.07	1.10	1.40	1.35	1.33	1.29
Head dropping	0.43	0.65	0.57	1.16	0.43	0.51
Glabella tap	1.00	1.51	1.00	1.51	0.47	0.92
Tremor	0.87	0.74	0.67	0.90	1.27	0.88
Salivation	0.20	0.41	0.07	0.26	0.40	0.63

Two participants withdrew from the study, one after the first and the other after the second assessment. This last participant also refused the head dropping item during the first and second SAS assessment.

Internal consistency

For the three successive assessments the Cronbach's α-coefficients were 0.83, 0.87 and 0.90 indicating that the SAS demonstrates good internal consistency. Table 2 shows corrected item-total correlation, the correlations between each item and the total score on the SAS. The items head dropping and salivation do not correlate very well with the overall score from the scale. Deleting of items head dropping and salivation leads to Cronbach's α of 0.84, 0.87 respectively 0.89. Deleting of only salivation leads to Cronbach's α of 0.84, 0.89 respectively 0.90.

Table 2. Internal consistency individual items

	Corrected item-total correlation		
	1st SAS	2nd SAS	3rd SAS
Gait	0.655	0.653	0.680
Arm dropping	0.648	0.773	0.746
Shoulder shaking	0.665	0.745	0.790
Elbow rigidity	0.788	0.768	0.829
Wrist rigidity	0.653	0.827	0.761
Leg pendulousness	0.771	0.749	0.721
Head dropping	0.177	0.428	0.589
Glabella tap	0.374	0.434	0.515
Tremor	0.364	0.448	0.525
Salivation	-0.055	0.116	0.388

Inter-rater reliability

Percentage agreement and K_w are displayed in table 3. Inter-rater reliability for overall score was good for the resident and very good for the physiotherapist compared to the geriatrician (k_w 0.71 and 0.85 respectively). Arm dropping, shoulder shaking, glabella tap and salivation showed slight to moderate agreement for the resident (k_w 0.19 – 0.53). For the physiotherapist only arm dropping (k_w 0.58) had moderate agreement, but salivation (k_w -0.11) even showed weaker agreement than expected by chance. 87 till 100% agreement on the individual items was reached with acceptance of one point difference between raters on a 5 point scale. Reliability was high with ICCs for overall score ranging from 0.88 to 0.93.

Concurrent validity

The concurrent validity was expressed as Spearman's correlation coefficients for the parkinsonism assessing subscale of the SADIMoD and the sum score of the SAS. A Spearman 's rho of 0.66 with a significance value < 0.01 was found. This means that the SAS demonstrates acceptable correlation with the subscale of the SADIMoD with high significance.

Table 3. Inter-rater reliability: weighted kappa values and percentages agreement

	Resident vs geriatrician			Physiotherapist vs Geriatrician			Resident vs Physiotherapist			All 3 raters
	(k_w)	95%CI	perc agreement	(k_w)	95%CI	perc agreement	(k_w)	95%CI	perc agreement	(k_w)
Gait	0.85	0.65 to 1.0	93%	0.77	0.56 to 0.98	88%	0.64	0.40 to 0.87	73%	0.75
Arm dropping	0.53	0.36 to 0.71	93%	0.58	0.18 to 0.98	87%	0.77	0.61 to 0.93	93%	0.63
Shoulder shaking	0.49	0.21 to 0.77	93%	0.79	0.64 to 0.94	100%	0.53	0.12 to 0.94	93%	0.60
Elbow rigidity	0.79	0.63 to 0.94	100%	0.73	0.53 to 0.93	100%	0.58	0.24 to 0.92	93%	0.70
Wrist rigidity	0.73	0.59 to 0.86	100%	0.78	0.59 to 0.96	93%	0.49	0.22 to 0.76	73%	0.67
Leg pendu-lousness	0.85	0.75 to 0.96	100%	0.75	0.55 to 0.95	93%	0.86	0.75 to 0.96	100%	0.67
Head dropping	0.77	0.55 to 1.0	100%	0.74	0.65 to 0.83	93%	0.43	0.22 to 0.64	93%	0.65
Glabella tap	0.54	0.05 to 1.0	87%	0.94	0.88 to 0.99	100%	054	0.08 to 1.0	87%	0.67
Tremor	0.72	0.45 to 0.98	100%	0.75	0.44 to 1.0	100%	0.67	0.44 to 0.91	100%	0.71
Salivation	0.19	-0.33 to 0.71	100%	-0.11	-0.29 to 0.06	100%	0.15	-0.16 to 0.45	93%	0.07
Overall score	0.71	0.56 to 0.86	73%	0.85	0.65 to 1.0	80%	0.60	0.37 to 0.81	67%	0.72

Discussion

In this study, the clinimetric properties of the SAS were evaluated. Firstly, the SAS shows good internal consistency with a Cronbach's alpha coefficient far above the required 0.70. Nevertheless the item salivation correlates poorly with the overall score. Cronbach's alpha scores increase slightly when the item salivation is omitted from the scale. As this item does not contribute to an improvement of evaluation of parkinsonism it can be deleted from the score.

Secondly, the inter-rater reliability of the SAS, administered by different instructed health care professionals, is good. To measure inter-rater reliability we calculated weighted kappa coefficients and also the intraclass correlation coefficient (ICC) for the total score. The results of the ICC did not deviate from the calculated kappa's. Although the kappa statistic is a popular measure for estimating inter-rater agreement and the use is common for data, it has shortcomings. The most striking problem is that the value of kappa depends upon the proportion of subjects (prevalence) in each category and the number of categories. As the raters mostly scored zero or one point and only once three points on the item salivation we found a low kappa value, representing a limited range of scores instead of slight agreement. To overcome this problem we calculated percentage of agreement between raters. We found 81 till 100 percent agreement with acceptance of one point difference on the items. We consider these results acceptable for use in daily clinical practice. In this study we assessed the SAS three times in order to evaluate the intra-rater agreement. Comparing the first and second ratings, agreement with acceptance of one point difference was reached in 9 patients: in 4 patients the severity of parkinsonism remained stable, in 2 patients the severity diminished and in 3 patients it increased. In the remaining 5 patients the results were varying. Although we were not able to calculate intra-rater agreement because of fluctuations in seriousness of parkinsonism, we can assume that the intra-rater agreement will be good considering the good inter-rater agreement we demonstrated.

Finally, the SAS showed acceptable correlation with the parkinsonism subscale of the SADIMoD, which was chosen as reference test based on its established reliability and validity. An important disadvantage of the SADIMoD is the necessity to carry out the complete assessment of 30 minutes and the availability of a video camera to be able to fill in the rating form afterwards and assess DIP. This complexity and time-consuming nature makes the SADIMoD less useful for routine application.

Although the results of this study suggest that the SAS is a valid tool to evaluate DIP there are some limitations. The lack of of clear instructions for examining and scoring of some items of the SAS has been criticised.[8,11,13] To overcome these difficulties we used the guide published by Hawley and developed an instruction video which contains an example of the examination of one patient with the SAS. Even though we examined

elderly with physical and cognitive impairment we did not experience major difficulties in the assessment.
Questions have risen whether the SAS is a good indicator of parkinsonism. Clinical experience shows that bradykinesia is frequently the first symptom of drug induced parkinsonism. The SAS includes 6 items measuring rigidity while only 1 item measures bradykinesia. The SADIMoD on the other hand consists of only 1 item measuring rigidity and 4 items measuring bradykinesia. A problem can be that bradykinesia may be caused by the psychiatric illness itself. So, in patients using APDs, it is difficult to distinguish akinesia as a adverse effect of treatment from a symptom related to the psychiatric illness.[19] Despite the differences in items we found acceptable correlation between the SAS and the parkinsonism subscale of the SADIMoD, confirming the results of Loonen et al, indicating that variation in these measuring scales do not influence the concept of parkinsonism.

In conclusion, the results of our study show that the SAS is a valid research tool to evaluate DIP. As it is also easy to perform by different instructed health care professionals the SAS can be used in daily clinical practice. The score can be simplified by omitting the item salivation and reducing rigidity items. Addition of more bradykinesia measuring items is advisable. Further research is needed to develop an optimized measuring instrument for drug induced parkinsonism applicable in the elderly in daily clinical practice.

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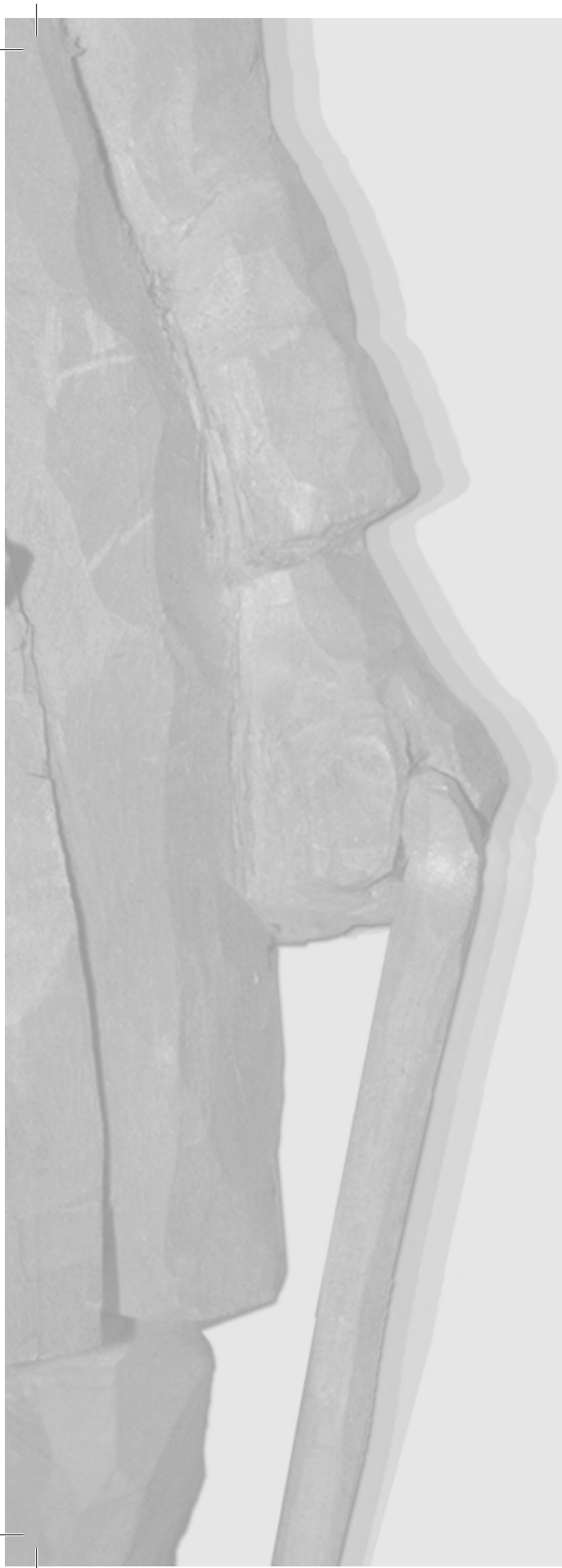


Chapter 3

Causes

Chapter 3.1

Haloperidol induced parkinsonism in elderly patients: relation with dose, plasma concentration and duration of use

Wilma Knol
Rob J. van Marum
Paul A.F. Jansen
Toine C.G. Egberts
Alfred F.A.M. Schobben

Abstract

Factors that influence the variation in occurrence of antipsychotic induced parkinsonism (AIP) in elderly have not been well elucidated. The aim of this study was to investigate the association between haloperidol induced parkinsonism and prescribed dose, plasma concentration and duration of use of haloperidol in elderly patients in a cross-sectional design.

This study included 150 inpatients aged 65 years and older who were treated with haloperidol. Parkinsonism assessed by the Simpson Angus Scale was present in 46% of the included patients. Prescribed haloperidol dose varied from 0.3-5.0 mg/day. Plasma concentration ranged from 0.13-4.11 µg/l, with one outlying measurement (21.43 µg/l). Dose is moderately, but significantly associated with haloperidol plasma concentration (weighted R^2=0.32; $p<0.001$). Variability in the total score on the SAS could not be explained by the variability in dose or concentration (resp. R^2=0.003 and 0.001). A not statistically significant trend toward a higher risk of AIP in elderly patients with a longer duration of use of haloperidol was observed; the OR for use longer than 3 months compared to use less than 2 weeks is 2.35 (95% CI 0.77-7.19). Smoking showed to be not significantly protective in the development of AIP (crude OR 0.39; 95% CI 0.15-0.997 and adjusted OR 0.44; 95% CI 0.17-1.17).

In a clinical practice setting dose or plasma concentration of haloperidol is not associated with occurrence of AIP. This study does not support the hypothesis of the peripheral pharmacokinetic explanation for the high prevalence of AIP and differences in AIP sensitivity in elderly during treatment with haloperidol.

Introduction

Despite the risk of serious adverse effects, antipsychotics are frequently prescribed to elderly patients for the treatment of acute and chronic psychotic symptoms or behavioural symptoms in dementia. The reported prevalence of antipsychotic drug use in nursing home residents varies between 12% and 52%.[1-3] A recent Italian study in a general population showed that haloperidol was still the most frequently prescribed antipsychotic drug in elderly.[4] Antipsychotic induced parkinsonism (AIP), which is characterized by tremor, bradykinesia, rigidity and postural instability during the use of an antipsychotic drug, affects about 40% of patients using conventional antipsychotics and may persist for several months after discontinuation of antipsychotics.[5,6] AIP can have a large impact on the patients' quality of life and may be a reason for stopping antipsychotic treatment or non-compliance.[7,8]

The efficacy and tolerability of antipsychotic drugs has been linked to their binding to dopamine D2 receptors.[9] Besides that elderly people are more prone to develop AIP, there are also notable variations in occurrence of this adverse effect in elderly people.[10] Guidelines advise the use of lower doses of antipsychotics in older patients. Potential mechanisms underlying the influence of age on antipsychotic (adverse-) effects are not clear. Furthermore factors that influence the variation in occurrence of AIP have not been well elucidated. Suggested explanations are either higher plasma concentrations in the elderly for a given dose (peripheral pharmacokinetic hypothesis), an increased brain access and distribution for a given plasma level (central pharmacokinetic hypothesis) or increased sensitivity at the receptor level (the pharmacodynamic hypothesis).[11]

Few studies have examined the relationship between oral dosage and plasma concentration of haloperidol or between dose or plasma concentration of haloperidol and occurrence of parkinsonism in elderly people. In the four available studies that examined these relationships in elderly, contradictory results were found.[12-15] Two studies showed a strong correlation between dose and plasma level of haloperidol. Of these, one study showed that plasma concentration showed stronger relation with extrapyramidal symptoms (EPS) compared to dose.[12] In contrast to haloperidol dose, plasma concentration was a significant predictor of EPS in the second study.[13] In the two other studies no significant relationship was found between haloperidol dose and plasma concentration and between haloperidol dose or serum concentration and EPS.[14,15] A clear explanation for these discrepancies is lacking.

Given these contradictory findings we studied the prevalence of AIP in elderly patients during treatment with haloperidol in a clinical practice setting and investigated the association between prescribed dose, plasma concentration, duration of use and AIP.

Materials and methods

Design, setting and study population

A cross-sectional study was performed in the department of old age psychiatry of three mental health care centers, the geriatric department of two hospitals and in eleven nursing homes in the centre of the Netherlands. On a random chosen date in the period of April to September 2008 in each participating centre the treating physicians identified all patients aged 65 and older who had been treated for at least five consecutive days with haloperidol. Excluded were terminally ill patients and patients previously diagnosed with Parkinson's disease or non-drug parkinsonism. Also patients using an anticholinergic antiparkinsonian drug (biperiden, trihexyphenidyl or dexetimide) indicated for treatment of drug induced parkinsonism (DIP) were excluded, since use of these drugs interferes with proper assessment of AIP. The physician asked all eligible patients and their legal representatives permission to be approached for this study. Written informed consent was obtained by the investigators from all participants or their legal representatives if patients were considered to be incapacitated. The assessment of AIP and collection of all determinants took place on the same day. The study was approved by the Dutch Central Committee on Research involving Human Subjects.

Outcome

Primary outcome of the study was the presence of AIP. In each patient the Simpson Angus Scale (SAS) was scored by an investigator, who was trained using an instruction guide and an instruction video.[16] The SAS consists of ten items, one item measuring gait (bradykinesia), six items measuring rigidity and three other items measuring glabella tap, tremor and salivation. Each item has to be scored on a 5-pointsscale (0-4). The total score of the SAS is obtained by summing the score of each of the ten items and dividing the sum of total score by 10 (range total score 0-4). The SAS is the most frequently used rating scale for the assessment of DIP and has shown to be a valid and easy to perform research tool.[17,18] Since many participants in this study were not able to walk independently, the score on the SAS was adapted by excluding the gait-subscore and standardizing the total score by summing the score of the nine remaining items and dividing the sum of total score by nine (range total score 0-4). Traditionally, a total SAS score of 0.3 or more is defined as parkinsonism.[19] Based on ROC analysis, Janno et al suggested a cut-off value of 0.65, whereby specificity could be doubled without loosing sensitivity.[20] Supported by these results and our own clinical experience we chose a total score ≥ 0.65 on the SAS as definition for the presence of AIP.[18]

Determinants

The investigators obtained the following data from the medical record: duration and current dosage of haloperidol, indication for haloperidol treatment, general characteristics (e.g. age, sex, race, smoking habits) and medical history including diagnosis of dementia and parkinsonism. Concomitant medication use included anticholinergic drugs according to the definition of Chew et al and drugs that have been reported to possibly induce extrapyramidal symptoms.[21,22]

Since older patients in general receive lower doses of haloperidol than the defined daily dose (8 mg), the daily dose was categorized into <1 mg, 1-2 mg, ≥2 mg. Duration of haloperidol use was assessed and subdivided in less than 14 days, 14 days – 3 months, and longer than 3 months.

Cognitive functioning was determined by the treating physician of the participants according to the Reisberg Global Deterioration Scale.[23] Diagnosis of dementia was based on a diagnosis mentioned in the medical record or cognitive impairment stage 4 or higher according to the Reisberg scale.

Blood samples were collected at least three hours after drug intake into a tube with EDTA-Na for determination of haloperidol concentration. Serum haloperidol concentration was determined using a validated liquid chromatography / mass spectrometry method according to Hoja et al with slight modifications.[24]

Statistic Analysis

Statistical Package for the Social Sciences (SPSS) version 15.0 was used for data analysis. Differences in characteristics in patients with and without AIP were tested using t-test, Mann-Whitney tests and chi-square tests. A two-tailed p-value of below 0.05 was considered statistically significant. The association between dose and concentration of haloperidol was investigated by weighted ($1/x^p$) least squares linear regression analysis. The association between total score on the SAS and respectively dose and plasma concentration of haloperidol was investigated by linear regression analysis with analysis of variability.

The association between AIP and respectively dose, plasma concentration and duration of use of haloperidol was investigated by multivariate logistic regression taking into account potential confounding covariates. Covariates were included in the regression model if they were univariately associated with AIP ($p<0.10$).[25] A value of 0.65 on the SAS was used as dichotomisation threshold for the analysis of AIP.

Results

All 157 selected patients or their legal representatives gave informed consent for participation in this study. Seven patients were excluded because of use of an anticholinergic antiparkinsonian drug. In six patients information about duration of treatment with haloperidol was missing.

AIP was present in 46% of the 150 patients in this study. The mean total SAS score in patients with AIP was 1.06. Characteristics of these 150 patients are presented in Table 1. Age, gender, use of anticholinergic drugs or drugs that have been reported to possibly induce extrapyramidal symptoms (metoclopramide [3], domperidon [1], cinnarizine [2], valproic acid [4], promethazine [1]) were not significantly different between patients with or without AIP. The most common indication of treatment with haloperidol was behavioural disorders in dementia (66.7%). The majority (87.3%) of all patients were diagnosed with dementia.

Relatively low doses of haloperidol were prescribed, from 0.3 up to 5.0 mg/day. Haloperidol plasma concentration ranged from 0.13 to 4.11 µg/l, with one outlying measurement of 21.43 µg/l (with daily dose of 2 mg). With exclusion of this single outlying measurement of 21.43 µg/l dose of haloperidol is moderately, but significantly associated with haloperidol plasma concentration (B=0.53, R^2=0.34; p<0.001 and weighted R^2=0.32; p<0.001) (figure 1).

Figure 1. Relation dose and plasma concentration of haloperidol

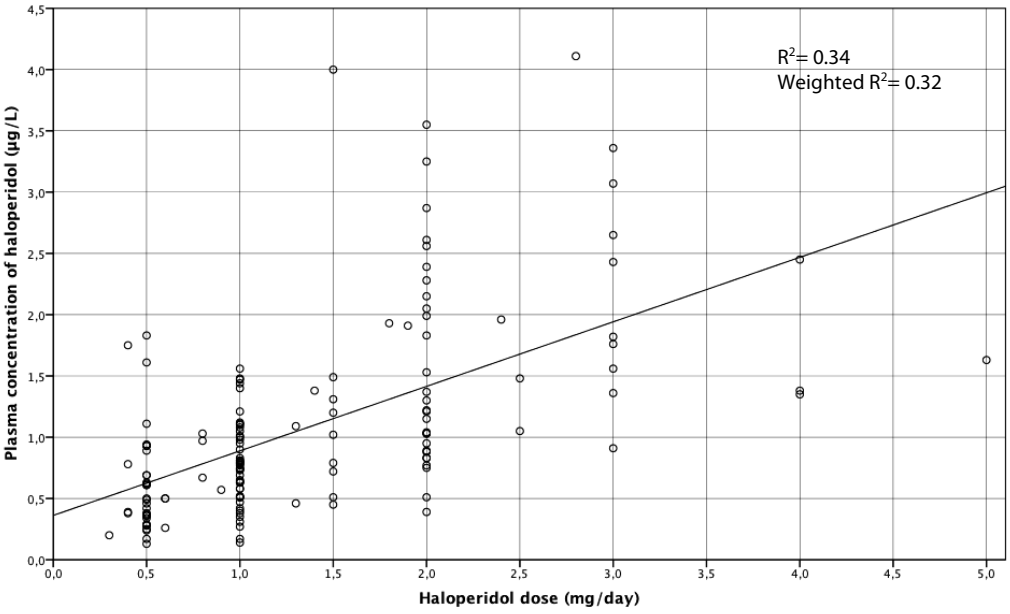


Table 1. Characteristics of elderly with and without antipsychotic induced parkinsonism (AIP)

Characteristics	AIP (N= 69)				No-AIP (N= 81)				p-value
	N	mean	SD	%	N	mean	SD	%	
Age –years		83.9	7.8			82.2	7.5		0.17
65 – 74	7			10.1	15			18.5	
75 – 84	27			39.1	34			42.0	
≥ 85	35			50.7	32			39.5	
Female	44			63.8	58			71.6	0.31
Indication haloperidol									0.55
Delirium	9			13.0	12			14.8	
Behavioural and Psychological Symptoms of Dementia	49			71.0	51			63.0	
Psychosis or other indication	11			15.9	18			22.2	
Daily dose									0.10
< 1 mg	13			18.8	28			34.6	
1 -2 mg	32			46.4	30			37.0	
≥ 2 mg	24			34.8	23			28.4	
	N	median	SD	%	N	median	SD	%	
Plasma concentration haloperidol in µg/l		0.93	0.8			0.83	2.4		0.71
< 1.0 µg/l	38			55.1	48			59.3	
1.0 – 2.0 µg/l	22			31.9	25			30.9	
≥ 2.0 µg/l	9			13.0	8			9.9	
Duration of use									0.33
5- 14 days	6			8.8	11			14.5	
14 days – 3 months	22			32.4	29			38.2	
≥ 3 months	40			58.8	36			47.4	
Smoking	7			10.1	18			22.2	0.05
Dementia	61			88.4	70			86.4	0.72
Drugs associated with extrapyramidal symptoms	7			10.1	4			4.9	0.22
Anticholinergic drugs	8			11.6	8			9.9	0.73
Living situation									0.12
Geriatric ward	3			4.3	6			7.4	
Psychiatric ward	5			7.2	14			17.3	
Nursing home	61			88.4	61			75.3	

Figure 2 shows the relationship between dose of haloperidol and AIP, both represented as continuous variables in a scatter diagram. We found a very low R square of 0.003 (p=0.5).

Figure 2. Relation dose of haloperidol and total score Simpson Angus Scale

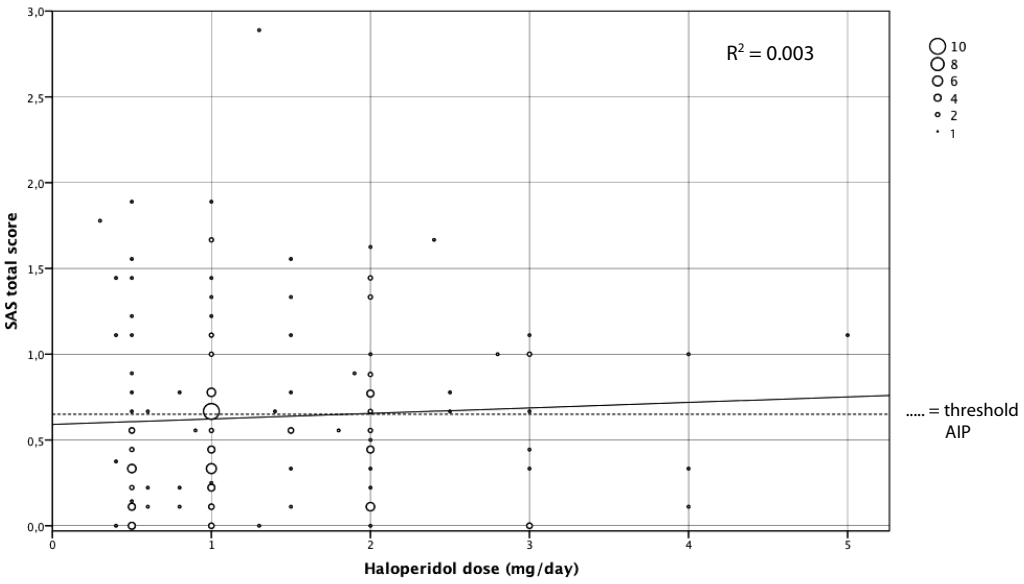


Figure 3 shows the relationship between plasma concentration of haloperidol and AIP, also represented as continuous variables in a scatter diagram. We found a very low R square of 0.001 (p=0.67). No further statistics were explored as neither dose nor plasma concentration was significantly associated with AIP.

A not statistically significant trend toward a higher risk of AIP in elderly patients with a longer duration of use of haloperidol was observed (figure 4 and table 2). The adjusted OR for use 14 days until 3 months and longer than 3 months compared to use less than 2 weeks are 1.55; 95% CI 0.48-4.55 and 2.35; 95% CI 0.77-7.19, respectively.

Figure 3. Relation plasma concentration of haloperidol and total score Simpson Angus Scale

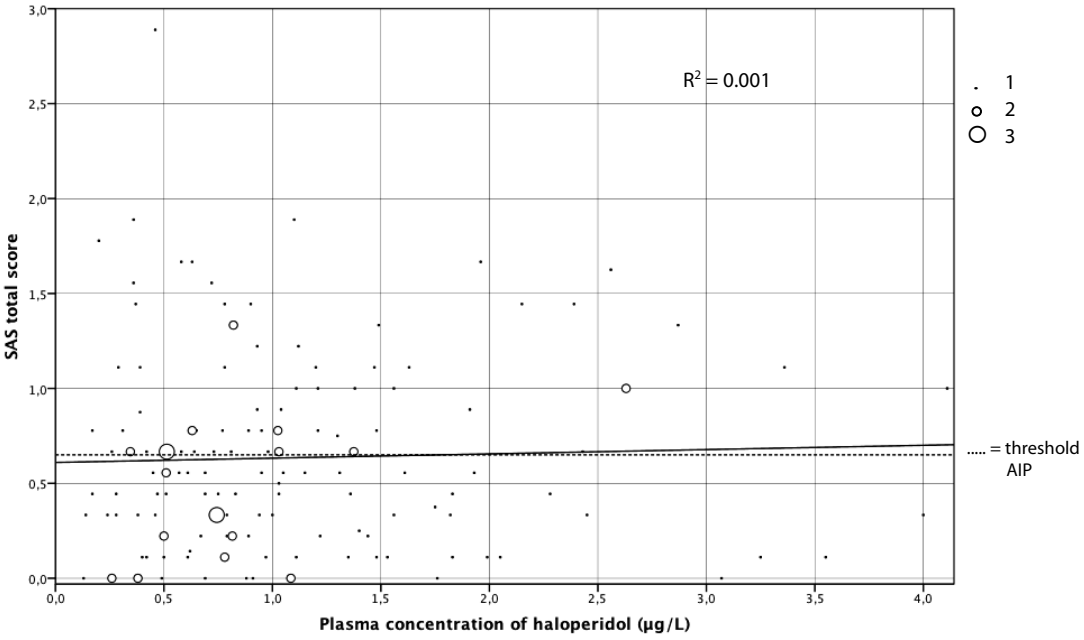
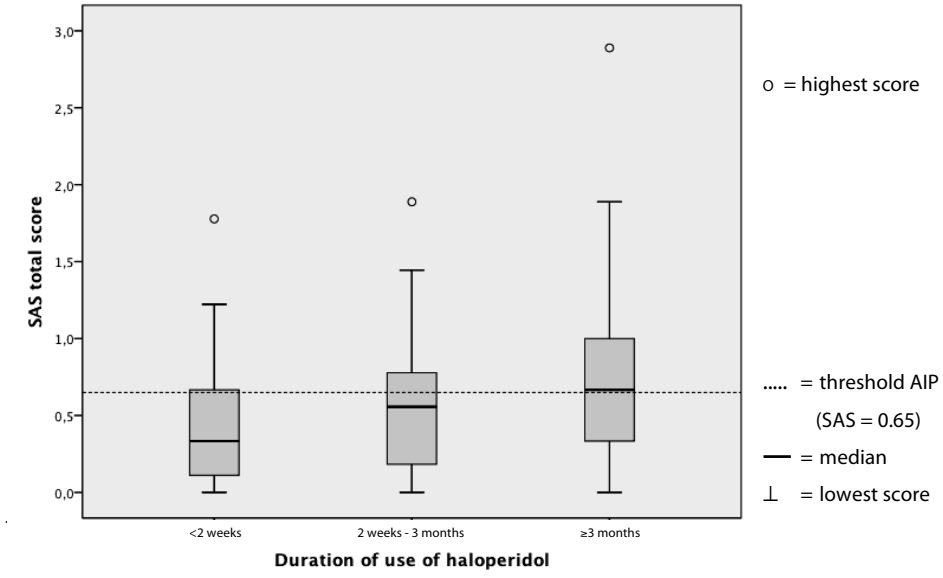


Figure 4. Relation duration of use of haloperidol and total score Simpson Angus Scale



The patients with AIP smoked significantly less frequent compared to the patients without AIP (10.1% vs 22.2%). In multivariate analysis smoking showed to be not significantly protective in the development of AIP (crude OR 0.39; 95% CI 0.15-0.997 and adjusted OR 0.44; 95% CI 0.17-1.17).

Table 2. Determinants of antipsychotic induced parkinsonism

determinant	crude OR	95% CI	adjusted OR*	95% CI
Age				
65 – 74	reference		reference	
75 – 84	1.75	0.63-4.92	1.55	0.54-4.43
≥ 85	2.34	0.85-6.48	1.93	0.68-5.51
Female gender	0.71	0.36-1.42	0.51	0.24-1.09
Duration of use				
5 - 14 days	reference		reference	
14 days – 3 months	1.39	0.45-4.34	1.55	0.48-4.95
≥3 months	2.10	0.70-6.25	2.35	0.77-7.19
Smoking	0.39	0.15-0.997	0.44	0.17-1.17
Dementia	1.22	0.46-3.22	1.35	0.50-3.68

* Adjusted for age and smoking

Discussion

In 46% of the 150 elderly patients in our study AIP was found during treatment with haloperidol. No statistically significant or clinically relevant association with dose or plasma concentration was found. A not statistically significant trend toward a higher risk of AIP in elderly patients with a longer duration of use of haloperidol was observed. We were not able to confirm suggested risk factors for AIP in elderly, such as higher age, female gender, a diagnosis of dementia or use of other drugs that have the potential to cause AIP.[26] Smoking was associated with a non significant reduction of the risk of occurrence of AIP.

Prevalence rates of AIP vary across different studies because of differences in patients demographics and assessments methods for AIP. We chose a higher threshold of 0.65 instead of the more traditional 0.3 on the SAS to define AIP. Nevertheless the frequency of AIP of 46% in our study population is comparable with previously reported prevalence estimates of approximately 40% in elderly treated with conventional antipsychotics.[5,6]

The prescribed doses of haloperidol are relatively low in this study (0.3 - 5.0 mg/day). Although to our knowledge published haloperidol dose-finding studies in elderly are lacking, the prescribed doses are in line with recommended lower doses of haloperidol in guidelines and doses prescribed in previous studies.[12-14] In a scatter diagram we show the relationship between dose of haloperidol and total score on the SAS, both represented a continuous variables. We found a very low R square of 0.003 (p=0.5) which means that 0.3% of the variability in the total score on the SAS could be explained by the variability in dose. A linear or curvilinear relation between dose and total score on the SAS is lacking. Therefore we decided not to compare the risk of occurrence of AIP in different categories of daily prescribed dose (<1 mg, 1-2 mg, ≥2 mg) and explored no further statistics. The four previous studies in elderly show comparable results concerning relation between dose of haloperidol and AIP.[12-15] Our results are in contrast to empirical information in younger patients suggesting a dose-dependent D2 receptor occupancy.[27]

Previous studies show an enormous variation in plasma concentration of haloperidol in patients on the same dose and several studies found an association with CYP2D6 genotype and higher risk of parkinsonism in poor metabolizers for CYP2D6.[28-30] In our study dose of haloperidol was moderate, but significantly associated with haloperidol plasma concentration. Because of this relationship variation in plasma concentration related to genetic variation in CYP2D6 seems not likely in our study population. Influence of genetic variation in cytochrome P450 enzymes in the individual patient can not be ruled out.

The haloperidol concentration range in this study (0.13 – 4.11 µg/l, with one outlying measurement of 21.43 µg/l) is well below the therapeutic window reported for haloperidol in adult schizophrenic patients, but is in line with results of previous studies in elderly patients.[12,14,15] No significant association was found between plasma concentration of haloperidol and total score on the SAS. We found a very low R square of 0.001 (p=0.67) which means that 0.1% of the variability in the total score on the SAS could be explained by the variability in plasma concentration of haloperidol. In contrast to results of Pelton et al and Devenand et al, our findings do not support the hypothesis that a higher plasma concentration of haloperidol in elderly patients increases the risk of AIP.[12,13] One major difference and advantage of the study of Pelton et al is that patients had on baseline no significant parkinsonism; this information is lacking in our study. Nevertheless, the four previous studies in elderly are small (19-40 participants) and use correlation for description of relationship between dose, concentration and adverse effect. Moreover EPS was assessed by different rating scales. One study[15] did not asses parkinsonism, but assessed tardive dyskinesia with the Abnormal Involuntary Movement Scale (AIMS), one[14] used the complex Extrapyramidal Side-effect Rating Scale (ESRS) and

two[12,13] used the modified Targeting Abnormal Kinetic Effects (TAKE). Validity data for drug induced parkinsonism of the last two rating scales are lacking. Three studies do not provide data about the absolute score on the rating scale or the used threshold.
We did not measure pyridinium concentrations, a potential neurotoxic metabolite of haloperidol which is associated with DIP, because of the low levels of haloperidol (0.13 – 4.11 µg/l) and the expectation that this metabolite would have been below the limit of detection in many patients.[32]
We were not able to confirm suggested risk factors for AIP, such as higher age, female gender, a diagnosis of dementia or use of other drugs that have the potential to cause DIP. The characteristics of the population we studied may explain the lack of associations. All patients were older than 65 years, only a small number used drugs that have to potential to cause DIP and more than 85% was diagnosed with dementia.
To our knowledge the association between smoking and AIP has not previously been studied among elderly patients. The influence of smoking on the expression of AIP has been examined in younger adults, in whom contradictory results are found.[33] Smoking is associated with increased clearance of haloperidol by enzyme inducing effect and for this reason a protective effect against AIP is plausible.[33,34] Smoking may also more directly effect the risk of AIP, possibly by enhancing dopamine release in the basal ganglia as a result of nicotine receptor stimulation, as considered in Parkinson's disease.[34] In our study smoking was associated with a non significant reduction of the risk for AIP. Future studies should include more patients to draw more clear conclusions about the influence of smoking on the risk of AIP.

This study has several limitations. An unknown number of potential participants or their legal representatives did not give informed consent, which could have resulted in selection bias. The second to consider is information bias. Because of its cross-sectional design, information about presence of parkinsonism before treatment with haloperidol is lacking. Although patients with known Lewy-body dementia, Parkinson's disease or non-drug parkinsonism were excluded, pre-existing parkinsonism as a consequence of neurodegenerative diseases not mentioned in the medical record can not be ruled out. Another limitation concerns the assessment of AIP. Although the SAS was especially developed to measure DIP and turned out to be a valid, reliable and easy-to-use instrument[18], questions have risen on whether the scale properly evaluates the different aspects of parkinsonism. For example, six items are used to evaluate rigidity, but only one item is used to evaluate bradykinesia.[35] As almost 40% of our patients were not able to walk independently, we decided not to include the item 'gait' in the current study, thereby not measuring bradykinesia at all. This adapted version of the SAS is not validated. Nevertheless the expected misclassification of outcome by this adaptation seems negligible.

The cross-sectional study design could have introduced bias by depletion of susceptible patients or dose reduction in susceptible patients. Blood samples were not taken at the same interval after starting or changing in dosage regimen. We can not rule out that the treating physicians recently changed the doses of haloperidol because of AIP. To determine the possibility of this kind of bias we analyzed the relation between duration and dose of haloperidol according to strata and the presence of AIP. In patients treated with haloperidol for more than 3 months and more than 1 year the percentage of AIP was higher in dose category 1-2 mg compared to dose category > 2mg (25% versus 20.5% and 28.1 versus 6.3%). Although small numbers and limitations related to the study design make it impossible to draw a clear conclusion we could suggest that a higher prevalence of AIP in dose category 1-2 mg compared to dose category >2 mg is suspect for previous dose reduction in susceptible patients.
Blood samples were collected at least three hours after haloperidol intake, in patients in which can be presumed that steady state of haloperidol is reached after treatment of at least 5 days. As different studies show wide variance for t_{max} values (1.7 – 6.1 hours) a minority of the patients may not have reached the peak concentration.[31] A limitation of our study is that in some patients haloperidol concentration was possibly determined before peak concentration was reached which may have contributed to lower plasma haloperidol concentrations.
Finally, residual confounding remains a possibility. We were able to adjust for dementia, but not for the degree of cerebrovascular damage or D2 receptor density. These unknown variables will probably not further weaken the relationship between dose, duration of use or plasma concentration and AIP, which we already found to be not significant or clinically relevant. With regard to comparable characteristics in patients with and without AIP, we consider our study population as representative of elderly patients in daily practice in hospitals and nursing homes.

In conclusion, in a clinical practice setting we did not find that dose or plasma concentration of haloperidol is associated with occurrence of AIP. Bias by dose reduction in patients susceptible for AIP or information bias related to the study design can not be ruled out. This study does not support the hypothesis of a peripheral pharmacokinetic explanation for the high prevalence of AIP and differences in AIP sensitivity in elderly patients during treatment with haloperidol. The contribution of central pharmacokinetic and dynamic factors seems more promising. Further research is necessary to evaluate the role of the central pharmacokinetic and pharmacodynamic hypothesis in elderly patients.

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Chapter 3.2

Genetic variation and the risk of haloperidol induced parkinsonism in elderly patients: a candidate gene approach

Wilma Knol
Rob J. van Marum
Paul A.F. Jansen
Eric Strengman
Asmar F.Y. Al Hadithy
Bob Wilffert
Alfred F.A.M. Schobben
Roel A. Ophoff
Toine C.G. Egberts

Abstract

Objective
Factors that influence the variation in occurrence of antipsychotic induced parkinsonism (AIP) in elderly have not been well elucidated. The aim of this study was to investigate whether previous identified and studied genetic polymorphisms at DRD2, ANKK1, DRD3, HTR2A, HTR2C, RGS2, COMT and BDNF genes are associated with AIP in elderly patients.

Methods
Cross-sectional study with 150 inpatients aged 65 years and older who were all treated with haloperidol. Presence of parkinsonism was assessed by the Simpson Angus Scale. The investigated determinants were polymorphisms in DRD2 (141CIns/Del and C957T), ANNK1 (TaqIA), DRD3 (Ser9Gly), HTR2A (-1438G>A and His452Tyr), HTR2C (Cys23Ser and -759C/T), RGS2 (+2971C>G), COMT (G158A) and BDNF (Val66Met).

Results
AIP was present in 46% of the patients included. Frequencies of the -759 T allele of the HTR2C gene and the 158A allele of the COMT gene were significantly higher in patients without AIP (nominal p=0.03 and p=0.02, respectively). The analysis of the -759C/T polymorphism was limited to females, since the HTR2C gene is located on the X chromosome and allele frequency calculations of this polymorphism were influenced by gender distribution between cases and controls. -759 T allele carriership in females was associated with a lower risk of AIP (adjusted OR 0.31; 95% CI 0.11-0.85). The decrease in risk of AIP in carriers of the COMT 158A allele did not reach statistical significance. No significant associations were found between AIP and the remaining selected polymorphisms.

Conclusions
Although validation is needed this study suggests that carriership of the -759 T allele of the HTR2C gene in females may be protective against development of parkinsonism in elderly patients during treatment with haloperidol.

Introduction

Antipsychotics are despite the risk of serious adverse effects, frequently prescribed to elderly patients for the treatment of acute and chronic psychotic symptoms or behavioural symptoms in dementia. The reported prevalence of antipsychotic drug use in nursing home residents, for example, varies between 12% and 52%.[1-3] Antipsychotic-induced parkinsonism (AIP), which is characterized by tremor, bradykinesia, rigidity and postural instability during the use of an antipsychotic drug, is an impacting adverse effect, affecting about 40% of patients using conventional antipsychotics.[4,5] The desired effects and some adverse effects of antipsychotic drugs have been linked to their binding to dopamine D2 receptors.[6] Positron emission tomography (PET) studies have indicated that the therapeutic effects of antipsychotics are achieved with a blockade of 60-70% of dopamine receptors and that AIP is more likely to occur when blockade of dopamine receptors is more than 80%.[7] A greater affinity of conventional antipsychotics compared to atypical antipsychotics for dopamine 2 (D2) receptors may account for their increased risk of AIP.[6] Elderly are more prone to develop AIP, but there are also notable differences in AIP susceptibility between individual elderly people of which the underlying mechanism is not clear.[8] In a previous study we showed that peripheral pharmacokinetic factors can not sufficiently explain the variation in AIP susceptibility.[9] Genetic factors may be partly responsible for this variation in occurrence of AIP,[10-13] but it has hardly been studied in elderly patients. Given the proposed pharmacological mechanism of action for antipsychotics, genes of interest may be related to either the synthesis and degradation of dopamine or to its transporters and receptors. DRD2 is an obvious candidate gene to study since several polymorphisms on or near this gene (ANKK1 gene) may alter the dopamine 2 receptor function or density.[14,15] Dopamine receptors are modulated by serotonin 2A and 2C receptors.[16] Serotonin interacts via serotonin 2 receptors on the dopamine neurons, this inhibits dopamine release. So, serotonin receptor genes HTR2A and HTR2C are also plausible candidate genes to study.[17] In contrast to tardive dyskinesia, the role of variation in dopamine D3 receptor encoded by the DRD3 gene as a determinant of AIP is poorly understood and scarcely investigated.[18,19]

Other possible pharmacodynamic determinants may be genetic variation in second-messenger proteins (e.g. Regulators for G-protein Signaling [RGS]). The RGS2 protein belonging to the large family of RGS influences several major receptor signaling systems in the central nervous system including dopaminergic and serotonergic receptors. Therefore variation in functionality of RGS2 encoded by the RGS2 gene may influence susceptibility to develop AIP.[20-23]

Furthermore genetic variation in the enzyme Catechol O-Methyltransferase (COMT), which metabolizes endogenous catecholamines such as dopamine is a possible

determinant. Carriers of COMT-defective alleles (COMT158A) metabolize dopamine more slowly which might result in greater dopamine availability. It is hypothesized that antipsychotics would have to compete with a larger amount of dopamine for the occupancy of the D2 receptor and development of AIP would therefore be less likely.[24]
Finally, it has been suggested that brain-derived neutrotrophic factor (BDNF), which is a member of the superfamily of neutrotrophins has a role in the pathogenesis of extrapyramidal symptoms (EPS). BDNF has an important role in promoting and modifying growth, differentiation and survival of neurons. BDNF regulates the expression of DRD3. In one study the Val66Met polymorphism of the BDNF gene was associated with orofacial tardive dyskinesia.[25] The BDNF gene seems an interesting determinant, although the role of this polymorphism in occurrence of AIP has not been studied before.
The objective of the study was to investigate whether previously studied and reported genetic polymorphisms at DRD2, ANKK1, DRD3, HTR2A, HTR2C, RGS2, COMT and BDNF genes are associated with AIP in elderly patients during treatment with haloperidol.

Methods

Design, setting, study population

A cross-sectional study was performed in the departments of old age psychiatry of three mental health care centers, the geriatric department of two hospitals and in eleven nursing homes in the Netherlands. In each participating centre, on a randomly chosen date in the period of April to September 2008, the treating physicians identified all patients aged 65 and older who had been treated for at least five consecutive days with haloperidol. Excluded were terminally ill patients and patients previously diagnosed with Parkinson's disease or non-drug parkinsonism. Also patients using an anticholinergic antiparkinsonian drug (biperiden, trihexyphenidyl or dexetimide) were excluded, since use of these drugs interferes with the occurrence or seriousness of AIP. The treating physician asked all eligible patients and their legal representatives permission to be approached for this study. Written informed consent was obtained by the investigators from all participants or their legal representatives if patients were considered to be incapacitated. The study was approved by the Dutch Central Committee on Research involving Human Subjects.

Outcome

Primary outcome of the study was the presence of AIP, assessed by the Simpson Angus Scale (SAS). The SAS was scored on the chosen date by an investigator who was trained using an instruction guide and an instruction video.[26] The SAS consists of ten items, one item measuring gait (hypokinesia), six items measuring rigidity and three other items

measuring glabella tap, tremor and salivation. Each item has to be scored on a 5-points scale (0-4). The total score of the SAS is obtained by summing the score of each of the ten items and dividing the sum of total score by 10 (range total score 0-4). The SAS has shown to be a valid and easy to perform research tool to assess drug induced parkinsonism (DIP).[27,28] Since many participants in this study were not able to walk independently, the score on the SAS was adapted by excluding the gait-subscore and standardizing the total score by summing the score of the nine remaining items and dividing the sum of total score by nine (range total score 0-4). Traditionally, a total SAS score of 0.3 or more is defined as parkinsonism.[29] Based on ROC analysis, Janno et al suggested a cut-off value of 0.65, whereby specificity could be doubled without loosing sensitivity.[30] Supported by these results and our own clinical experience we chose a total score ≥ 0.65 on the SAS as definition for the presence of parkinsonism.[28]

Determinants

The primary determinants were polymorphisms of candidate genes which were selected based on specific pathophysiological hypotheses and through prior association studies (see introduction). The following polymorphisms were investigated rs1799732 (141CIns/Del; DRD2), rs6277 (C957T; DRD2), rs1800497 (TaqIA; DRD2), rs6280 (Ser9Gly; DRD3), rs6311 (-1438G>A; HTR2A), rs6314 (His452Tyr; HTR2A), rs6318 (Cys23Ser; HTR2C), rs3813929 (-759C/T; HTR2C), rs4606 (+2971C>G; RGS2), rs4680 (G158A; COMT) and rs6265 (Val66Met; BDNF). The Taq1A polymorphism is located on the ANKK1 gene, which is closely linked to the DRD2 gene (10-kb upstream of the 3'-noncoding region of the DRD2 gene).[31]

DNA isolation and genotyping

Genomic DNA was isolated from EDTA-anticoagulated peripheral blood using standard methods. All single nucleotide polymorphisms (SNPs) were determined using KASPar On Demand assays.[32] The assays were ordered from KBiosciences (Hoddesdon, UK). The assays utilized 10 ng of genomic DNA and 10 µl reaction volumes. Genotyping was performed according to manufacturers protocol.[32] Fluorescent readout was performed with 7900 Real Time PCR System and analyzed with Sequence Detection System (SDS) version 2.3. Genotyping was performed blinded for patient data.

Potential confounders

The investigators obtained from the patients' medical records the following factors known to be associated with AIP: duration and current dosage of haloperidol, indication for haloperidol treatment, general characteristics (e.g. age, sex, race, smoking habits), medical history including diagnosis of dementia and concomitant medication use.

Medication was checked for anticholinergic drugs according to the definition of Chew et al and for drugs that have been reported to possibly induce extrapyramidal symptoms.[33,34]
Duration of haloperidol use was assessed and subdivided in less than 14 days, 14 days – 3 months and longer than 3 months.
Level of cognitive functioning was determined by the treating physician of the participants according to the Reisberg Global Deterioration Scale (GDS).[35] Diagnosis of dementia was based on a diagnosis mentioned in the medical record or cognitive impairment stage 4 or higher according to the Reisberg scale.

Data analysis
Differences in characteristics in patients with and without AIP were calculated using t-test, Mann-Whitney tests and chi-square tests. A two-tailed p-value of below 0.05 was considered statistically significant. For all genetic variants Hardy-Weinberg equilibrium (HWE) testing was performed. Chi-square or Fisher's exact tests was used for comparison of allele and genotype frequencies between patients with and without AIP. A two-tailed p-value of below 0.05 without correction for multiple testing was considered nominally significant. The association between AIP and alleles and AIP and genotypes was determined through binary logistic regression. The strength of the association was expressed as an odds ratio (OR) with a 95% confidence interval (CI).
A variable was included in the multivariate logistic regression model if the OR between genetic determinant and AIP changed with more than 10% when added or if it was univariately associated with AIP ($p<0.1$).[36]
A stratified analysis was performed for males and females for the polymorphisms of the HTR2C gene as this gene is located on the X chromosome.
Statistical Package for the Social Sciences (SPSS) version 15.0 was used for data analysis.
The power analysis in this study was based on the assumption of a prevalence of AIP in 30% of the participants and a prevalence of a common polymorphism (TaqIA) at the DRD2 gene of 30%. Based on an estimation of risk of AIP of 60% in participants with this polymorphism and risk of AIP of 20% in participants without this polymorphism, we calculated that a study sample of at least 80 patients was needed to reach 80% power to detect this difference.

Results

All 157 selected patients or their legal representatives gave informed consent for participation in this study. Seven patients were excluded because of use of an anticholinergic antiparkinsonian drug. Information about duration of treatment with haloperidol was missing in six patients.

The characteristics of the study population are shown in table 1. Mean age of the patients was 83 years (SD 7.7) and the majority of the group was female (68%). The most common indication of treatment with haloperidol was behavioural disorders in dementia (66.7%). The majority (87.3%) of all patients were diagnosed with dementia.

AIP was present in 46% of the 150 patients in this study. The mean total score on the SAS in patients with AIP was 1.06 (SD 0.42), in patients without AIP 0.27 (SD 0.19). Age, gender, use of anticholinergic drugs or drugs that have been reported to possibly induce extrapyramidal symptoms (metoclopramide [3], domperidon [1], cinnarizine [2], valproic acid [4], promethazine [1]) were not significantly different between patients with or without AIP. Six patients were non-Caucasians and were excluded from further analysis. Determination of SNPs had success rates between 93.7% and 99.3% (genotype data could not be determined in maximally 9 patients per SNP).

All SNPs in the candidate genes were in HWE in the control (no-AIP) study population, genotype distribution of the polymorphisms TaqIA, Cys23Ser and -759C/T deviated from HWE in the total study population (p=0.03, p=0.0008 and p=0.007, respectively).

Table 2 shows the distribution of frequencies of alleles and genotypes of all polymorphisms in patients with and without AIP. Carriers of the -759 T allele of the HTR2C gene and carriers of the 158A allele of the COMT gene were significantly more frequently present in patients without AIP (nominal p=0.03 and p=0.02, respectively, in the allele based distribution).

A stratified analysis was performed for males and females for the polymorphisms at the HTR2C gene as this gene is located on the X chromosome. Due to skewed gender distribution between cases and controls in allele and genotype frequency of polymorphisms at the HTR2C gene further analysis for this polymorphism was limited to females only (table 3).

Genotype distribution of the -759C/T and Cys23Ser polymorphism was in HWE in the control (no-AIP) and total female population. The -759T allele frequency of the HTR2C gene in the total female population is 18.6%, in females with AIP 13.1% and in females without AIP 23.1% (nominal p=0.08).

The 158A allele frequency of the COMT gene in the total study population is 51.5%, in patients with AIP 43.8% and in patients without AIP 58.5% (nominal p=0.02).

The risk of AIP was significantly lower among female -759 T allele carriers of the HTR2C gene compared to female non carriers of -759 T allele (adjusted OR 0.31; 95% CI 0.11-

0.85). The decrease in risk of AIP in carriers of the COMT 158A allele did not reach statistical significance (crude OR 0.47; 95% CI 0.22-1.02 and adjusted OR 0.58; 95% CI 0.26-1.29) (table 4). No significant associations were found between AIP and the selected polymorphisms of the DRD2, ANNK1, DRD3, HTR2A, RGS2 and BDNF gene (data not shown).

Table 1. Characteristics of elderly patients with and without antipsychotic induced parkinsonism

	AIP (N= 69)				No-AIP (N= 81)				p-value
Characteristics	**N**	**mean**	**SD**	**%**	**N**	**mean**	**SD**	**%**	
Age –years		83.9	7.8			82.2	7.5		0.17
65 – 74	7			10.1	15			18.5	
75 – 84	27			39.1	34			42.0	
≥ 85	35			50.7	32			39.5	
Female	44			63.8	58			71.6	0.31
Caucasian ethnicity	67			97.1	77			95.1	0.69
Indication haloperidol									0.55
Delirium	9			13.0	12			14.8	
Behavioural and Psychological Symptoms of Dementia	49			71.0	51			63.0	
Psychosis or other indication	11			15.9	18			22.2	
Dose haloperidol in milligrams/day		1.47	0.9			1.23	0.84		0.19
Duration of use									0.33
5- 14 days	6			8.8	11			14.5	
14 days – 3 months	22			32.4	29			38.2	
≥ 3 months	40			58.8	36			47.4	
Smoking	7			10.1	18			22.2	0.05
Dementia	61			88.4	70			86.4	0.72
Drugs associated with extrapyramidal symptoms	7			10.1	4			4.9	0.22
Anticholinergic drugs	8			11.6	8			9.9	0.73
Living situation									0.12
Geriatric ward	3			4.3	6			7.4	
Psychiatric ward	5			7.2	14			17.3	
Nursing home	61			88.4	61			75.3	

Table 2. Distribution of genotypes and allele frequencies studied in elderly patients (n=144) with and without antipsychotic induced parkinsonism

polymorphism	group	genotype			p-value	allele		p-value
DRD2								
-141Ins/Del		Ins/Ins	Ins/Del	Del/Del		Ins	Del	
	AIP	49	14	2		112	18	
	no AIP	60	9	1	0.31	129	11	0.11
C957T		TT	CT	CC		T	C	
	AIP	15	35	13		65	61	
	no AIP	26	34	15	0.35	86	64	0.34
TaqIA		A2A2	A2A1	A1A1		A2	A1	
	AIP	39	27	1		105	29	
	no AIP	51	25	0	0.35	127	25	0.26
DRD3								
Ser9Gly		SerSer	SerGly	GlyGly		Ser	Gly	
	AIP	31	30	5		92	40	
	no AIP	30	38	6	0.74	98	50	0.53
HTR2A								
-1438G>A		GG	GA	AA		G	A	
	AIP	28	28	11		84	50	
	no AIP	24	38	12	0.47	86	62	0.43
His452Tyr		HisHis	HisTyr			His	Tyr	
	AIP	49	16			114	16	
	no AIP	59	15		0.53	133	15	0.57
HTR2C								
Cys23Ser		CysCys	CysSer	SerSer		Cys	Ser	
	AIP	49	11	6		109	23	
	no AIP	47	19	5	0.35	113	29	0.53
-759C/T		CC	CT	TT		C	T	
	AIP	55	7	4		117	15	
	no AIP	46	22	4	**0.02**	114	30	**0.03**
RGS2								
+2971C>G		CC	CG	GG		C	G	
	AIP	32	32	2		96	36	
	no AIP	30	36	7	0.26	96	50	0.21
COMT								
G158A		AA	AG	GG		A	G	
(A=Met)	AIP	14	28	22		56	72	
	no AIP	26	31	14	0.08	83	59	**0.02**
BDNF								
		GG	GA	AA		G	A	
Val66Met	AIP	48	15	2		111	19	
(Met=A)	no AIP	45	24	4	0.30	114	32	0.12

Table 3. Distribution of genotype and allele frequencies of polymorphisms at the HTR2C gene in females

polymorphism	group	genotype			p-value	allele		p-value
Cys23Ser		CysCys	CysSer	SerSer		Cys	Ser	
	AIP	29	10	3		68	16	
	no AIP	30	19	1	0.21	79	21	0.74
-759C/T		CC	CT	TT		C	T	
	AIP	33	7	2		73	11	
	no AIP	29	22	1	**0.03**	80	24	0.08

Table 4. Association between allele carriership (HTR2C-759C/T and COMT G158A) and antipsychotic induced parkinsonism

	OR (95%CI)	Adjusted OR (95%CI)*
HTR2C -759C/T in females		
T allele – C allele	0.50 (0.23-1.01)	
T carriership (TT+TC) – T non carriership (CC)	0.34 (0.14-0.86)	0.31 (0.11- 0.85)
COMT G158A		
A allele – G allele	0.55 (0.34–0.90)	
A carriership (AA+AG) - A non carriership (GG)	0.47 (0.22-1.02)	0.58 (0.26-1.29)

* adjusted for smoking and duration of haloperidol use

Discussion

In the present study in elderly patients in a clinical practice setting, carriership of the –759 T allele of the HTR2C gene in females is most consistently associated with a decreased risk of AIP, with a -759 T allele carriership protection of 70%. The analysis of the -759C/T polymorphism was limited to females, since the HTR2C gene is located on the X chromosome and allele frequency calculations of this polymorphism are influenced by gender distribution between cases and controls.

This result seems to be in contrast with the four previous studies in which no evidence or support for a significant association between carriership of -759 T allele and AIP was observed in both females and males.[15,17,37,38] However, our results are not directly

comparable with these previous studies assessing antipsychotic induced extrapyramidal symptoms in different ways (different definition of phenotype). Three studies assess several antipsychotic induced extrapyramidal symptoms with respectively combination of the SAS and the Barnes Akathisia Scale (BAS) or the SAS and the Abnormal Involuntary Movement Scale (AIMS) or the Udvalg for Kliniske Undersøgelser (UKU), the AIMS and modified tardive dyskinesia criteria.[17,37,38] Non of these three studies shows separate results on the SAS or investigate the association between genetic variations and AIP as a separate entity. Although the pathophysiology of the different types of extrapyramidal symptoms is largely unknown, each type has specific features and different neuroanatomical constructs with possibly different genetic vulnerability.[39] Pooling of them may be detrimental for the analysis. Al Hadithy et al use the Unified Parkinson's Disease Rating Scale which is primarily designed to assess symptoms of Parkinson's disease and not to assess AIP.[15] Another explanation for the contrasting results could be that our population is different from previously studied populations. Ethnic variability (African Caribbean versus European Caucasian population) can have influence on genetic susceptibility. Furthermore our study population is very old, and although we assume that genetic effects are relatively independent of age, an age-related association of both the Cys23Ser polymorphism of the HTR2C gene and the 102T/C polymorphism of the HTR2A gene was observed with susceptibility to tardive dyskinesia.[40]

The 5HT2C gene is located on the X chromosome at q24. The -759C/T polymorphism consists of a C-T transformation at position -759 in the 50 flanking region. The C allele is the common allele and the T allele is the rare allele with a frequency from 4% in African and 18% in European.[41] Previous studies showed that the T allele is significantly protective against antipsychotic induced weight gain.[42]

The mechanism that may explain the association between polymorphisms of the HTR2C gene and occurrence of AIP is not clear. Variation in the serotonin 2C receptor is encoded by the HTR2Cgene. It is well established that systemic administration of a specific 5-HT2C receptor antagonist (SB 206553), increases the firing rate of dopamine neurons. It is suggested that 5-HT2C receptors posses a unique ability to tonically regulate dopamine release form the nigrostriatal pathway. Intracerebral infusion of SB 206553 showed an antiparkinsonian effect in a 6-hydroxydopamine-lesioned rat model of Parkinson's disease.[16] Whether these effects reflect 5-HTC actions on nigrostriatal dopamine function remains to be determined.

Concerning the COMT gene the results of this study show that carriership of the 158A allele is associated with a non significant decrease of risk of AIP. However, the large CI possible means that our study has not the power to reveal a true association. In the single available previous study of Lafuente et al who investigated the role of the G158A

polymorphism of the COMT gene and the risk of AIP, a protective effect of the 158A allele was found in patients with a bipolar disorder (OR 0.3; 95% CI 0.1-0.8). In the schizophrenic patients in this study carriership of 158A allele showed a non significant decreased risk of AIP. Our results are therefore largely comparable with the results of the study of Lafuente et al in which AIP was also assessed with the SAS.
The COMT polymorphism has been widely studied as a susceptible gene for schizophrenia and tardive dyskinesia, because of its role in the monoamine metabolism.[43] The 158A allele carriers have lower enzyme activity and metabolize dopamine more slowly than the homozygotes for the common allele (=158G allele) and may therefore have a greater dopamine availability. It is hypothesized that the antipsychotic drug would have to compete with a larger amount of dopamine for the occupancy of the DRD2 receptor and development of AIP would therefore decrease. Furthermore the COMT genotype may contribute to AIP because of indirect and complex downstream effects on dopamine regulation between the prefrontal cortex and striatum.[44]

We did not find any association between the polymorpisms in the DRD2 gene (141CIns/Del, C957T and TaqIA) and occurrence of AIP. Al Hadithy et al divided AIP into three sub-symptoms (bradykinesia, tremor and rigidity) and found an association between rigidity and -141CDel carriership (OR 11.46; 95% CI 1.6-111.1), an association between the other components of AIP and polymorphisms in the DRD2 gene is in this study also lacking.[15] Güzey et al report a higher frequency of the A1 allele of the DRD2 TaqIA polymorphism in patients with EPS and found an increased risk of EPS with OR of 2.4 (1.1-5.7).[14] The analysis was based on allele frequencies and the outcome is less clear as it consists of a pooling of scores on the SAS and the AIMS. In the majority of genetic studies an association between AIP and polymorphisms in the DRD2 gene is lacking (table 4).

Concordant to previous studies we found no association between the Ser9Gly polymorphism of the DRD3 gene and AIP. This is contrary to several meta-analyses[12] that have demonstrated an association between the Gly allele and tardive dyskinesia with reported OR of 1.16-1.33 and therefore a strong argument to consider tardive dyskinesia and parkinsonism as separate types of extrapyramidal symptoms.

We found no association between AIP and the polymorphisms of the HTR2A gene. Gunes et al report a higher frequency of the 102C allele in patients with EPS and found an increased risk of EPS with OR of 3.18 (1.2-8.8).[17] This result is also based on allele based analysis and unclear definition of EPS. Other studies that showed no association are described in table 4.

We were not able to replicate the significant association between +2971C>G polymorphism in RGS2 gene and AIP reported by Greenbaum et al.[20,21] The association is found in Jewish, African-American and Caucasians. The lack of association of our results is comparable with results of Al Hadithy et al and Higa et al.[22,23] An explanation could be the difference in studied age group and difference in type of prescribed antipsychotic drug (mostly atypical in the study of Greenbaum, mostly typical in the study of Al Hadity and all haloperidol in our study). As RGS2 is involved in the intracellular signalling mediated by serotonin 2A receptor it seems plausible that the effect of the polymorphism of the RGS gene is related to an antagonism of HTR2A receptor; the atypical antipsychotic drugs have strong affinity for this receptor in contrast to conventional antipsychotic drugs.
Finally, comparable with findings of Xu et al we found no association between Val166Met polymorphism of the BDNF gene and AIP.[45]

The small sample size, which resulted in small numbers of patients in each genotype group, was a major limitation of this study. Especially the number of participating male patients was too small to stratify properly for gender.
Another drawback of the study is the cross-sectional study design. Information about presence of parkinsonism before treatment with haloperidol is lacking. Although patients with known Lewy-body dementia, Parkinson's disease or non drug parkinsonism were excluded, pre-existing parkinsonism as a consequence of neurodegenerative diseases not mentioned in the medical record can not be ruled out and therefore there is a possibility of information bias. Another limitation concerns the assessment of AIP. Although the SAS was especially developed to measure DIP and turned out to be a valid, reliable and easy-to-use instrument[27], questions have risen on whether the scale properly evaluates the different aspects of parkinsonism. As almost 40% of our patients were not able to walk independently, we decided not to include the item 'gait' in the current study, thereby not measuring bradykinesia at all. This adapted version of the SAS has not been validated. Nevertheless the expected misclassification of outcome by this adaptation seems negligible. Based on results of a previous ROC analysis[30] and in order to be more confident to select cases with a clinical relevant degree of AIP we chose a higher threshold of 0.65 instead of the more traditional total score of 0.3 on the SAS.
With regard to comparable characteristics in patients with and without AIP, we consider our study population as representative of elderly patients in daily practice in hospitals and nursing homes.
The intention of our study was to investigate the impact of previously studied genetic factors in susceptibility to develop AIP in elderly. Since our approach is hypothesis

driven, exploring pathophysiological plausible pathways in a relatively small study sample, we decided not to correct for multiple testing but to present the uncorrected nominal p-values in our study.[46]

In conclusion, this study adds to the evidence of the role of pharmacogenetics in susceptibility of development of AIP, although available evidence does not allow a firm conclusion on whether pharmacogenetics is an important factor in the explanation of the increased AIP susceptibility in elderly. Even though validation is needed, this study suggests that carriership of -759 T allele of the HTR2C gene may be protective against development of AIP in female elderly. Further studies, preferable in a larger study population with a longitudinal design are necessary to investigate whether the 158A allele of the COMT gene has also a protective effect. Notably, our data do not support a major role for genetic variation in the dopamine gene to predispose to AIP in elderly. Dopamine availability could be more important for AIP susceptibility than the abundance of dopaminergic receptors.

Table 4. Studies of associations between polymorphisms and antipsychotic induced parkinsonism (AIP) or antipsychotic induced extrapyramidal symptoms (AIEPS) including AIP

Gene	SNP	Allele	N patients (with /without AIP)	Ethnicity or nationality	age	Sex F (%)	Diagnosis and Type of antipsychotic drug (APD)	Assessment of AIP	Odds ratio / p-value	Reference
DRD2	141Clns/Del (rs1799732)	Del	328 (234/94[A])	Japanese	Cases 54 (20-81) Controls 46[A](33-64)	44 50	Schizophrenia haloperidol	DIEPSS	NS (p >0.1) genotype and allele frequencies	Inada 1999[47]
			52 (33/19)	Japanese	36.2 SD±11.8	46	Schizophrenia bromperidol (27) nemonapride (25)	UKU	NS (p>0.1) genotype InsIns - InsDel	Mihara 2001[48]
			584 (40/544)	European Caucasian	38.3 SD±12.1	46.4	Schizophrenia mostly typical APDs	SAS	NS genotype frequencies	Kaiser 2002[49]
			19	Japanese	55.1	73.7	Schizophrenia haloperidol in combination with other APDs	DIEPSS	**p <0.01** Mean score higher in -141C allele carriers	Nakazono 2005[50]
			47 (25/22)[B]	Estonian	17-68	46.8	Schizophrenia perphenazine	SAS BAS	NS allele frequencies[B]	Gunes 2007[17]
			268 (80/188)	European Caucasian	Cases: 32.6±13 Controls: 37.6±16	[C]	Schizophrenia (195) bipolar disorders (42), other (31) mostly risperidone (60%) and haloperidol (16%)	SAS	NS genotype and allele frequencies	Lafuente 2008[24]
			126 (47/79)	African-Caribbean	49.2 SD±13.4	27	Mostly schizophrenia	UPDRS	**OR 11.46 (1.6-111.1) Rigidity and genotype DelDel+InsDel - InsIns** NS AIP total	Al Hadithy 2008[15]
DRD2	C957T (rs6277)	T	126 (47/79)	African-Caribbean	49.2 SD±13.4	27	Mostly schizophrenia	UPDRS	NS genotype frequency TT+CT - CC	Al Hadithy 2008[15]
	Pro310Ser	Ser_{310}	584 (40/544)	European Caucasian	38.3 SD±12.1	46.4	Schizophrenia mostly typical APDs	SAS	NS trend lower EPS heterozygous Ser_{310}[D]	Kaiser 2002[49]
	Ser311Cys		47 (25/22)[B]	Estonian	17-68	46.8	Schizophrenia perphenazine	SAS BAS	NS[B] allele frequencies	Gunes 2007[17]
ANNK1	TaqIA (rs1800497)	A1	52 (33/19)	Japanese	36.2 SD±11.8	46	Schizophrenia bromperidol (27) nemonapride (25)	UKU	NS (p>0.1) genotype frequency A1A1+A1A2 – A2A2	Mihara 2000[51]
			584 (40/544)	European Caucasian	38.3 SD±12	46.4	Schizophrenia mostly typical APDs	SAS	NS trend lower EPS homozygous A1	Kaiser 2002[49]
			19	Japanese	55.1	73.7	Schizophrenia haloperidol in combination with other APDs	DIEPSS	NS genotype frequencies	Nakazono 2005[50]

Gene	SNP	Allele	N patients (with /without AIP)	Ethnicity or nationality	age	Sex F (%)	Diagnosis and Type of antipsychotic drug (APD)	Assessment of AIP	Odds ratio / p-value	Reference
			93 (63/56)[E]	European Caucasian	50 SD±12	17	Schizophrenia mostly typical APDs	SAS AIMS	**OR 2.4 (1.1-5.7) A1-allele[E]**	Güzey 2007[14]
			47 (25/22)[B]	Estonian	17-68	46.8	Schizophrenia perphenazine	SAS BAS	NS allele frequencies[B]	Gunes 2007[17]
			268 (80/188)	European Caucasian	Cases: 32.6±13 Controls: 37.6±16	[C]	Schizophrenia (195) bipolar disorders (42), other (31) risperidone(60%) and haloperidol (16%)	SAS	NS genotype and allele frequencies	Lafuente 2008[24]
ANNK1			126 (47/79)	African-Caribbean	49.2 SD±13.4	21	Mostly schizophrenia	UPDRS	NS genotype A1A1+A1A2 – A2A2	Al Hadithy 2008[15]
	TaqIB[F]		584 (40/544)	European Caucasian	38.3 SD±12.1	46.4	Schizophrenia mostly typical APDs	SAS	NS trend lower EPS homozygous A1	Kaiser 2002[49]
			19	Japanese	55.1	73.7	Schizophrenia haloperidol in combination with other APDs	DIEPPS	NS genotype frequencies	Nakazono 2005[50]
	[F]		268 (80/188)	European Caucasian	Cases: 32.6±13 Controls: 37.6±16	[C]	Schizophrenia and bipolar disorders (42), other (31) mostly risperidone (60%) and haloperidol (16%)	SAS	NS genotype and allele frequencies	Lafuente 2008[24]
DRD3	Ser9Gly (rs6280)	Ser	47 (25/22)[B]	Estonian	17-68	46.8	Schizophrenia perphenazine	SAS BAS	NS allele frequency[B]	Gunes 2007[17]
		Ser	126 (47/79)	African-Caribbean	49.2 SD±13.4	21	Mostly schizophrenia	UPDRS	NS genotype SerSer+GlySer - GlyGly	Al Hadithy 2008[15]
	rs167771	G	132 (48/84)[N]	European Caucasian	Cases: 32.6±13 Controls 37.6±16[N]	?	Mostly schizophrenia and bipolar disorder risperidone	SAS	OR 3.3 (1.8-6.9) G-allele p=0.0001[G]	Gasso 2009[52]
HTR2A	1438G>A (rs6311)	A	126 (47/79)	African-Caribbean	49.2 SD±13.4	21	Mostly schizophrenia	UPDRS	NS AA+GA - GG	Al Hadithy 2008[15]
	His452Tyr (rs6314)	Tyr	93 (63/56)[E]	European Caucasian	50 SD±12	17	Schizophrenia mostly typical APDs	SAS AIMS	NS genotype and allele frequencies[E]	Güzey 2007[14]
			47 (25/22)[B]	Estonian	17-68	46.8	Schizophrenia Perphenazine	SAS BAS	NS allele frequencies[B]	Gunes 2007[17]
			126 (47/79)	African-Caribbean	49.2 SD±13.4	21	Mostly schizophrenia	UPDRS	NS genotype TyrTyr+HisTyr-HisHis	Al Hadithy 2008[15]
			425 (194/231)[L]	US Caucasian	27.9 SD±12.4	47	Mostly schizophrenia, bipolar and depressive disorder	UKU AIMS TD criteria[K]	NS genotype and allele frequencies p=0.08[L]	Al-Janabi 2009[38]
	102T/C	102C	47 (25/22)[B]	Estonian	17-68	46.8	Schizophrenia perphenazine	SAS BAS	**OR 3.18 (1.2-8.8) C-allele p=0.02[B]**	Gunes 2007[17]

			93 (63/56)[E]	European Caucasian	50 (SD±12)	20	Schizophrenia mostly typical APDs	SAS AIMS	NS genotype and allele frequencies[E]	Güzey 2007[14]
		102T	126 (47/79)	African-Caribbean	49.2 SD±13.4	21	Mostly schizophrenia	UPDRS	NS genotype TT+CT – CC	Al Hadithy 2008[15]
			425 (194/231)[H]	US Caucasian	27.9 SD±12.4	47	Mostly schizophrenia, bipolar and depressive disorder	UKU AIMS TD criteria[I]	NS genotype and allele frequencies[H]	Al-Janabi 2009[38]
	516 C/T		93 (63/56)[E]	European Caucasian	50 SD±12	20	Schizophrenia mostly typical APDs	SAS AIMS	NS genotype and allele frequency[E]	Güzey 2007[14]
HTR2C	Cys23Ser (rs6318)	23Ser	47 (25/22)[B]	Estonian	17-68	46.8	Schizophrenia perphenazine	SAS BAS	Allele Ser p=0.02 NS after correction[B]	Gunes 2007[17]
			99 (51/48)[J]	European Caucasian	25-75	0	Schizophrenia Typical APDs	SAS AIMS	NS allele frequency OR 2.4 (0.9-6.7)[J]	Gunes 2008[37]
			126 (47/79)	African-Caribbean	49.2 SD±13.4	21	Mostly schizophrenia	UPDRS	**OR 2.61 (1.2-5.7) genotype SerSer+CysSer - CysCys** Bradykinesia OR 2.3 (0.99-5.2)[K]	Al Hadithy 2008[15]
			425 (194/231)[H]	US Caucasian	27.9 SD±12.4	47	Mostly schizophrenia, bipolar and depressive disorder	UKU AIMS TD criteria[I]	NS genotype and allele frequencies[H]	Al-Janabi 2009[38]
	-697G/C	-697C	47 (25/22)[B]	Estonian Caucasian	17-68	46.8	Schizophrenia Perphenazine	SAS BAS	**OR 4.3 (1.42-13.0) C allele p=0.01** [B]	Gunes 2007[17]
			99 (51/48)[J]	European Caucasian	25-75	0	Schizophrenia Typical APDs	SAS AIMS	NS allele frequency[J]	Gunes 2008[37]
	-759C/T (rs3813929)	T	47 (25/22)[B]	Estonian Caucasian	17-68	46.8	Schizophrenia perphenazine	SAS BAS	NS allele frequency[B]	Gunes 2007[17]
			99 (51/48)[J]	European Caucasian	25-75	0	Schizophrenia Typical APDs	SAS AIMS	NS allele frequencies[J]	Gunes 2008[37]
			126 (47/79)	African-Caribbean	49.2 SD±13.4	21	Mostly schizophrenia	UPDRS	NS TT+CT - CC	Al Hadithy 2008[15]
			425 (194/231)[H]	US Caucasian	27.9 SD±12.4	47	Mostly schizophrenia, bipolar and depressive disorder	UKU AIMS TD criteria[I]	NS genotype and allele frequencies p=0.06[H]	Al-Janabi 2009[38]
	-997 G/A[L]	A	99 (51/48)[J]	European Caucasian	25-75	0	Schizophrenia Typical APDs	SAS AIMS	NS allele frequencies[J]	Gunes 2008[37]
	-995 G/A[M]		425 (194/231)[H]	US Caucasian	27.9 SD±12.)	47	Mostly schizophrenia, bipolar and depressive disorder	UKU AIMS TD criteria[I]	NS genotype and allele frequencies p= 0.08[H]	Al-Janabi 2009[38]

Gene	SNP	Allele	N patients (with /without AIP)	Ethnicity or nationality	age	Sex F (%)	Diagnosis and Type of antipsychotic drug (APD)	Assessment of AIP	Odds ratio / p-value	Reference
RGS2	+2971C>G (rs4606)	G	115 (33/82)	Jewish	Cases 36.4±11.8 Controls 38.9±12.9	29.6	Schizophrenia Typical or combi with risperidone	SAS	**OR 0.31 (0.11-0.84) G-allele p=0.002[G]**	Greenbaum 2007[20]
			112 (37/75)	African-Caribbean	48.5 SD±13.5	17	Mostly schizophrenia	UPDRS	NS genotype CC - CG+GG	Al Hadithy 2009[22]
			184 (141/43) AfricanAmerican (AA) 115 (86/29) Caucasians 69 (39/14)	US AA 115 Caucasian 69	Cases 40.3±9.8 Controls 39.9±9.1	8.2	Schizophrenia Typical (26.2%) or atypical APDs	SAS	Overall sample: **OR 0.23 (0.10-0.54) G allele p=0.001** AA: **OR 0.20 (0.07-0.57) G allele p=0.003**	Greenbaum 2009[21]
			103	Japanese	33.6±11.9	51.5	Schizophrenia Typical (1/3), atypical APDs (1/3) or both (1/3)	DIEPSS	DIEPSS score higher in GG genotype p=0.009 After controlling for covariates ANCOVA analysis showed no association between DIEPSS score and rs4606 genotypes	Higa 2010[23]
COMT	G158A (rs4680)	A = Met	268 (80/188)	European Caucasian	Cases: 32.6±13 Controls: 37.6±16	[C]	Schizophrenia (195) bipolar disorders (42), other (31) mostly risperidone (60%) and haloperidol (16%)	SAS	NS in total group OR 0.6 (0.4-1) NS in schizophrenia OR 0.9 (0.5-1.7) **In bipolar OR 0.3 (0.1-0.8) p=0.01[G]**	Lafuente 2008[24]
BDNF	Val166Met (rs6265)	Val=G	147 (64/83)[P]	Han Chinese	Cases 40.4±12.4 Controls 41.9±13.7	47.6	Schizophrenia	SAS AIMS BAS	NS genotype and allele frequencies	Xu 2008[45]
		GT_n repeat	147 (64/83)[P]	Han Chinese	Cases 40.4±12.4 Controls 41.9±13.7	47.6	Schizophrenia	SAS AIMS BAS	**OR 0.4 (0.21-0.75) 230-bp allele p=0.003** **OR 2.26 (1.29-3.95) 234-bp allele p=0.004**	Xu 2008[45]
DAT1		VNTR 9/10-repeat	61 (32/29)	European Caucasian	Cases: 27.9±8.4 Controls 31.4±12.3	42.6	Schizophrenia Mostly risperidone (50%) and haloperidol (17%)	SAS	NS genotype and allele frequencies	Lafuente 2007[53]
			93 (63/56)[B]	European Caucasian	50 SD±12	17	Schizophrenia mostly typical APD	SAS AIMS	**OR 1.9 (1.1-3.3) 9 repeat allele p=0.04[B,Q]**	Güzey 2007[14]

A controls; were mostly medical staff with no history of psychosis, substance abuse or receiving antipsychotic drugs

B 25 patients with EPS: 12 parkinsonism, 2 akathisia, and 11 both. Association studies in total EPS group, no separate analysis for patients with parkinsonism

C similar distribution of gender between cases and controls

D Inconsistent with in vitro data of Cravchik, since we would expect increased adverse effect due to the less ineffective inhibition of the c-AMP synthesis upon exposure to various APD

E 63 patients with EPS: 37 parkinsonism, 23 acute dystonia, 15 tardive dsykinesia (12 patients had two or more different EPS in combination). Association studies in total EPS group, no separate analysis for patients with parkinsonism

F TaqIA and TaqIB in complete linkage disequilibrium (LD); D'=1

G The association remained significant after adjustment for multiple allele testing (Bonferroni's correction)

H 194 patients with any EPS: 143 with tardive dyskinesia, in 138 patients stiffness was present; unclear definition of EPS

I modification of criteria by Schoolar and Kane (1982)

J 51 patients with EPS: 22 parkinsonism, 13 dystonia, 6 tardive dyskinesia, 5 parkinsonism and dystonia and 5 parkinsonism and tardive dyskinesia

K In males OR 3.4 (1.2-9.4)

L Complete LD between -997 G/A and -759 C/T polymorphisms

M Near complete LD between -995 G/A and -759 C/T polymorphisms

N Total study population N=321 (81/198); subgroup risperidone users N=132 (38/84). Presented age in total study population

P Total chlorpromazine treatment group 147 (64/83); Unclear definition of EPS (BAS,AIMS AND SAS), no separate analysis for patients with parkinsonism rs6265G/A genotyped for 82 cases and controls (?)

Q Carriers of both A1 allele and common 9 repeat allele risk of EPS OR 4.0 (95% CI 1.05-15.2)

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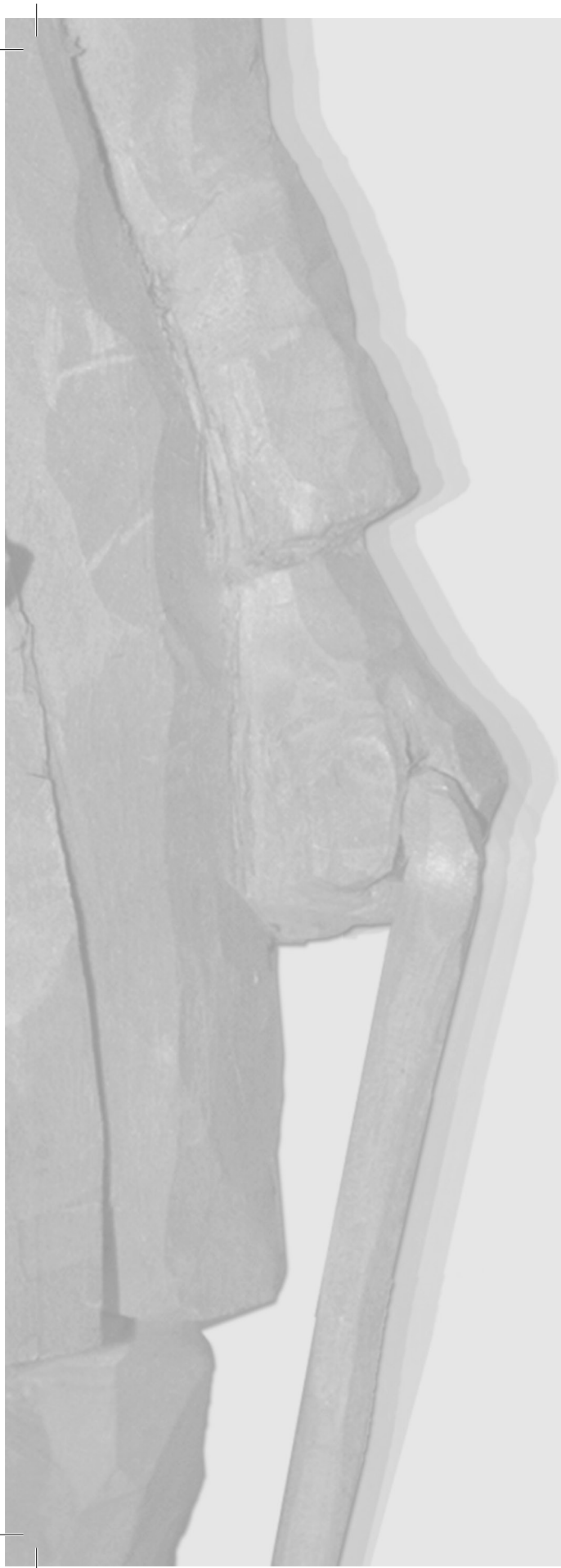

Chapter 4

Consequences

Chapter 4.1

Quality of life of elderly patients with antipsychotic induced parkinsonism: a cross-sectional study

Henrike J. Schouten
Wilma Knol
Toine C.G. Egberts
Alfred F.A.M. Schobben
Paul A.F. Jansen
Rob J. van Marum

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Abstract

Objectives
Antipsychotic induced parkinsonism (AIP) is one of the most common adverse effects of haloperidol. The purpose of this study was to investigate the association between AIP and quality of life of elderly patients treated with haloperidol.

Design
Cross-sectional study design.

Setting
Eleven nursing homes, geriatric departments of two hospitals, and three mental health care centers in the Netherlands.

Participants
140 elderly patients aged 65 years and older treated for at least 5 days with haloperidol.

Measurements
The presence of AIP was determined with the Simpson Angus Scale. Quality of life was scored with the QUALIDEM scale. Multivariate linear regression analysis was used to assess whether the presence of AIP and quality of life were associated. The data of patients with advanced dementia were analyzed separately.

Results
Of the 140 included patients, 65 (46%) were diagnosed with AIP. Patients with AIP scored lower than patients without AIP on the QUALIDEM subscales 'positive affect', 'negative affect', 'social relations', 'social isolation', and 'having something to do'. In patients with advanced dementia, quality of life was not significantly different in patients with or without AIP.

Conclusion
The presence of AIP is negatively associated with the quality of life of elderly patients treated with haloperidol.

Introduction

Despite the risk of serious adverse effects, antipsychotics are commonly prescribed to elderly patients for the treatment of acute and chronic psychotic symptoms or behavioural symptoms in dementia. The reported prevalence of antipsychotic drug use in nursing home residents is between 12% and 52%.[1-3] About 40% of elderly treated with conventional agents develop antipsychotic induced parkinsonism (AIP).[1,4] AIP is characterized by the presence of tremor, rigidity, and bradykinesia, symptoms which can adversely affect quality of life (QoL) and which may interfere with activities of daily living (ADL).[1]

Five studies of patients with schizophrenia (aged 18-67 years) treated with antipsychotic drugs showed that patients with AIP had lower QoL scores[5-8] and lower scores on affect balance scales[9], which are considered to reflect mood. In contrast, two other studies involving patients with schizophrenia (aged 30-60 years)[10,11] did not find a significant correlation between severity of extrapyramidal symptoms (including parkinsonism) and QoL. Several studies of patients with Parkinson's disease (PD) have shown the adverse effect of disability due to extrapyramidal symptoms on QoL, with postural instability and gait abnormalities being detrimental to ADL independence.[12,13] A poorer QoL has also been reported in the presence of bradykinesia[12] and dyskinesia associated with more severe PD.[14]

Although AIP is the second most common cause of parkinsonism,[15] the relation between AIP and QoL has not yet been investigated in elderly patients or in patients with dementia. The aim of this study was to investigate the association between AIP and different aspects of QoL in elderly patients treated with haloperidol.

Methods

Setting and study design

A cross-sectional design was used to investigate the relationship between AIP and QoL in elderly patients treated with haloperidol. The study took place between April and September 2008. Sixteen health care institutions in the Netherlands (3 mental health care centers, the geriatric departments of 2 hospitals and 11 nursing homes) participated in this study. In each participating center, physicians identified and included all patients aged 65 years and older who had been treated for at least 5 consecutive days with haloperidol until the day of inclusion, so a steady state plasma concentration of haloperidol can be presumed. Terminally ill patients and patients already diagnosed with parkinsonism were excluded, the latter to prevent misdiagnosis of AIP. Written informed consent was obtained from all participants or their legal representatives if

participants were considered to be incapacitated. The study was approved by the Dutch Central Committee on Research involving Human Subjects.

Assessment instruments

QoL was examined with the QUALIDEM.[16] As the applicability of certain items of the QUALIDEM is dependent on the severity of cognitive dysfunction, cognitive functioning was assessed by the treating physician, using the Reisberg Global Deterioration Scale (GDS).[17] This scale rates the severity of cognitive decline, with scores ranging from 1 ('no cognitive decline') to 7 ('very severe cognitive decline'). Diagnosis of dementia was based on a diagnosis mentioned in the medical record or cognitive impairment stage four or higher according to the Reisberg model.

The QUALIDEM is a validated and reliable QoL instrument specifically developed for elderly patients with dementia in residential settings and is the most appropriate instrument for evaluating QoL in patients with cognitive disorders who are not able to self-report.[18,19] The multidimensional behaviour observation scale contains 37 items allocated to 9 subscales: 'care relationship' (7 items, Cronbach's alpha 0.83), 'positive affect' (6 items, Cronbach's alpha 0.89), 'negative affect' (3 items, Cronbach's alpha 0.71), 'restlessness tense behavior' (3 items, Cronbach's alpha 0.74), 'positive self-image' (3 items, Cronbach's alpha 0.64), 'social relations' (6 items, Cronbach's alpha 0.80), social isolation (3 items, Cronbach's alpha 0.59), 'feeling at home' (4 items, Cronbach's alpha 0.73), and 'having something to do' (2 items, Cronbach's alpha 0.62).[16] The nursing staff selected a closely associated relative or a nurse who knew the participant well if committed relatives of the participant were not available. These relatives and nurses studied an instruction guide of the QUALIDEM [20] and scored the 37 items on a 4-point scale (never, seldom, sometimes, and often) after observing the participants for 1 week directly after inclusion. The score on each subscale was linearly transformed from 0 to 100, such that higher scores reflect a better QoL.[16] However, certain items, namely, 'positive self-image', 'feeling at home', and 'having something to do', cannot be reliably scored in patients with advanced dementia (GDS Reisberg score = 7), and so only 18 of the 37 QUALIDEM items were scored in these patients and results were calculated separately.[16]

To determine the presence of AIP, each participant was examined using the Simpson Angus Scale (SAS).[21] The investigators were trained previously in using the SAS by an instruction guide and an instruction video.[22] This SAS is developed to measure the presence of drug induced extrapyramidal disorders and is the most frequently used and one of the best-validated assessment scales to determine AIP.[23] The test has a good internal consistency (Cronbach's alpha 0.70) and a good inter-rater reliability (kappa 0.72).[24] The test scores 10 items assessing the severity of the specific motor symptoms rigidity, bradykinesia, and tremor. The items are scored on a 5-point scale (0-4), with the

total SAS score being the mean score of these 10 items (range 0–4); higher scores are indicative of more severe parkinsonism. Since many patients in this study were not able to walk independently, the SAS score was corrected for this by excluding the subscore 'gait' when calculating the mean total SAS score. Traditionally, a total SAS score of 0.3 or more is defined as parkinsonism,[21] but Janno et al showed that this score resulted in low specificity in a study in 99 inpatients with schizophrenia.[25] They suggested a cut-off score of 0.65, whereby specificity in diagnosing AIP was doubled to 0.62 without loss of sensitivity (1.0). We used a cut-off score of 0.65 to compare patients with (defined as a SAS score ≥ 0.65) or without (defined as a SAS score <0.65) AIP.

The following data were obtained from the medical record: general patient characteristics (e.g. age, sex, race), medical history including diagnosis of dementia, duration and dosage of haloperidol, indication for treatment and concomitant medication, including antidepressants (defined as drugs in WHO-ATC classification code N06 or N05AN), benzodiazepines (WHO-ATC classification code N05AH, N05BA, N05CD, or N05CF) and anticholinergic antiparkinsonian drugs (biperiden).[26]

Data analysis

Differences between patients with AIP or without AIP were tested using t-test for continuous data, chi-square test for categorical data, and Mann-Whitney U tests in case of skewed distributions. A two-tailed p-value less than 0.05 was considered statistically significant.

The strength of the association between AIP and QoL was investigated using univariate and multivariate linear regression analyses, taking into account all variables as mentioned in table 1 as potential confounders. Covariates were included in the regression model when addition induced a 10% change or more in the effect estimate (B-coefficient).[27] A subanalysis was performed in patients with advanced dementia (GDS = 7). Analysis where performed using Statistical Package for the Social Sciences (SPSS) version 15.0.

Results

Baseline demographics and AIP

Of the 157 patients who gave informed consent, 17 had missing QUALIDEM scores, so that the data of 140 patients were analyzed, 65 (46%) of whom had AIP. Information on baseline characteristics (Table 1) was missing for maximally two patients per characteristic. The patients with AIP were older (mean age 84.1 [SD 7.7] versus 81.4 [SD 7.6]) than the patients without AIP. Neither duration of treatment nor dose of haloperidol was significantly different between patients with or without AIP. The majority (85%) of all patients were diagnosed with dementia. Twenty patients were diagnosed with advanced dementia (GDS = 7). Three patients had dementia as well as schizophrenia. Of the 21 patients without dementia, patients were diagnosed with delirium (n=9), psychotic disorder not otherwise specified (n=5), schizophrenia or schizoaffective disorder (n=2), psychotic depression (n=1), or unknown diagnosis (n=4).

Quality of life

The overall QoL in the sample was moderate, with relatively high scores on the subscales 'positive self-image' and 'feeling at home' and relatively low scores on the subscales 'restless tense behaviour' and 'having something to do'. The patients with AIP scored significantly lower than the patients without AIP on 6 ('positive affect', 'negative affect', 'positive self-image', 'social relations', 'social isolation', and 'having something to do') of the 9 QUALIDEM subscales (Table 2). The difference between patients with and without AIP was the most apparent on the subscale 'having something to do', patients without AIP sometimes had something to do, whereas patients with AIP seldom had something to do. The characteristics 'age', 'admission to a nursing home', and 'use of anti-depressants' changed the association between AIP and one or more of the QUALIDEM subscales. After adjustment for these factors, the difference in 'positive self-image' between patients with or without AIP was no longer significant.

Table 1. Baseline characteristics of patients with or without antipsychotic induced parkinsonism (AIP)

Characteristics	AIP (n=65)	no AIP (n=75)	*p* -value
SAS-score , mean (SD)	1.10 (0.42)	0.28 (0.20)	<0.01
Male, n (%)	22 (34)	24 (32)	0.82
Age in years, mean (SD)	84.1 (7.7)	81.4 (7.6)	0.04
Smoking, n (%)	4 (6,3)	18 (24)	<0.01
Admitted, n (%) to a:			0.08
Mental health care centre	7 (11)	18 (24)	
Geriatric department of a hospital	3 (4.6)	6 (8.0)	
Nursing home	55 (85)	51 (68)	
Dementia	57 (90)	62 (84)	0.25
Cognitive functioning according to the Reisberg Global Deterioration Scale, n (%)			<0.01
1-3	10 (16)	17 (23)	
4-6	37 (59)	53 (72)	
7	16 (25)	4 (5.4)	
unknown	2	1	
Indication for antipsychotic drug prescription, n (%)			0.10
Delirium	7 (11)	13 (18)	
Behavioural problems in dementia	47 (72)	41 (55)	
Psychosis or other indication	11 (17)	21 (28)	
Dose haloperidol in milligrams/day, mean (SD)	1.50 (0.92)	1.86 (4.0)	0.49
Duration of haloperidol treatment, n (%)			0.06
5-14 days	5 (7.8)	12 (16)	
14 days-3 months	18 (28)	31 (43)	
3 months-1 year	23 (36)	17 (23)	
≥1 year	18 (28)	13 (18)	
unknown	1	2	
Concomitant medication, n (%)			
Biperiden	1 (1.5)	5 (6.7)	0.14
Antidepressants	23 (35)	18 (24)	0.14
Benzodiazepine derivates	15 (23)	15 (20)	0.66

Table 2. Association between antipsychotic induced parkinsonism (AIP) [defined as a SAS score ≥ 0.65] and observed quality of life (patients with advanced dementia, defined as a Reisberg Global Deterioration Score = 7 were excluded)

	No AIP (n=71)	AIP (n=49)	No AIP versus AIP					
QUALIDEM subscales	*Mean scale score* (SD)*	*Mean scale score* (SD)*	*B-unadj.*[†]	*95% CI for B-unadj.*[†]	*p-value*	*B –adj*[†,‡]	*95% CI for B-adj.*[†,‡]	*p-value*
Care relationship	67.74 (21.75)	63.56 (23.14)	-4.18	-12.39 to 4.03	0.32	-3.74	-12.33 to 4.84	0.39
Positive affect	70.74 (22.12)	59.75 (24.70)	-10.99	-19.52 to -2.45	0.01	-10.22	-18.89 to -1.56	0.02
Negative affect	67.76 (25.35)	52.61 (26.13)	-15.15	-24.60 to -5.71	0,00	-14.68	-24.50 to -4.85	<0.01
Restless tense behaviour	47.26 (28.53)	41.50 (26.91)	-5.77	-16.02 to 4.49	0.27	-6.19	-16.75 to 4.37	0.25
Positive self image	75.28 (23.70)	63.83 (29.83)	-11.44	-22.14 to -1.75	0.02	-10.13	-20.38 to 0.11	0.05
Social relations	58.06 (22.86)	46.82 (19.58)	-11.23	-19.17 to -3.30	0.01	-10.62	-18.88 to -2.36	0.01
Social isolation	67.76 (23.47)	51.47 (25.73)	-16.29	-25.27 to -7.31	<0.01	-13.79	-23.12 to -4.45	<0.01
Feeling at home	69.25 (22.87)	71.09 (25.86)	1.84	-7.04 to 10.72	0.68	1.89	-7.30 to 11.09	0.68
Having something to do	40.85 (34.13)	21.43 (27.64)	-19.42	-31.06 to -7.78	<0.01	-16.43	-28.52 to -4.33	0.01

CI, confidence interval; SAS, Simpson Angus Scale; SD, standard deviation

* QUALIDEM mean scale scores range: 0-100, higher scores indicate a better quality of life.

† Unstandardized coefficients. No AIP =0; AIP=1.

‡ All outcome variables are adjusted for age, nursing home, and prescription of antidepressants.

Association between AIP and QoL in advanced stage of dementia (GDS-Reisberg 7)

Patients with advanced dementia had higher mean scores on the subscales 'negative affect' and 'social isolation' than those without advanced dementia (73.3 vs. 52.2 and 54.4 vs. 51.1, respectively); the mean scores on the other subscales were all lower than those of patients without advanced dementia (GDS<7). Univariate and multivariate linear regression analyses showed no significant differences in the QUALIDEM subscale scores of the patients with advanced dementia with or without AIP (data not shown).

Discussion

To our knowledge, this is the first study that compared QoL in elderly patients with and without AIP. Since it is difficult to evaluate the QoL of elderly with poor communication abilities because of dementia or psychosis, we used the QUALIDEM. The QoL for the participants in the current study was moderate, with mean QUALIDEM subscales scores being lower than 75%. The presence of AIP was negatively associated with the QoL of elderly patients treated with haloperidol. After adjustment for known confounding factors, AIP was associated with a lower score on five of the nine QUALIDEM subscales. The presence of AIP resulted in lower scores on QUALIDEM domains assessing positive (mood) and negative (dissatisfaction) affect. Furthermore, the patients with AIP scored lower on social functioning, measured by observation of social interaction between the patient and other residents, and between patient and caregivers. Lastly, the patients with AIP had less to do, and performed fewer activities without the support of caregivers.

As parkinsonism flattens mimicry and renders individuals unable to express emotions, the ability to measure affect in these patients may be reduced. This could have resulted in the lower scores of the patients with AIP on the QUALIDEM subscales that quantify positive and negative affect. Several features of parkinsonism can explain the negative effect of AIP on social functions. For example, mobility limitations and communication problems due to deteriorated articulation may interfere with social functioning. Furthermore, hypersalivation may lead to embarrassment and social withdrawal. Most patients with AIP did not participate in daily activities. Axial impairment and bradykinesia as a result of parkinsonism have shown to be detrimental to daily self-care activities. A minimum level of ADL self-care ability is required to explore other types of activities.

More than 80% of the sample was diagnosed with dementia, yet the stage of dementia appeared to have little effect on patients' QoL. The patients with advanced dementia generally had a lower QoL, but QoL was not associated with the presence of AIP.

This study has some limitations. Its cross-sectional design means that we could not draw conclusions about the causality of the association between AIP and QoL. However, with exception of age and smoking frequency, none of the baseline characteristics were significantly different between patients with or without AIP, and adjustment for the use of antidepressants and the care setting did not substantially change our results. Unfortunately, no information was available on the participants' education and marital status. These sociodemographic characteristics might have biased the results if they were associated with QoL. However, a clear and consistent association between sociodemographic variables and QoL has not been found in patients with dementia.[28] An

unknown number of potential participants or their legal representatives did not give informed consent, which could have resulted in selection bias.

The QUALIDEM was validated in elderly individuals with dementia with a GDS-Reisberg score of 2-7, without PD and living in a residential setting.[16,18] However, there is currently no suitable scale for measuring the QoL of elderly patients with concomitant dementia or psychiatric disorders and parkinsonism. Furthermore, 24% of the patients were not living in a nursing home. Since the living situation interfered with the association between AIP and some of the QUALIDEM subscales, we adjusted for this in the analysis. Moreover, 15% of the patients were not clinically diagnosed with dementia. However, subanalysis of the data of patients with moderate to severe cognitive decline (GDS 4-6, n= 90) and no or mild cognitive decline (GDS 1-3, n=27) revealed the same effect of AIP on QoL. Therefore, it seems unlikely that the patients with less severe cognitive decline biased the results.

Another limitation concerns the assessment of different aspects of parkinsonism. Although the SAS was especially developed to measure drug induced parkinsonism, the scale has some restrictions. For example, 6 items are used to evaluate rigidity, but only one item is used to evaluate bradykinesia (gait). As almost 40% of our patients were not able to walk independently, we decided not to include the item 'gait' thereby not measuring bradykinesia at all.

Conclusion and recommendation

This study demonstrates a negative association of AIP and the QoL of elderly patients treated with haloperidol. For this reason, we recommend that the advantages and disadvantages of haloperidol should be carefully assessed before treatment is started in elderly patients. Even in patients on treatment less than 14 days, AIP was in almost 30% present. During treatment with haloperidol, clinicians and other caregivers should evaluate patients for signs of parkinsonism and for changes in QoL. Extrapyramidal symptoms can be reduced by switching from conventional antipsychotic drugs to atypical antipsychotic drugs.[29,30] It remains to be established whether the disadvantages caused by the adverse effects of atypical antipsychotic agents outweigh the poorer QoL attributable to the parkinsonism induced by conventional antipsychotics.

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Chapter 4.2

Antipsychotic drug use and risk of pneumonia in elderly people

Wilma Knol
Rob J. van Marum
Paul A. F. Jansen
Patrick C. Souverein
Alfred F. A. M. Schobben
Toine C. G. Egberts

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Abstract

Objectives
To investigate the association between antipsychotic drug use and risk of pneumonia in elderly people.

Design, setting and participants
A nested case-control analysis. Data were used from the PHARMO database, which collates information from community pharmacies and hospital discharge records. A cohort of 22,944 elderly people with at least one antipsychotic prescription; 543 cases of hospital admission for pneumonia were identified. Cases were compared with four randomly selected controls matched on index date.

Measurements
Antipsychotic drug use in the year before the index date was classified as current, recent, or past use. No prescription for an antipsychotic in the year before the index date was considered as no use. The strength of the association between use of antipsychotics and the development of pneumonia was estimated by multivariate logistic regression analysis and expressed as odds ratios (OR) with 95% confidence intervals (CIs).

Results
Current use of antipsychotics was associated with an almost 60% increase in the risk of pneumonia (adjusted OR 1.6; 95% CI 1.3-2.1). The risk was highest during the first week after initiation of an antipsychotic drug (adjusted OR 4.5; 95% CI 2.8-7.3). Similar associations were found after exclusion of elderly people with a diagnosis of delirium. Current users of atypical agents showed a higher risk of pneumonia (adjusted OR 3.1; 95% CI 1.9-5.1) compared to users of conventional agents (adjusted OR 1.5; 95% CI 1.2-1.9). There was no clear dose-response relationship.

Conclusion
Use of antipsychotics in elderly people is associated with an increased risk of pneumonia. This risk is highest shortly after the initiation of treatment with the greatest increase in risk found for atypical antipsychotics.

Introduction

Antipsychotic drugs are frequently being prescribed to elderly patients. Recent Canadian and European studies reported a prevalence of antipsychotic drug use of 0.5% in a community based population older than 65 years.[1,2] A Swedish study of non-institutionalized subjects aged over 80 shows antipsychotic drug use of 1.7% in elderly without dementia and 12.8% in elderly people with dementia.[3] In nursing homes, up to 40% of the residents may be prescribed antipsychotics.[4,5] It has been suggested that, among residents of nursing homes who receive antipsychotic therapy, more than half are prescribed for inappropriate reasons.[6]

Despite being frequently prescribed, antipsychotics often cause serious adverse effects, especially in elderly people. Recent studies showed an increased risk of death in elderly people using atypical and conventional antipsychotics. In a meta-analysis of 15 randomized clinical trials, Schneider and colleagues concluded that elderly with dementia using atypical antipsychotics were 1.5 times as likely to die as those taking a placebo.[7] In a retrospective cohort study using a Pennsylvania prescription database, Wang and colleagues demonstrated a 37% increased risk of death among elderly people treated with conventional antipsychotics compared to atypical drugs. The greatest increase in the risk of death was found early in treatment.[8] In an observational study, Trifiro and colleagues confirm that the risk of death is similarly elevated in users of atypical and conventional antipsychotics.[9]

In April 2005, the U.S. Food and Drug Administration (FDA) issued a warning against the use of atypical antipsychotics in the treatment of behavioural disorders in elderly patients with dementia, based on the results of a meta-analysis of 17 placebo-controlled clinical trials of various atypical antipsychotics. (http://www.fda.gov/cder/drug/advisory/antipsychotics.htm). In the FDA analysis, most deaths seemed related to cardio- and cerebrovascular events, or infections. Anticholinergic and alpha-adrenergic properties (affecting blood pressure and heart rate), prolongation of QT interval (causing arrhythmias) and hyperprolactinemia (promoting platelet aggregation) are potential mechanisms to explain the cardiovascular toxicity of antipsychotics. The effect of antipsychotic drugs on glucose and lipid metabolism is also an important long-term risk factor for cerebro- and cardiovascular disorders, but it seems unlikely that these adverse effects explain the increased risk of death shortly after initiation of antipsychotic drug therapy.[10-15] The relation between infections, mostly pneumonia, and antipsychotics, however, is unclear. The pathophysiologic mechanisms behind this supposed relation has not been investigated.

Because pneumonia is a major cause of morbidity and mortality in elderly people, it is important to be aware of the possible association between the use of antipsychotics and pneumonia.[16] The objective of the current study was to investigate the association between use of antipsychotics in elderly people and the risk of pneumonia in a nested case-control study design.

Methods

Setting

Data were derived from the PHARMO record linkage system. PHARMO includes pharmacy dispensing records from community pharmacies of approximately 950,000 community-dwelling residents from 25 population-defined areas in the Netherlands from 1985 onwards that can be linked to hospital discharge records.[17,18] Since virtually all patients in the Netherlands are registered with a single community pharmacy, independently of prescriber, pharmacy records are virtually complete with regard to the prescription drugs. Participants of the PHARMO population enter the database with the first prescription filled in a PHARMO community pharmacy and are followed to the last prescription.

The computerized drug dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed and the prescribed dosage regimen. The duration of use of each dispensed drug is estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. Patient information includes gender and date of birth. The database does not provide information concerning the indications for use of the medicines nor registration of non-prescription medicines.

The hospital discharge records were obtained from PRISMANT, an institute that collects all hospital discharge records nationally in the Netherlands since the 1960s. These records include detailed information concerning the primary and secondary discharge diagnosis; diagnostic, surgical, and treatment procedures; type and frequency of consultations with medical specialist; and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM).

Source population

The study was conducted in a cohort of patients aged 65 and older with at least one prescription for an antipsychotic drug during their recorded dispensing history from April 1985 to December 2003. The source population comprised only patients with at least one year of valid database history before their first prescription date in order to verify their previous drug use and history of pneumonia. To select new users, we

excluded patients with antipsychotic prescriptions in the 6 months before the inclusion date. In order not to retain patients with recent serious pneumonia, all patients with a prior hospital diagnosis of pneumonia in the year before prescription date were excluded. Follow-up started on the date of the first antipsychotic prescription. All individuals were followed until pneumonia developed, death or the end of the study period, whichever occurred first.

Case and control definition

A nested case-control study design was conducted within the cohort of antipsychotic drug users. Cases were defined as patients with a hospital diagnosis of pneumonia as the first-listed or as any-listed discharge diagnosis (ICD - 9 codes 480-486 and 507) during follow-up. Because the subcategorization of pneumonia is not always recorded appropriately, we included all types of pneumonia. The date of hospital admission was defined as the index date. For each case of pneumonia, we randomly selected four controls (i.e. no hospitalisation for pneumonia) from the same source population. Controls were assigned the same index date as the corresponding case.

Exposure assessment

Exposure of interest was the use of antipsychotic drugs. All antipsychotic drugs were classified according the Anatomical Therapeutic Classification (ATC) system of the World Health Organization.[19] Drugs starting with the four digits ATC-code N05A were classified as antipsychotics, with the exception of lithium, which is not an antipsychotic. Medication use during the year before the index date was analyzed. Drug use was classified as "current" if the most recent prescription ended within 7 days of the index date and classified as "past" if the prescription had ended more than 7 days earlier than the index date. Past use was then further categorized into "recent past" if the last prescription ended between 8 and 30 days and "past" if the last prescription ended more than 30 days before the index date. If patients had no prescription for an antipsychotic in the year before the index date, they were considered not exposed. To evaluate the effect of duration of the current episode of antipsychotic drug use, the cumulative number of days of antipsychotic medication prescribed before the index date was assessed. Duration was subdivided into 1-7 days, 8 -14 days, 15-30 days, 31- 90 days and > 90 days.

Among the current users of antipsychotics, we distinguished between users of atypical antipsychotics (risperidone, olanzapine, clozapine and quetiapine), conventional antipsychotics and concurrent use of more than one antipsychotic agent.

The dose of the antipsychotic was based on the last prescription. It was standardized to the number of Defined Daily Doses (DDD), a technical unit of measurement defined as the average dose per day for a drug used for its main indication in adults. Although the

heterogeneity of the elderly patient population demands an individualized approach to antipsychotic treatment, in general older patients receive lower doses of antipsychotic medications than younger patients. DDD was categorized into less than 0.25 DDD, 0.25-0.5 DDD and more than 0.5 DDD.

Potential confounders

Drugs and medical conditions that have previously been associated with the risk of pneumonia were considered as potential confounders. The diagnosis of medical conditions during the 6 months before the index date included lung diseases, heart failure, diabetes mellitus, Parkinson's disease, cerebrovascular disease, lung cancer and stomach cancer. Medication use in the 6-month period before the index date included antibiotics, benzodiazepines, immunosuppressive agents, gastric acid-suppressive drugs and use of drugs that have been reported to induce extrapyramidal symptoms.[20-22] Diagnosis of delirium was based on hospital diagnosis (ICD-9 code 293). New prescription or dose increases of benzodiazepine in the 2 weeks before hospital admission was also considered as suspect for manifestation of delirium.

Furthermore, potential markers for frailty of patients as the number of hospital admissions in 6 months before the index date and the prescribed number of different drugs on the index date were also gathered.

Data analysis

The strength of the association between current and past use of antipsychotics and the development of pneumonia was estimated by multivariate logistic regression analysis and expressed as odds ratios (OR) with 95% confidence intervals (CIs) taking into account potential confounding covariates. Covariates were included in the regression model if they were univariately associated with pneumonia ($p<0.10$) and the outcome induced a 10% or greater change in the crude matched OR for antipsychotics. Whether there were differences in the risk of development of pneumonia according to strata of the manifestation of delirium, new prescription of benzodiazepine and antibiotic use before hospital admission was assessed. Data were analyzed using SPSS for Windows, version 12.0 (SPSS, Inc., Chicago, IL).

Results

During the study period, 22,944 elderly people received a prescription for antipsychotic drugs. During or after treatment with antipsychotics 543 elderly were hospitalized with pneumonia. For the nested case control analysis, 2,163 controls were assigned to 543 elderly people who developed pneumonia (approximate case:control ratio 1:4). There were 65 cases (12%) of aspiration pneumonia (ICD–9 code 507) and 478 cases (88%) of other pneumonia.

The characteristics of this study population are shown in table 1**.** There were no major differences in age between cases and controls; the median age of the study population was 81 years. Approximately 60% of cases were male compared with 30% of the controls. All known potential risk factors for pneumonia were more prevalent among the cases. The most prevalent medical conditions in cases were chronic obstructive pulmonary disease and diabetes mellitus. Manifestation of delirium was slightly more prevalent among cases. Cases used antibiotics, immunosuppressants, acid-suppressive drugs and drugs that have the potential to cause extrapyramidal side effects more frequently than controls. Furthermore, the number of hospital admissions and the number of prescribed drugs were higher among cases than among controls.

Table 2 shows the association between antipsychotic drug use and the risk of pneumonia. Current use of antipsychotics was associated with a 60% increase in the risk of pneumonia (adjusted OR 1.6; 95% CI 1.3-2.1). Past use of antipsychotics was not associated with an increased risk of pneumonia. In a secondary analysis, elderly people with a diagnosis of delirium during hospital admission were excluded. The corresponding estimate for pneumonia in remaining patients was 1.9 (95% CI 1.6-2.4). Excluding elderly people with antibiotic use or benzodiazepine use in the week before hospital admission resulted in an estimated risk of 1.8 (95% CI 1.4-2.3) and 1.9 (95% CI 1.5-2.3), respectively.

Table 1. Characteristics of cases and control patients

Characteristics	Cases (n=543) n (%)	Controls (n=2163) n (%)	Crude Odds Ratio (95% Confidence Interval)
Age (years)			
65 – 74	127 (23.4)	563 (26.0)	Reference
75 – 84	260 (47.9)	948 (43.8)	1.2 (0.96-1.5)
≥ 85	156 (28.7)	652 (30.1)	1.1 (0.8-1.4)
Sex			
Female	226 (41.6)	1504 (69.3)	Reference
Male	317 (58.4)	659 (30.4)	3.2 (2.6-3.9)
Somatic drugs			
Antibiotics			
≤ *7 days*[*]	105 (19.3)	61 (2.8)	10.3 (7.3-14.4)
> *7 days*[*]	168 (30.9)	494 (22.8)	2.0 (1.6-2.5)
Immunosuppressants	71 (13.1)	123 (5.7)	2.5 (1.8-3.4)
Acid-suppressive drugs	131 (24.1)	369 (17.1)	1.5 (1.2-1.9)
Potential EPS-drugs	74 (13.6)	229 (10.6)	1.3 (1.0-1.8)
Benzodiazepines	272 (50.1)	934 (43.2)	1.3 (1.1-1.6)
< 14 days[*]	32 (5.9)	122 (5.6)	1.1 (0.7-1.6)
Delirium	7 (1.3)	15 (0.7)	1.9 (0.8-4.6)
Neurological condition			
CVA	20 (3.7)	24 (1.1)	3.4 (1.9-6.2)
Parkinson's disease	47 (8.7)	108 (5.0)	1.8 (1.3-2.6)
Internal condition			
COPD	138 (25.4)	206 (9.5)	3.2 (2.5-4.1)
Lung cancer	6 (1.1)	8 (0.4)	3.0 (1.0-8.7)
Diabetes mellitus	96 (17.7)	267 (12.3)	1.5 (1.2-2.0)
Heart failure	44 (8.1)	112 (5.2)	1.6 (1.1-2.3)
Number of hospital admissions			
0	275 (50.6)	1617 (74.8)	Reference
1	156 (28.7)	358 (16.6)	2.6 (2.0-3.2)
>1	112 (20.6)	188 (8.7)	3.5 (2.7-4.6)
Number of drugs			
0-3	96 (17.7)	767 (35.5)	Reference
4-9	184 (33.9)	727 (33.6)	2.0 (1.5-2.6)
>9	263 (48.4)	669 (30.9)	3.1 (2.4-4.1)

[*] Prescription period relative to hospital admission

Table 2. Association between use of antipsychotics and risk of pneumonia

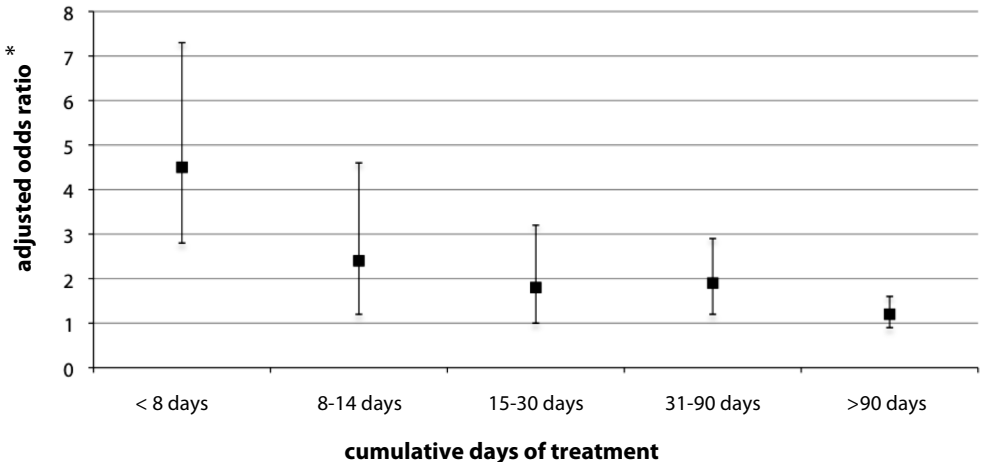
Antipsychotic Use	Cases (n=543) n (%)	Controls (n=2163) n (%)	Crude Odds Ratio (95% Confidence Interval)	Adjusted* Odds Ratio (95% Confidence Interval)
No use	189 (34.8)	963 (44.5)	Reference	Reference
Current use	243 (44.8)	641 (29.6)	1.9 (1.6-2.4)	1.6 (1.3-2.1)
Recent past 8-30 days	19 (3.5)	96 (4.4)	1.0 (0.6-1.7)	0.89 (0.5-1.6)
Past >30 days	92 (16.9)	463 (21.4)	1.0 (0.7-1.3)	0.69 (0.5-1.0)

*Adjusted for age, sex, medication (antibiotics, benzodiazepines, immunosuppressants, potential extrapyramidal symptom causing drugs, cardiovascular drugs, acid suppressive drugs), medical conditions (delirium, diabetes, chronic obstructive pulmonary disease, lung cancer, cerebrovascular events, heart failure, Parkinson's disease) and number of drugs and hospital admissions

Figure 1 shows the association between duration of antipsychotic use and risk of pneumonia in current users. An almost 5-fold increased risk of pneumonia in the first week of use of an antipsychotic drug was found (adjusted OR 4.5; 95% CI 2.8-7.3). With longer use of antipsychotics, the risk of pneumonia decreased. An effect of the prescribed daily dose was not found.

Of the 243 current users of antipsychotics 201 (83%) were prescribed a conventional antipsychotic, 37 (15%) an atypical antipsychotic and 5 (2%) received a combination. Although there was a stronger association between use of atypical antipsychotics and pneumonia (adjusted OR 3.1; 95% CI 1.9-5.1) compared to conventional agents (adjusted OR 1.5; 95% CI 1.2-1.9), numbers of users of an atypical antipsychotic drug were small (table 3). Subanalysis showed no dosing differences between atypical and conventional antipsychotics.

Figure 1. Risk of pneumonia and effect of duration of antipsychotic treatment



*Adjusted for age, sex, medication (antibiotics, benzodiazepines, immuno-suppressants, potential extrapyramidal symptom-causing drugs, cardiovascular drugs, acid suppressive drugs), medical conditions (delirium, diabetes mellitus, chronic obstructive pulmonary disease, lung cancer, cerebrovascular events, heart failure, Parkinson's disease), and number of drugs and hospital admissions.

Table 3. Risk of pneumonia and type of antipsychotic drug

Antipsychotic	Cases (n=243) n (%)	Controls (n=641) n (%)	Crude Odds Ratio (95% Confidence Interval)	Adjusted* Odds Ratio (95% Confidence Interval)
Atypical AP	37 (6.8)	63 (2.9)	2.9 (1.9-4.6)	3.1 (1.9-5.1)
Typical AP	201 (37.0)	572 (26.4)	1.8 (1.4-2.2)	1.5 (1.2-1.9)
Typical and atypical	5 (0.9)	6 (0.3)	4.2 (1.3-14.1)	1.9 (0.5-7.4)

*Adjusted for age, sex, medication (antibiotics, benzodiazepines, immunosuppressants, potential extrapyramidal symptom-causing drugs, cardiovascular drugs, acid suppressive drugs), medical conditions (delirium, diabetes, chronic obstructive pulmonary disease, lung cancer, cerebrovascular events, heart failure, Parkinson's disease) and number of drugs and hospital admissions

Discussion

The results of this nested case-control study show that current use of antipsychotics in elderly people is associated with an increased risk of developing pneumonia. After adjustment for known confounding factors, current use of antipsychotics was associated with a 60% higher risk of pneumonia than using no antipsychotics. The increase in risk showed an inversely proportional relationship to duration of treatment. The highest risk was found to occur shortly after the initiation of the antipsychotic drug treatment. Atypical drugs did not seem to be safer than conventional antipsychotics. No dose related association was found, and dosing differences could not explain the higher risk of pneumonia in the users of atypical antipsychotics than in users of conventional agents.

We are not aware of other studies that have assessed the use of antipsychotics and the risk of pneumonia to compare with our results, but our results may be considered to be in line with the results of a recent study of Wang et al who have investigated the risk of death with antipsychotics in elderly people. They also found that the greatest increase in risk of death occurred shortly after the initiation of antipsychotic therapy.

The mechanism to explain this effect of antipsychotic drugs remains speculative. It is well known that aspiration is an important pathogenic mechanism for pneumonia in elderly people.[23,24] Swallowing disorders and decreased cough reflex are important risk factors for community acquired pneumonia in elderly people,[25,26] although drug induced dysphagia (or its prevalence) is not well known and probably underreported. Antipsychotic induced dysphagia is only described in case reports.[27-36] It has been suggested that blocking of dopamine receptors may result in hyperfunctional involuntary movements (dyskinesia) of the oral pharyngeal musculature, rigidity and spasm of the pharyngeal musculature, which can result in aspiration. Dryness of the mouth, or xerostomia, is another possible mechanism, because it leads to impaired oropharyngeal bolus transport. Xerostomia results from antipsychotics with significant anticholinergic activity. Furthermore, sedation is also a well-known cause of swallowing problems, particular caused by histamine-1-receptor blocking in the central nervous system.[37] Some antipsychotics are known to have direct or indirect effect on the immune system.[38] Clozapine may cause agranulocytosis, which increases the risk of infections but occurs in less than 1% of the treated patients.

Although atypical antipsychotics have a less tendency to cause extrapyramidal symptoms than conventional antipsychotics, a stronger association was found between atypical antipsychotics and pneumonia. Perhaps the strength of histamine-1 blocking effect and anticholinergic effect can explain these findings. Risperidone was the most dispensed atypical antipsychotic in our study, and therefore, our results may not be generalizable to all types of atypical antipsychotics. Unfortunately, the small numbers of atypical antipsychotic drug users and the heterogeneity in conventional agents in this

study make it impossible to draw clear conclusions about the association between pneumonia and the degree of blockade of different receptors.

In this study, we were able to take advantage of the fact that in the PHARMO database all drug and medical information is prospectively collected at community pharmacies (and linked to hospital discharge records) that cover the general elderly population instead of just those presenting in clinical setting. Nevertheless, there are limitations to this study. The results of this observational study should be interpreted cautiously regarding the etiology of the increased risk of pneumonia in elderly people using antipsychotics. The crucial question is whether antipsychotics are a true etiologic agent in developing pneumonia. Earlier manifestations of another disease that is related to developing pneumonia may influence antipsychotic drug prescription. One of the reasons for prescribing antipsychotics in elderly people is treatment of psychotic symptoms in delirium. Because pneumonia is a potential cause of delirium, we cannot eliminate that pneumonia existed when treatment with antipsychotics was initiated. This so-called protopathic bias could have occurred in this study.[39] To determine the possibility of protopathic bias, we analyzed the data according to strata of the manifestation of delirium, new prescription of benzodiazepine and antibiotic use before hospital admission. We found no difference in risk by excluding cases and controls with manifestation of delirium or new prescription for benzodiazepine (OR 1.9 with or without delirium and with or without new benzodiazepine use). The association with pneumonia was slightly stronger for users of antibiotics before hospital admission (with antibiotic use OR 1.9 and without OR 1.8). Because previous studies show that physicians and nurses fail to recognize more than half of delirium cases, it is likely that the incidence of delirium in this study was underestimated.[40] Unfortunately, no information was available on psychiatric diagnosis, existence of dementia or underlying disease for which patients were being treated with antipsychotic medication. Concurrent diagnoses may have biased the results whenever they were associated with the occurrence of pneumonia.

False-negative misclassification by underestimation of pneumonia may have occurred because not all pneumonia in elderly people require hospital treatment. Jackson et al show that 59% of the patients aged 65 and older with community-acquired pneumonia are treated on an outpatient basis.[41] Furthermore, because the diagnosis of pneumonia came from hospital discharge records, medical records could not be reviewed, so misclassification of information cannot be ruled out. Misclassification of exposure may have occurred, because we used dispensed medication data and had no information about treatment compliance. Nevertheless, it is likely that such misclassification was random and evenly distributed among cases and controls.

The analysis was adjusted for a range of medical conditions and drugs that are associated with an increased risk of developing pneumonia; however, residual

confounding arising from unavailable or unknown risk factors cannot be ruled out. The PHARMO database does not provide information about smoking, alcoholism, institutionalization or influenza vaccination.

The severity of disease may affect choice of type and dosing of antipsychotics. We adjusted for dosing in the analysis. Confounding would be possible if we hypothesize that physicians prefer atypical antipsychotics in frail elderly people. Our data do not support this view; prescription of atypical antipsychotics was comparable with prescription of conventional antipsychotics in elderly people taking more than 9 drugs or admitted to the hospital more than once a year.

In conclusion, these results suggest that use of antipsychotics is associated with an increased risk of pneumonia in elderly people. The risk is highest shortly after the initiation of the antipsychotic treatment, and the greatest risk is found in users of atypical agents. Our results suggest that antipsychotics should not be overlooked as a potential cause of pneumonia, and although the underlying mechanism remains speculative, clinicians may need to monitor patients for swallowing disorders and sedation. At this time, we recommend a careful weighing of the possible risks against the benefits before starting antipsychotic treatment in elderly people.

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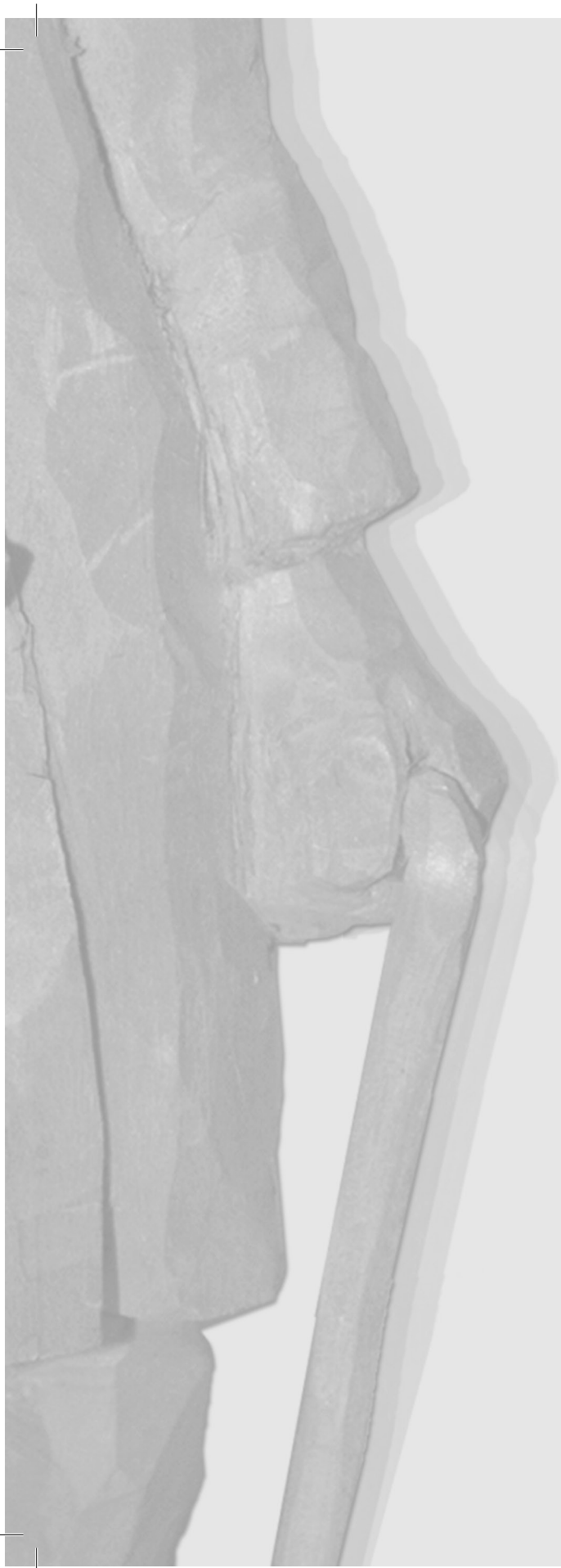


Chapter 5

General discussion

Introduction

The main objective of this thesis was to gain more knowledge about antipsychotic induced parkinsonism (AIP) in elderly patients. The studies that have been conducted focused on three subjects A) to qualify the available rating scales for drug induced parkinsonism (DIP) and to give a recommendation for use in daily practice, B) to quantify the influence of several potential determinants that may explain variability in susceptibility for AIP, including the role of genetic factors, and C) to investigate consequences of AIP in elderly patients.

Compared to their widespread use for the assessment of drug induced parkinsonism (DIP), rating scales have rarely been sufficiently evaluated for validity and reliability. We made an evidence based choice to use the Simpson Angus Scale (SAS) in our further studies by performing a systematic review of available instruments for the assessment of DIP (chapter 2.1) and by performing a clinimetric study in elderly patients in which the SAS appears to be a valid and easy to perform tool to evaluate DIP in daily clinical practice (chapter 2.2).

In our very old study population (mean age 83) we found a 46% prevalence of parkinsonism during use of haloperidol. As presence of haloperidol induced parkinsonism (HIP) adversely affects the quality of life of elderly patients (chapter 4.1), better understanding of causes of HIP is needed. In our study population we found, unexpectedly, no association between HIP and prescribed dose nor plasma concentration. A trend toward a higher risk with a longer duration of use of haloperidol was observed, although not statistically significant (chapter 3.1). The results of our candidate gene association study indicate that carriership of the -759 T allele of the HTR2C gene might be protective for development of HIP in female elderly patients (chapter 3.2).

The results of our study do not support the hypothesis of a peripheral pharmacokinetic explanation for increased sensitivity to HIP. Our results add evidence of the role of pharmacogenetics, but do not support a major role for pharmacogenetics in the central pharmacodynamic hypothesis. Consequently the central pharmacokinetic hypothesis may play a more important role in explaining variability of HIP in elderly patients.

Furthermore is shown in this thesis that the risk of pneumonia should be added to the possible adverse effects of antipsychotic drugs in the elderly (chapter 4.2). The higher risk with atypical than conventional antipsychotics suggests that mechanisms other than extrapyramidal adverse effects (on oral phyaryngeal musculature) may contribute.

In this final chapter, the results of the individual studies will be placed in a broader perspective, focusing on three major topics:

1. Balancing between limited effectiveness of antipsychotics and serious adverse effects in the elderly;
2. Susceptibility for haloperidol induced parkinsonism (HIP) in elderly patients and the gaps in the proposed pathofysiological framework for increased HIP susceptibility;
3. Methodological considerations related to research in elderly people in general and more specifically related to pharmacokinetic and pharmacogenetic studies.

In addition, we give recommendations for clinical practice and future research.

Balancing between limited effectiveness of antipsychotics and serious adverse effects in the elderly

Antipsychotic drugs (APDs) are widely prescribed to elderly patients. The reported annual prevalence of antipsychotic drug use is approximately 3.6% in elderly in a general population, which is more than three times higher than in patients below 65 years of age.[1] In nursing home residents the prevalence of antipsychotic drug use is clearly higher and varies between 12% and 52%.[2-4] Approved indications for antipsychotics in general are schizophrenia and bipolar disorder (mania). Haloperidol has also a regulatory approval for certain symptoms associated with Gilles de la Tourette (tics), Huntington's disease (chorea), and nausea and vomiting when other treatment options fail.[5] The atypical antipsychotics clozapine and risperidone have received approval for the treatment of respectively psychosis in Parkinson's disease and agitation in patients with Alzheimer's disease.[5] However, in daily clinical practice antipsychotics are prescribed to elderly patients for a much broader range of symptoms and diseases, i.e. off-label.[1] Conventional and atypical antipsychotics were prescribed off-label in respectively 68% and 75% of patients aged 65 years and older in 2008 in the U.S., 1% respectively 12% of this off-label use was based on moderate to good evidence.[6] Especially the efficacy of antipsychotics in dementia, which has been studied more extensively than the efficacy in delirium or schizophrenia in elderly is considered modest.[7-11] Although well-designed studies comparing pharmacological interventions in a controlled environment are lacking for delirium in elderly, available studies suggest benefits in reducing symptom severity and duration of delirium for haloperidol.[8]

Despite the fact that antipsychotics have been applied for more than half a century, the knowledge about adverse effects is far from complete. New adverse effects are still detected, the mechanism behind more and less common adverse effects are often not elucidated and the effect of risk management strategies are unknown. This hampers therapeutic decision making for the individual patient. Ongoing observational research is particularly important in older patients who are frequently excluded from registration studies, although they are at higher risk and experience more harm of adverse effects

because of diminished physiological reserves. Increased risk for falls and fractures (Relative Risk 1.59)[13], cardiac arrhythmias (OR 1.86 for risk of hospitalization for ventricular arrhythmias or cardiac arrest in users of conventional APDs compared to non users)[14], cerebrovascular events (OR 1.6-1.7)[15], venous thromboembolism (conventional APDs OR 0.9/Hazard Ratio (HR) 1.0, atypical APDs HR 2.0)[16] and metabolic abnormalities including obesity (OR >1.56, with olanzapine and quetiapine in particular)[17] are reported.[18] Anticholinergic (increasing risk of confusion), alpha-adrenergic (affecting blood pressure and heart rate), histaminergic (increasing risk of excessive sedation) and dopaminergic (bone demineralization by raising prolactin levels) properties are possible etiologic factors for falls and related fractures.[21] Prolongation of QT interval (causing arrhythmias), orthostatic hypotension, thromboembolic effects by raising anti-phospholipid and prolactin levels, serotonine-related altered platelet function and deregulation of glucose and lipid metabolism are potential mechanisms to explain the cardio- and cerebrovascular effects of antipsychotics.[14,15,22,23] However, it seems unlikely that deregulation of glucose and lipid metabolism contributes to the risk of cerebrovascular events as the risk is highest less than a week after initiating of antipsychotic drug treatment (OR 9.9; 5.7-17.2).[15] Moreover the metabolic effects, especially the risk of diabetes tends to be attenuated in elderly patients.[24]

Conventional antipsychotics such as haloperidol are particularly associated with an increased risk for extrapyramidal symptoms (30% more likely during treatment with conventional [with HR of 1.44] than atypical APDs).[12] A greater affinity to block dopamine 2 (D2) receptors and a slower dissociation from the D2 receptors are suggested explanations for the higher risk.[19,20]

Furthermore, in a meta-analysis and several observational studies it is suggested that treatment with both atypical and conventional antipsychotic drugs may increase mortality (1.6-2 fold increased risk) in patients with dementia.[25-28] In a 12 month Randomized Controlled Trial (RCT) an increase in mortality (5-8%) was found in patients with dementia who continued antipsychotic treatment compared to patients who switched to placebo.[29] To put the results in the right perspective it is important to realize that the absolute increase in risk is considered to be small compared with the high mortality rates in elderly patients, which is often estimated as 30% or more per year in nursing homes.[30] Increase in mortality in relation to treatment with APDs in elderly is to our knowledge not studied in elderly patients with delirium and not confirmed in elderly patients with schizophrenia. In contrast, an integrated analysis of results from short-term placebo controlled trials, conducted in the pre-authorization phase, showed a non significant risk of mortality in schizophrenic elderly patients with placebo compared to treatment with atypical antipsychotics (crude OR 1.58; 95% CI 0.14-17.45).[31]

The risk of death in patients with dementia increased early after initiation of treatment and death seems to be related to cardio- and cerebrovascular events, or infections.[26-28]

The relation between infections, mostly pneumonia, and antipsychotics is not entirely clear. As pneumonia is a major cause of morbidity and mortality in the elderly, it is important to be aware of the possible relation with the use of antipsychotics.[32] We studied the association between antipsychotic drug use and the risk of pneumonia in a nested case-control study with data from the Dutch PHARMO record linkage system which collates information from community pharmacies and hospital discharge records (chapter 4.2). After adjusting for confounding current antipsychotic drug use showed an increased risk of pneumonia in elderly people (adjusted OR 1.6; 95% CI 1.3–2.1). This risk is highest in the first week after the initiation. Atypical drugs did not seem to be safer than conventional antipsychotics. Our finding was replicated in several observational studies. Trifero et al demonstrated in a nested case-control study that exposure to a conventional antipsychotic drug as well as to an atypical antipsychotic drug increases the risk of pneumonia (respectively adj. OR 1.76; 95% CI 1.22-2.53 and 2.61; 95% CI 1.48-4.61).[33] Also, Gau et al reaffirmed the association between atypical antipsychotics and pneumonia (adj OR 2.26; 95% CI 1.23-4.15).[34] In contrast, in a cohort of elderly nursing home patients Huybrechts et al used a proportional hazard model to study major medical events after initiation of psychotropic medications and found no clinically meaningful differences for risk of pneumonia between conventional and atypical antipsychotic drug exposure (RR 1.03; 95% CI 0.62-1.69).[35] The underlying mechanism remains speculative. Impaired oro-pharyngeal bolus transport induced by dryness of the mouth as an anticholinergic effect, excessive sedation as an antihistaminergic effect or extrapyramidal effects on oral pharyngeal musculature causing aspiration are suggested mechanisms. The latter hypothesis seems less plausible as atypical antipsychotics show a stronger association with pneumonia than conventional antipsychotics. For clinical practice, the results of three observational studies suggest that treatment with an antipsychotic drug increases the risk of pneumonia. This finding implicates a need to monitor elderly patients for swallowing disorders and sedation, particularly at the early phase of treatment with APDs.

The first step in taking appropriate antipsychotic treatment decisions in daily clinical practice remains deciphering the underlying cause of psychotic symptoms. This can be complex in elderly patients for reasons as not being able to give a clear description of their symptoms, presence of comorbidity, atypical presentation of symptoms of underlying disease or adverse effects of medication and possible interference of environmental factors. Reversible causes (e.g. adverse effects of medication, urinary retention, pain etc) should always be considered and adequately treated. Non-pharmacological interventions, for example modifying the environment, improving communication, structured activities and sensory interventions need to be sought. The extent of distress caused by psychotic symptoms and possible interference with the ability to take care of patients with psychosis should be central in the decision whether

prescription of an antipsychotics is necessary. The choice of an antipsychotic drug should depend on the cause of psychosis and evidence for effectiveness. Because of limited evidence and serious adverse effects restrictive prescription in elderly patients with dementia is necessary. Moreover choice of antipsychotics should be guided largely by the potential adverse effects in the individual elderly patient. The risk of pneumonia should be added to other possible risks that need careful weighing against the benefit before starting antipsychotic treatment in the elderly.

Nevertheless there is a considerable discrepancy between available scientific evidence and the reality of prescribing of APDs to elderly in daily clinical practice. A survey study in Dutch nursing homes shows that physicians expect better response of treatment with APDs for behavioural symptoms of dementia (48%) than available evidence justifies.[30] Although not studied, three possible explanations could be hypothesized. Firstly, nonpharmacological interventions may be not sufficiently available, mostly due to financial reasons leading to understaffing or insufficiently trained staff. Secondly, studies on the (adverse) effects of APDs for behavioural problems in dementia are seldomly performed in populations comparable with those in daily clinical practice, especially not with nursing home residents. Thirdly, the proxies for clinical outcomes used in studies (for example a score on a rating scale) frequently differ from the target symptoms which need an intervention in daily clinical practice (for example relieve of burden of symptoms to postpone admissions into a nursing home). It is therefore not surprising that physicians tend to value their own subjective experience with APDs more than research evidence. As long as scientific evidence provides limited answers on essential questions in daily clinical practice, prescribing of APDs in elderly patients remains a balancing act with careful weighing of benefits and possible adverse effects and uncertainty about outcomes. When decision is made to prescribe antipsychotics to elderly patients, careful monitoring of both course of sympoms that led to treatment initiation and occurrence of possible adverse effects is needed. Physicians should periodically re-evaluate the need for continuation of antipsychotic treatment among elderly patients and dare to stop.

Susceptibility for haloperidol induced parkinsonism (HIP) in elderly patients and the gaps in the proposed pathofysiological framework for increased HIP susceptibility

Despite substantial differences in the pharmacological properties between conventional and atypical antipsychotics and inconsistencies in epidemiological studies concerning previously mentioned risks of antipsychotics, the most updated research evidence seems to suggest that atypical antipsychotics are not safer and not more efficacious than the conventional antipsychotics when used in elderly patients.[36,37] In general, preference of prescription of an atypical antipsychotic drug above prescription of haloperidol in elderly patients is not supported by evidence. Haloperidol is a conventional antipsychotic drug of the butyrophenone class which was first synthesized by Janssen Laboratories in 1958. In the elderly general population haloperidol is still the most frequently prescribed antipsychotic drug.[1,38] AIP was soon after introduction of haloperidol recognized as an adverse effect. It is standard practice to avoid prescription in patients with Parkinson's disease, parkinsonism or Lewy body dementia. Nevertheless AIP develops in about 40% of elderly patients using conventional antipsychotics. In our study population of very old patients, with mean age of 83 years old we even found a prevalence of parkinsonism of 46% during use of haloperidol (chapter 3.1). It is well known that elderly people are more prone to develop AIP, but there are also notable variations in occurrence of this adverse effect in individual elderly people. Given that our understanding of the underlying mechanisms of this age related sensitivity is mostly hypothetical, it is even more difficult to predict which individual older patient is more likely to develop AIP. As presence of HIP adversely affects the quality of life of elderly patients (chapter 4.1), better understanding of causes of HIP is needed to develop effective treatment strategies tailored to the individual susceptible older patient.

A greater affinity for and possibly a slower dissociation from the D2 receptor of haloperidol compared to atypical antipsychotics contribute to an increased risk of AIP.[39,20] Suggested explanations for increased sensitivity for AIP in elderly and interindividual variations in sensitivity in elderly are either higher plasma concentration for a given dose (peripheral pharmacokinetic hypothesis), an increased brain access and distribution for a given plasma level (central pharmacokinetic hypothesis) or increased sensitivity at the receptor level (pharmacodynamic hypothesis).[40] Little is known about the extent of contribution of each of the three hypothesis to sensitivity to AIP in elderly patients.

The results of our study do not support the hypothesis of a peripheral pharmacokinetic explanation for increased sensitivity to HIP in elderly in clinical practice. In a daily practice setting we found no association between HIP and prescribed dose (0.3-5.0 mg/day) nor plasma concentration (0.14-4.11µg/l) of haloperidol (chapter 3.1). Dose of haloperidol was moderately, but significantly associated with haloperidol plasma concentration (B=0.53, weighted r^2=0.32; p<0.001). Because of this relationship large variation in plasma concentration related to genetic variation in CYP2D6 seems not important in our study population. However, influence of genetic variation in cytochrome P450 enzymes in the individual patient can not be ruled out. In two of the four available previous studies in which relationship between dosage and concentration of haloperidol in elderly was examined, no correlation was found between dose or concentration and extrapyramidal symptoms (EPS),[41,42] while the other two studies did find a correlation.[43,44] The last two studies showed that plasma level, but not dose, significantly correlated with increase in EPS.[43,44] One major advantage of the study of Pelton et al is that patients on baseline had no significant parkinsonism; this information is lacking in our study. Nevertheless, the four previous studies are small (19-40 participants) and use correlation for description of relationship between dose, concentration and adverse effect. Moreover, our results are not directly comparable with previous studies as different ratings scales are used to assess the outcome EPS or parkinsonism. Previous studies show that gender, race and smoking status were contributors to the ratio of concentration to dose.[40,42,45-47] In our very old study population we found no significant association between different age groups and risk of HIP. We were also not able to confirm that female gender is a risk factor for AIP. Our results seem to indicate that smoking is associated with a decreased risk. However, the confidence interval is wide and after controlling for confounding, the association between smoking and HIP lost its significance. This means that either there is no association or our study lacks the power to reveal this association. Our study adds to the existing evidence that support is lacking for a major role of the peripheral pharmacokinetic hypothesis in the explanation for the variation in HIP sensitivity in elderly during treatment with low doses (<5 mg) of haloperidol. A central pharmacokinetic or pharmacodynamic explanation seems therefore more likely.

We studied therefore in the same study population the effect of genetic variability on the central pharmacodynamics of antipsychotics. We used a (hypothesis driven) candidate gene approach to evaluate the modifying effect of Single Nucleotide Polymorphisms (SNPs) in genes encoding for receptors in the dopamine (DRD2 and DRD3) and 5-HT systems (5-HT2A and 2C), as well as a gene coding for a protein that regulates these receptors (RGS2), an enzyme involved in the biosynthesis and biotransformation of dopamine (COMT) and a neutrotropin, which has an important role in promoting and modifying growth differentiation and survival of neurons (BDNF)

(chapter 3.2). Candidate gene polymorphisms that might play a role in susceptibility for AIP are the HTR2C and COMT gene. Female carriers of the -759 T allele of the HTR2C gene showed a significantly decreased risk of AIP (adj. OR 0.31; 95% CI 0.11-0.85). The association between HIP and carriership of the COMT 158A allele did not reach statistical significance (adj. OR 0.58; 95% CI 0.26-1.29). However, the large confidence interval may mean that our study has not the power to reveal a true association. No significant associations were found between HIP and the polymorphisms of DRD2, DRD3, HTR2A, RGS2 and BDNF gene. Notably, our data do not support a major role for genetic variation in the dopamine receptor gene to predispose to AIP. Dopamine availability could be more important for HIP susceptibility than the availability of dopaminergic receptors. The impact of the endogenous dopamine level in vivo may warrant further research.

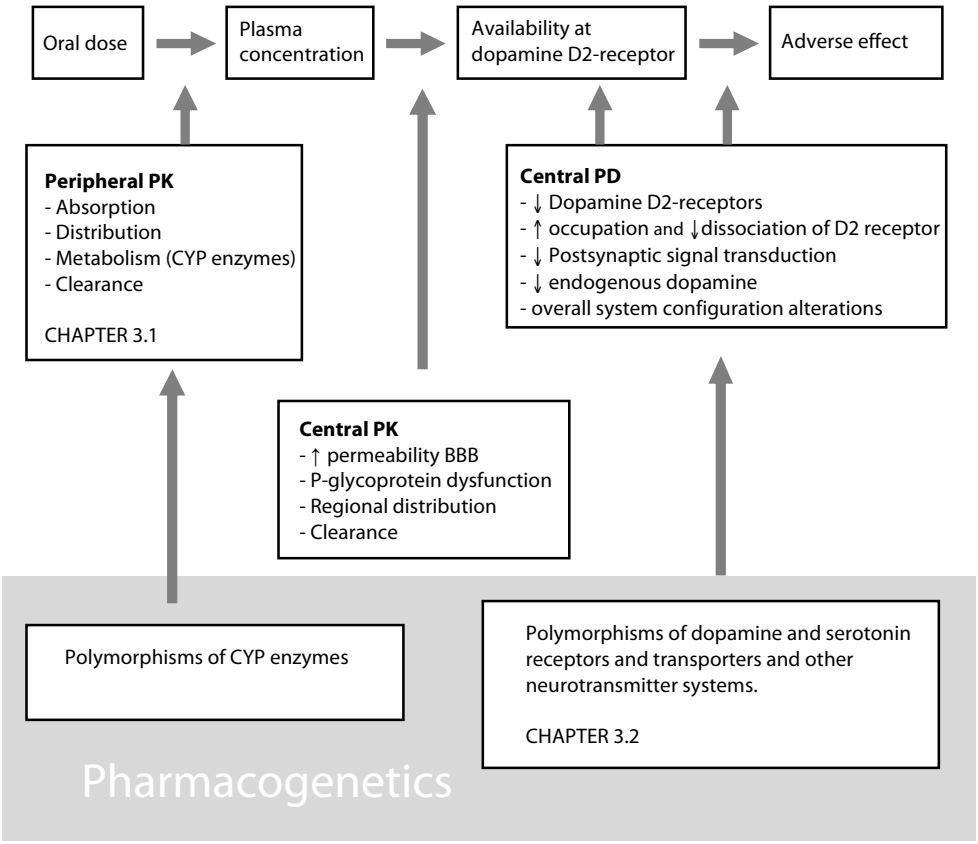
The results of our study show a limited contribution of examined SNPs to sensitivity for HIP. Other possible contributors to the sensitivity for HIP in the central pharmacodynamic hypothesis are decrease in number of dopamine neurons and decline of dopamine D2 receptors with age, as shown in post-mortem studies as well as in vivo studies.[48,49] This decline in receptor number does not necessary lead to an increase of occupancy of dopamine receptors. According to a classical receptor theory, the percentage occupancy of a receptor by an antipsychotic is determined mainly by a first-order process and independent of the absolute number of receptors.[50] It is the magnitude of the biological response that is dependent on the absolute number of receptors occupied by agonists. Therefore, as either the endogenous agonist or its receptor population decrease in number, the absolute number of receptors occupied by the endogenous agonist declines, resulting in a lower downstream response. Thus, a system with a lower number of receptors- as is the case in the brain of older patients- would be expected to require a higher occupancy for the same downstream effect. In younger patients with schizophrenia, occupancy of more than 80% of striatal D2 receptors with antipsychotics has been associated with extrapyramidal symptoms, suggesting that a minimum of 20% of the receptor population must be free of antagonist for physiological transmission to overcome extrapyramidal symptoms. Therefore, if drug concentrations are the same, cells that have higher receptor densities must possess more receptors occupied by drugs than cells that have lower receptor densities because receptor occupancy rates in both cells are the same. In view of decline in absolute receptor number with age, therefore, a greater percentage of receptors (20 + x%) must be free to provide an adequate level of physiological transmission in elderly patients. Therefore, this would predict that while the younger patient would present with extrapyramidal symptoms when antipsychotic occupancy is >80%, older patients with schizophrenia would show extrapyramidal symptoms at lower occupancy (100%-20%-x% = <80%).[40] This threshold may even be lower in persons with Alzheimer's disease. A decrease in dopamine D2 receptors in patients with Alzheimer's disease

compared to healthy elderly controls has been reported,[51] comparison of D2 receptor density between patients with Alzheimer's disease and schizophrenia is not available. Recently Uchida et al described an interesting method to predict dopamine D2 receptor occupancy levels from the peripheral plasma or serum levels of the used antipsychotic drug.[52] The therapeutic window for haloperidol corresponding with dopamine receptor occupancy of 60-78% is estimated between 0.8 and 4.2 ng/mL (=µg/l) with over- or underestimation from true occupancy of 7.0%. The mean age of patients involved in the positron emission tomography (PET) studies which were used to develop the model ranged form 28 to 62 years, with only one PET study in patients aged 50 and older (mean 62 +/- 9 years). Therefore, the model could not be generalized to our study population or to elderly patients in general. Nevertheless the findings in this single available antipsychotic drug-binding PET study in elderly with schizophrenia (whom received risperidone) adds important evidence to the framework of contributors to sensitivity to AIP. AIP was observed at D2 occupancy of 34%-79%, which is in contrast with published literature in younger patients in whom occurrence of AIP is consistently associated with occupancy levels higher than 80%.[53] Confirmation of these findings, preferable also in elderly patients using haloperidol and in elderly patients with dementia or delirium is needed before the results can be extrapolated to an older population.
Adding to the complexity, individual variability likely exists in pre- and postreceptor compensatory mechanisms, including precipitants of endogenous dopamine level decline and G-protein-signaling dysfunction. However, the latter is not confirmed for dopamine receptors.

In this thesis we did not investigate the contribution of the central pharmacokinetic hypothesis and the contribution of the level of endogenous dopamine (which belongs to the central pharmacodynamic hypothesis). Suggested age-related mechanisms are firstly increased drug access in the brain because of loosening of tight junctions in the blood brain barrier (BBB) and decline in P-glycoprotein (P-gp) function[54], which restrict the permeability of the BBB indirectly by transporting drugs back into the peripheral circulation and secondly decreased availability of dopamine in the brain related to a decline in synthesis and release of dopamine in the brain[55], a decline in density of dopamine transporters[56] and an increase of MAO-B activity[57], the principal enzyme responsible for the catabolism of dopamine. As haloperidol is not a P-gp substrate it is unlikely that the first mechanism is a contributor to increased sensitivity to HIP. The role of the central pharmacokinetic hypothesis in sensitivity for AIP is largely unrevealed. Release of dopamine in the brain, density of dopamine transporters and P-gp function could be investigated using PET, the other above suggested age-related mechanisms are based on post-mortem studies. As PET studies also offer the possibility to asses the binding of antipsychotics to central dopamine D2 receptors it could be a promising

method to reduce the gap in knowledge in both the central pharmacokinetic and central pharmacodynamic hypothesis (figure 1).

Figure 1. Framework of potential contributors to increased haloperidol induced parkinsonism susceptibility



Abbreviations: PK= pharmacokinetics; PD= pharmacodynamics

Methodological considerations related to research in elderly people in general and more specifically related to pharmacokinetic and pharmacogenetic studies

Multiple designs are possible to study effectiveness and adverse effects of drugs, but not all designs will be either suitable or practically realizable. Data from randomized controlled trials (RCTs) constitute the highest order of evidence for efficacy. A fundamental problem in making treatment decisions is that older people with chronic diseases and polypharmacy are underrepresented in most clinical trials and that older people with frailty nearly always are excluded.[58] In 1993 the International Conference on Harmonisation (ICH) released the ICH E7 document that provides recommendations in the design and conduct of clinical trials of medicines that are likely to have significant use in the elderly.[59] Nevertheless exclusion of older patients from clinical trials is still widespread.[60] To investigate the extent of exclusion of older individuals from RCTs, to identify the reasons underlying this exclusion, and to reach a paradigm shift the PaRticipation of ElDerly In Clinical Trials (PREDICT)[61] project was started in 2008. Another step forward in this field is the recognition that the needs of older people are being taken into account in the development and evaluation of new medicines by the regulatory agencies. An example of this is the Geriatric Expert Group (GEG) of the EMA, which was installed in May 2011. The GEG has the objective and mandates to give the Committee for Medicinal Products for Human Use (CHMP) input on geriatric aspects of medicines development and guidelines.[62]

Although inclusion of older people in RCTs needs high priority, RCTs may not always be feasible mainly due to practical, financial or ethical reasons. Even with inclusion of large numbers, it will remain a challenge to create homogeneous, comparable study arms with heterogeneous multimorbidities in elderly patients. Furthermore, RCTs are generally of too short duration to detect later onset adverse effects. Observational studies, which include intensive monitoring programs performed by network organisation like the Netherlands Pharmacovigilance Centre Lareb are the main alternatives.[63] If large enough and of assured quality observational studies can generate a large amount of essential data.[64] Dealing with potential bias caused by confounding is the main challenge in observational studies. Regarding etiology of studied intended and unintended effects, results of an observational study should be interpreted cautiously.

We experienced that performing a prospective observational study in an elderly population is also complex. Our study was integrated in daily clinical activities since financial support was lacking. As a result not all approached physicians or the management of the approached institutions did agree with participation. Besides, the possible burden of research assessment for elderly patients, frequently diagnosed with dementia could be a reason for refusal of participation. Particularly when it concerns incapacitated patients, physicians or legal representatives who carry responsibility seem reserved. For reasons of limited inclusion in a longitudinal observational study we

changed our study design and performed a cross-sectional study. The main limitations of this design is not being able to determine the temporality of an association and particularly in our study, the lacking assessment of parkinsonism before treatment with haloperidol (information bias). Our very old study population with mean age of 83 years old comprised 69 cases and 81 controls and should be considered as small, although two- three times larger than previous dose-concentration-EPS studies in elderly patients. To evaluate impact of all possible covariates in variability in plasma concentration of haloperidol between elderly individuals a mixed effect modeling approach would be preferable. More variables such as weight, creatinine clearance, liver function laboratory parameters and more plasma samples per subject, that were not available in our study, would be necessary. For practical reasons mentioned above, such a study was not realizable.

Adequately powered studies are of cause necessary to detect statistically significant genetic differences between affected and unaffected patients. However a common limitation in pharmacogenetic research of antipsychotic induced parkinsonism is limited sample-size. Furthermore pharmacogenetic research of antipsychotic induced parkinsonism has been less extensive than that of antipsychotic induced tardive dyskinesia, although parkinsonism is much more commonly encountered in clinical practice in elderly. Our intention in this thesis was to determine whether genotyping of pharmacodynamic polymorphisms in daily clinical practice in an older population has a positive contribution in understanding sensitivity to HIP. To maximize the a priori chance of detecting an association we selected polymorphisms of candidate genes based on specific pathophysiological hypothesis and through prior association studies. This approach does not provide comprehensive coverage of the genetic variation as in haplotype and genomic wide analysis. However, as in these approaches multiple comparisons are being made, correction of multiple testing is required; which implies that even larger study populations are needed to provide sufficient power to detect significant associations. Performing meta-analyses of available studies would be another possibility to increase power. Lack of consensus on which instrument should be used to asses antipsychotic induced parkinsonism hampers performing a meta-analysis. Al Hadity et al are the first to suggest to divide AIP in the three sub-symptoms; bradykinesia, tremor and rigidity.[65] Based on studies in patients with Parkinson's disease they assume that sub-symptoms find their origin in distinct neurological circuits with different etiology and pathophysiology, and therefore different genetic vulnerability. It remains speculative and further research is necessary to elucidate whether pathofysiologic findings in different disease entities are generalizable.
Since genetic factors are relatively independent of age, the proportion of phenotypic variation that is contributed to genetic factors may decline with increasing age, which

has been demonstrated in disorders of later life like dementia.[66] We suppose that the contribution of genetics to the development of HIP will be largest in patients who develop HIP in a serious degree and shortly after initiating antipsychotic treatment. In analogy, the protective effect of genetic factors or the contribution of genetics to non-HIP phenotype will be largest in patients who do not develop HIP. In our study population both groups are small; total score on the SAS was 0 in 8.7% and >1.8 in 1.9% of the study population. To compare genetic variation in two groups a good match between the genetic background of cases and controls should be ensured, so that any genetic difference between them is related to HIP and not to biased sampling. We adjusted for smoking, as patients with HIP smoked significantly less frequent compared to patients without HIP. However, smoking was associated with a non significant reduction of the risk for HIP. With regard to comparable characteristics in patients with and without HIP and recruitment, we consider our study population as representative of elderly patients in daily practice in hospitals and nursing homes.

By performing a systematic review of available instruments we made an evidence based choice to use the Simpson Angus Scale to assess AIP (chapter 2.1 and 2.2). Nevertheless evidence based practice and practice based evidence not always go hand in hand with each other. As 40% of our elderly patients was not able to walk independently we decided to adapt the scale by excluding the gait-subscore and re-standardizing the total score. This adapted version of the SAS is not validated. Nevertheless the expected information bias by this adaptation seems negligible as internal consistency decreases slightly when the item gait is omitted from the scale (maximum decrease in Cronbach's α of 0.03). Lack of consensus on which instrument should be used to asses antipsychotic or drug induced parkinsonism and as a consequence a diversity in measuring AIP in different studies with use of unclear cut off points could lead to biased effect estimates (information bias/misclassification of diagnosis) and hampers comparing of results with previous studies.
Active recruitment of study participants could result in selection bias if the selection of the participants with and without the outcome depends on the exposure status. Lacking information about the selection method by the treating physician could have resulted in selection bias. In observational studies factors that determine whether a patient receives a specific drug or not could result in differences between groups in prognostic factors related to the outcome (confounding by indication). As all our participants were users of haloperidol and had an indication for treatment confounding by indication has probably not influenced our results. Introduction of bias by depletion of susceptible patients or dose reduction in susceptible patients can not be ruled out. Finally, although characteristics of patient with and without HIP were comparable with exception of

smoking, residual confounding remains possible. We were able to adjust for dementia, but not for the degree of cerebrovascular damage or D2 receptor density.
Pharmacokinetic, -dynamic and –genetic research in elderly as well as application of research in daily clinical practice has many challenges that have to be overcome in order to provide a comprehensive pathofysiological framework to increased sensitivity for AIP.

Implications for clinical practice

In this thesis we have shown that occurrence of AIP has a negative effect on quality of life of elderly patients treated with haloperidol. In elderly patients, especially in the very old and those who are living in nursing homes, purpose of therapy is to improve quality of life more than improve quantity of the remaining months or years. Appropriate evaluation of effectiveness and adverse effects of antipsychotic drug treatment includes assessment of quality of life as it is an important health outcome. In our thesis the QUALIDEM proved to be a feasible instrument to assess quality of life in elderly with poor communication abilities because of psychosis or dementia. The negative impact on quality of life is a strong argument for structured assessment of AIP both in daily practice as in research.
Presence of parkinsonism should be assessed before prescription of an APD and also be monitored during use of APDs. Ideally according standard diagnostic assessment methods, about which currently no consensus exists. Adequate documentation, preferably in an electronic system will also need attention. Because of the association between APD use and pneumonia, closely monitoring of elderly patients for sedation or aspiration is particularly necessary in the first 2 weeks of treatment with APDs and with increasing of dose. Whenever possible, simultaneous use of APDs and other psychotropic drugs with possible sedative effect should be avoided or limited to short periods of use with careful observation.

Implications for research

Although haloperidol induced parkinsonism is known for more than half a century, the studies presented in this thesis indicate that there is still a need to increase our knowledge about this adverse effect. Clinical experts and researchers firstly need to achieve consensus on which instrument should be used to assess AIP to be able to minimize information bias, to be able to compare results and perform meta-analyses.
Our study adds to the existing evidence that support is lacking for a major role of the peripheral pharmacokinetic hypothesis in the explanation for the variation in HIP sensitivity in elderly. The available evidence does also not allow a firm conclusion on whether pharmacogenetics is a important factor in the explanation of the increased HIP susceptibility. Prospective data are needed to validate the possible protective effect of carriership of the HTR2C -759 T and the COMT 158A allele. In contrast to candidate gene

based studies, which are hypothesis driven, genome wide association (GWA) studies, in which the entire genome is analyzed have the potential to discover new DNA variants. GWA studies may reveal a more complete picture of genetic polymorphisms involved in development of AIP. However, GWA studies can give computational complexities, as they could include 500.000 or more SNPs. So, even larger study populations are needed to provide sufficient power to detect significant associations. Large multicenter prospective studies will be required to establish the value of genotyping in daily clinical practice. It is an interesting question whether further investigation of the central pharmacokinetic hypothesis will be more promising in understanding the increased susceptibility for HIP in elderly patients. PET and cerebrospinal fluid studies could elucidate the role of the central pharmacokinetic hypothesis and also that part of the central pharmcodynamic hypothesis (regarding endogenous dopamine level) we did not study. Although it should be taken into account that the more invasive character of these kind of studies will increase the threshold to participate for elderly people.

The benefit of scientific evidence in clinical practice could be increased if research is conducted in "real clinical practice" conditions. Involvement of clinicians with experience of treating geriatric patients to asses relevant clinical outcomes instead of surrogate parameters and involment of a study population that is representative for geriatric patients in daily clinical practice may reduce the gap between scientific knowledge and clinical application.

Continuation of research in post-authorization studies or large, probably practice-oriented observational studies with registration of drug use and clinical data is necessary to fulfil the expectations of developing effective antipsychotic treatment strategies tailored to the individual older patient.

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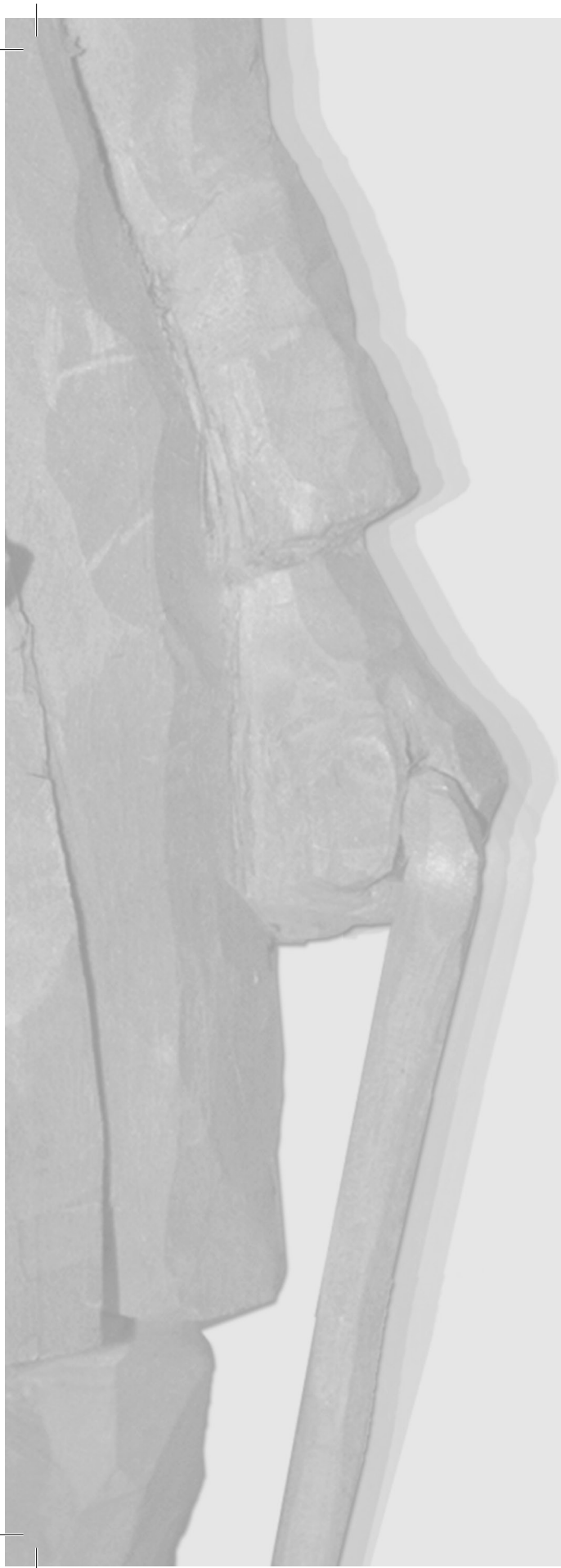

Chapter 6

Summary
Samenvatting
Dankwoord
List of co-authors
List of publications
About the author

Summary

Despite the risk of serious adverse effects, antipsychotic drugs are frequently prescribed to elderly patients to relieve psychotic or behavioural symptoms. Antipsychotic induced parkinsonism (AIP), which is characterized by tremor, bradykinesia, rigidity and postural instability during the use of an antipsychotic drug, is an impacting adverse effect affecting about 40% of patients using conventional antipsychotics. Besides that it is well known that elderly people are more prone to develop AIP, there are also notable variations in occurrence of this adverse effect in individual elderly people. Improvement of knowledge about the mechanisms underlying susceptibility for AIP is essential to develop methods to individualize antipsychotic drug therapy that minimizes adverse drug reactions while balancing the need to treat symptoms and maintain well being in the elderly.

The main objective of this thesis was to gain more knowledge about antipsychotic-induced parkinsonism (AIP) in elderly patients. The studies that have been conducted focused on three subjects A) to qualify the available rating scales for drug induced parkinsonism (DIP) and to give a recommendation for use in daily practice, B) to quantify the influence of several potential determinants that may explain variability of AIP, including the role of genetic factors, and C) to investigate consequences of AIP in elderly patients.

Chapter 2 of this thesis describes the assessment of antipsychotic induced parkinsonism. Compared to their widespread use for the assessment of drug induced parkinsonism (DIP), rating scales are seldom sufficiently evaluated for validity and reliability. **Chapter 2.1** provides a systematic review of the available instruments and their clinimetric qualities and feasibility. We identified seventeen different rating scales used for the assessment of DIP. For ten of these we identified validation studies. The most frequently used scale is the Simpson Angus Scale (SAS), followed by the Extrapyramidal Symptom Rating Scale (ESRS) and the Unified Parkinson Disease Rating Scale (UPDRS). None of the indentified scales fulfil all criteria of an appropriate ratings scale for DIP (good conceptual approach, feasible and evidence for validity and reliability). Validation studies for DIP are lacking for the comprehensive UPDRS, which is primarily designed to assess symptoms of Parkinson's disease and not to assess DIP. The SADIMoD has the best evidence for reliability and validity, but it's complexity hampers use in daily practice. The SAS, the St Hans Rating Scale for Extrapyramidal Syndromes (SHRS) and the Drug-Induced Extrapyramidal Symptom Scale (DIEPSS) seem the most valid, reliable and easy to use instruments to evaluate DIP in clinical practice, although it can be questioned whether these rating scales actually measure all aspects of parkinsonism.

Subsequently, we evaluated in **chapter 2.2** the clinimetric properties of the SAS by assessing 15 elderly diagnosed with DIP by three independent investigators. The SAS demonstrated good internal consistency reliability (Cronbach's α coefficients 0.83). We found 87-100% agreement on the individual items with acceptance of one point difference, reflecting good inter-rater reliability. The SAS also demonstrated an acceptable correlation with the SADIMoD (Spearman's rho=0.66; p<0.01). We concluded that the SAS appears to be a valid and by different instructed health care professionals easy to perform research tool to evaluate DIP in daily clinical practice. We decided to use the SAS in our further studies (**chapter 3.1, 3.2 and 4.1**).

Chapter 3 describes factors that possibly influence the variation in occurrence of AIP in elderly patients. Suggested mechanisms underlying increased sensitivity and variation in sensitivity in elderly patients are either higher plasma concentration at a given dose (peripheral pharmacokinetics), an increased brain access and distribution for a given plasma level (central pharmacokinetics), or an increased sensitivity at the receptor level (central pharmacodynamics).

In our very old study population, with mean age of 83 years old we found a prevalence of parkinsonism of 46% during use of haloperidol. In **chapter 3.1** we investigated the association between haloperidol induced parkinsonism (HIP) and dose, plasma concentration and duration of use of haloperidol. Dose of haloperidol was moderate, but significantly associated with haloperidol plasma concentration (weighted r^2=0.32; p<0.001). We found no association between HIP and prescribed dose nor plasma concentration. A not statistically significant trend toward a higher risk with a longer duration of use of haloperidol was observed.

In **chapter 3.2** we investigated whether previous identified genetic polymorphisms at DRD2, ANKK1, DRD3, HTR2A, HTR2C, RGS2, COMT and BDNF genes are associated with AIP in elderly patients. Frequencies of the -759T allele of the HTR2C gene and the 158A allele of the COMT gene were significantly higher in patients without AIP (nominal p=0.03 and p=0.02, respectively). The analysis of the -759 C/T polymorphism was limited to females, since the HTR2C gene is located on the X chromosome and allele frequency calculations of this polymorphism were influenced by gender distribution. Allele carriership in females was associated with a lower risk of AIP (adjusted odds ratio (OR) 0.31; 95% confidence interval (CI) 0.11-0.85). The decrease in risk of AIP in carriers of the COMT 158A allele did not reach statistical significance. Further studies in a larger study population are necessary to investigate whether the 158A allele of the COMT gene has also a protective effect. No significant associations were found between AIP and the remaining selected polymorphisms.

Our study adds to the existing evidence that support is lacking for a major role of the peripheral pharmacokinetic hypothesis in the explanation for the variation in HIP sensitivity in elderly. The results do also not allow a firm conclusion on whether pharmacogenetics is a important factor in the explanation of the increased HIP susceptibility. Further investigation of the central pharmacokinetic hypothesis seems more promising in understanding the increased HIP susceptibility.

Chapter 4 focuses on consequences of AIP in elderly patients.

In **chapter 4.1** we evaluated quality of life in elderly patients with AIP in the same population as in **chapter 3**. Since it is difficult to evaluate the quality of life (QoL) in elderly with poor communication abilities because of psychosis or dementia, we used the QUALIDEM which offers the caregiver the possibility to rate several domains of QoL by observation. We found that the presence of AIP adversely affects the quality of life of elderly patients treated with haloperidol. The presence of AIP resulted in lower scores on QUALIDEM domains assessing positive (mood) and negative (dissatisfaction) affect. Furthermore, on social functioning, measured by observation of social interaction between the patient and other residents, and between patient and caregivers. Lastly, the patients with AIP had less to do, and performed fewer activities without the support of caregivers.

Previous studies suggest that treatment with antipsychotics may increase mortality in elderly. The causes of death appeared to be cardiovascular of infectious (pneumonia). The relation between pneumonia and antipsychotics is not entirely clear. In **chapter 4.2** we investigated the association between antipsychotic drug use and pneumonia in a nested case-control study. We used data from the Dutch PHARMO record linkage system which collates information from community pharmacies and hospital discharge records. After adjusting for confounding current antipsychotic drug use showed an increased risk of pneumonia in elderly people (adjusted OR 1.6; 95% CI 1.3–2.1). This risk is highest in the first week after the initiation. Atypical drugs did not seem to be safer than conventional antipsychotics. The underlying mechanism remains speculative. Impaired oro-pharyngeal bolus transport induced by dryness of the mouth as an anticholinergic effect, excessive sedation as an antihistaminergic effect or extrapyramidal effects on oral pharyngeal musculature causing aspiration are suggested mechanisms. The latter hypothesis seems less plausible as atypical antipsychotics show a stronger association with pneumonia than conventional antipsychotics. This finding implicates a need to monitor elderly patients for swallowing disorders and sedation, particularly at the early phase of treatment with antipsychotics.

Chapter 5 provides a general discussion of the results of the individual studies in this thesis placed in a broader perspective. Three topics are discussed: balancing between limited effectiveness of antipsychotics and serious adverse effects in the elderly; susceptibility for haloperidol induced parkinsonism (HIP) and the gaps in the proposed pathophysiological framework for increased HIP susceptibility; methodological considerations related to research in elderly persons in general and more specifically ralated to pharmacokinetic and pharmacogenetic studies. In addition, implications for clinical practice and research are discussed.
Continued research in elderly people is necesarry to fulfil the expectations of developing effective antipsychotic treatment strategies tailored to the individual older patient.

Samenvatting

Hoewel het gebruik van antipsychotica met ernstige bijwerkingen gepaard kan gaan, worden deze geneesmiddelen regelmatig voorgeschreven aan ouderen om psychotische verschijnselen of gedragsproblemen bij dementie te verminderen. Door antipsychotica geïnduceerd parkinsonisme (AIP), wat zich kenmerkt door bewegingsarmoede, spierstijfheid, tremor en houdingsinstabiliteit ten gevolge van antipsychotica, is de meest bekende en een bijzonder hinderlijke bijwerking die bij ongeveer 40% van de ouderen die een klassiek antipsychoticum gebruiken optreedt. Ouderen zijn niet alleen gevoeliger voor het ontwikkelen van AIP, in de klinisch praktijk wordt bij ouderen ook een opmerkelijke individuele variabiliteit waargenomen in het optreden van deze bijwerking. Het vergroten van kennis over het onderliggende mechanisme van deze gevoeligheid voor AIP is essentieel om methodes te kunnen ontwikkelen die het mogelijk maken om een advies op maat te geven aan de individuele oudere patiënt. Geïndividualiseerde farmacotherapie heeft tot doel hinderlijke ziekte-symptomen te verhelpen en welbevinden te bevorderen, maar het risico op bijwerkingen te verkleinen.

Met de onderzoeken, die in het kader van dit proefschrift zijn uitgevoerd, was het de bedoeling om een bijdrage te leveren aan kennisvergroting op het gebied van door antipsychotica geïnduceerd parkinsonisme bij ouderen. Het doel van dit proefschrift is drieledig;

A) de beschikbare meetinstrumenten voor medicatie geïnduceerd parkinsonisme te beoordelen en het doen van een aanbeveling voor gebruik in de dagelijkse praktijk, B) dieper in te gaan op de invloed van verschillende factoren die de variabiliteit in het optreden van AIP zouden kunnen verklaren, waaronder de bijdrage van genetische factoren en C) de consequenties van AIP voor oudere patiënten te onderzoeken.

Hoofdstuk 2 van dit proefschrift gaat over beschikbare meetinstrumenten voor de beoordeling van door antipsychotica geïnduceerd parkinsonisme**.** Hoewel meetinstrumenten voor de beoordeling van medicatie geïnduceerd parkinsonisme veel worden gebruikt, is de betrouwbaarheid (de mate waarin de uitkomsten op een schaal beïnvloed zijn door toevallige omstandigheden) en validiteit (de mate waarin daadwerkelijk gemeten wordt wat men wil meten) van de bestaande meetinstrumenten zelden voldoende onderzocht. In **hoofdstuk 2.1** geven we een overzicht van de beschikbare meetinstrumenten, beschrijven we de methodologische kwaliteiten en geven we praktische informatie over toepassing van de meetinstrumenten. Er werden 17 verschillende meetinstrumenten voor het beoordelen van medicatie geïndiceerd parkinsonisme in de literatuur gevonden. Van 10 van deze meetschalen zijn validatie studies beschikbaar. De meest gebruikte meetschalen zijn de Simpson Angus Scale (SAS), gevolgd door de Extrapyramidal Symptom Rating Scale (ESRS) en de Unified

Parkinson Disease Rating Scale (UPDRS). Geen van de geselecteerde meetschalen voldeed aan alle criteria waaraan een meetschaal moet voldoen om bruikbaar te zijn (een goed conceptueel model, goede uitvoerbaarheid en voldoende bewijs voor validiteit en betrouwbaarheid). Validatie studies voor medicatie geïnduceerd parkinsonisme ontbreken voor de UPDRS, welke oorspronkelijk is ontwikkeld voor het beoordelen van verschillende aspecten van de ziekte van Parkinson en niet om door medicatie geïnduceerd parkinsonisme te beoordelen. Van de verschillende meetschalen is de validiteit en betrouwbaarheid van de SADIMoD het best onderzocht, echter de complexiteit van deze meetschaal belemmert toepassing in de dagelijkse praktijk. De SAS, de St. Hans Rating Scale for Extrapyramidal Syndromes (SHRS) en de Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) lijken het meest geschikt voor het beoordelen van door medicatie geïnduceerd parkinsonisme in de dagelijkse praktijk, hoewel er twijfel bestaat of alle aspecten van parkinsonisme voldoende beoordeeld worden.
Vervolgens, beschrijven we in **hoofdstuk 2.2** de evaluatie van de SAS door drie onafhankelijke onderzoekers (arts-assistent, fysiotherapeut en klinisch geriater) bij 15 ouderen bij wie tevoren medicatie geïnduceerd parkinsonisme door de behandelend arts was vastgesteld. Ten eerste bleken de verschillende items van de SAS goed met elkaar samen te hangen (Cronbach's α coëfficiënt 0,83). Ten tweede bleek de betrouwbaarheid van de SAS goed te zijn wanneer de scores van de onafhankelijke onderzoekers werd vergeleken. Wij vonden een overeenstemming van 87-100% op individuele items wanneer we 1 punt verschil per item accepteerden. Ten derde bleek de overeenstemming met de SADIMoD acceptabel (Spearman's rho=0,66; p<0,01). Op basis van deze resultaten concluderen wij dat de SAS een valide en betrouwbare schaal is om door medicatie geïnduceerd parkinsonisme in de dagelijkse praktijk te beoordelen. De uitvoering van de SAS was eenvoudig voor verschillende geïnstrueerde gezondheidszorgmedewerkers. In aansluiting hierop besloten we de SAS te gebruiken in onze vervolg studies (**hoofdstukken 3.1, 3.2 en 4.1**).
Hoofdstuk 3 beschrijft factoren die mogelijk van invloed zijn op de individuele variabiliteit in het optreden van AIP bij ouderen. Er bestaan drie algemene theorieën voor een verhoogde gevoeligheid bij ouderen in het algemeen en voor een individuele variabiliteit in gevoeligheid bij ouderen, namelijk een bepaalde dosis leidt tot een hogere concentratie in het bloedplasma dan verwacht (perifere farmacokinetiek), een bepaalde plasmaconcentratie leidt tot een hogere beschikbaarheid en distributie in de hersenen dan verwacht (centrale farmacokinetiek) en/of er bestaat een verhoogde gevoeligheid op het niveau van de receptoren (centrale farmacodynamiek).
In onze zeer oude studie populatie, met gemiddelde leeftijd van 83 jaar, constateerden we dat er bij 46% van de ouderen sprake was van parkinsonisme bij het gebruik van haloperidol. **In hoofdstuk 3.2** hebben we gekeken of er een relatie bestaat tussen door haloperidol geïnduceerd parkinsonisme en de voorgeschreven dosis, de plasma

concentratie of duur van gebruik van haloperidol. De dosis van haloperidol was matig, maar significant geassocieerd met plasma concentratie van haloperidol (gewogen r^2=0,32; p<0,001). Er was geen associatie tussen haloperidol geïnduceerd parkinsonisme en voorgeschreven dosis of plasmaconcentratie. Alhoewel het niet statisch significant bleek te zijn, was er een trend waar te nemen in toename van risico op haloperidol geïnduceerd parkinsonisme bij een langere gebruiksduur.

In **hoofdstuk 3.2** bestudeerden we de relatie tussen verschillende genetische polymorfismen en door haloperidol geïnduceerd parkinsonisme. De selectie van genen (DRD2, ANKK1, DRD3, HTR2A, HTR2C, RGS2, COMT and BDNF) vond plaats op basis van eerder bestudeerde genen in relatie met door antipsychotica geïnduceerd parkinsonisme en/of op basis van een hypothese over hoe ze betrokken zijn bij het ontstaan van haloperidol geïnduceerd parkinsonisme. De frequentie van het variant allel (-759T) van het HTR2C gen en van het COMT gen (158A) bleken significant hoger in patiënten zonder door haloperidol geïnduceerd parkinsonisme (respectievelijk nominale p=0,03 en p=0,02). De analyse van het -759C/T polymorfisme is beperkt tot vrouwen aangezien het HTR2C gen X-chromosoom gebonden is en allel frequentie berekeningen van dit polymorfisme beïnvloed worden door de geslachtsverdeling. We constateerden een afname van risico op door haloperidol geïnduceerd parkinsonisme bij vrouwelijke dragers van het -759T allel (gecorrigeerde odds ratio (OR) 0,31; 95% betrouwbaarheidsinterval (BI) 0,11-0,85). Het lagere risico onder dragers van het COMT 158A allel bleek niet statisch significant te zijn. Toekomstige grotere studies zijn nodig om aan te tonen of dragerschap van het 158A allel van het COMT gen daadwerkelijk geassocieerd is met een beschermend effect. We vonden geen associatie tussen de overige polymorfismen en door haloperidol geïnduceerd parkinsonisme.

Concluderend suggereren deze twee studies dat de perifere farmacokinetische hypothese geen belangrijke rol speelt in het verklaren van de variabiliteit in optreden van door haloperidol geïnduceerd parkinsonisme bij ouderen. Ook vinden we in deze kleine studie geen overtuigend bewijs dat de bestudeerde genetische variaties (welke onderdeel uitmaken van de centrale farmacodynamische hypothese) in belangrijke mate deze variabiliteit kunnen verklaren. Waarschijnlijk verdient de centrale farmacokinetische hypothese meer aandacht; toekomstige studies zijn nodig om deze veronderstelling te bevestigen.

Hoofdstuk 4 concentreert zich op gevolgen van door antipsychotica geïnduceerd parkinsonisme bij ouderen. In **hoofdstuk 4.1** beoordelen we de kwaliteit van leven van ouderen met door antipsychotica geïnduceerd parkinsonisme in dezelfde populatie als in **hoofdstuk 3**. Door afname van communicatieve mogelijkheden en oordeelsvermogen van ouderen met een psychose of dementie is zelfbeoordeling van kwaliteit van leven moeilijker. Wij hebben daarom gebruik gemaakt van de QUALIDEM, een

instrument dat professionele of informele zorgverleners de mogelijkheid biedt om verschillende domeinen van kwaliteit van leven te beoordelen door observatie. Aanwezigheid van door antipsychotica geïnduceerd parkinsonisme bleek te zijn geassocieerd met een slechtere kwaliteit van leven. Dit kwam tot uiting in de QUALIDEM domeinen positief affect (bv heeft een tevreden uitstraling) en negatief affect (bv is verdrietig), maar ook in afname van sociaal functioneren, gemeten door observatie van sociale interactie tussen de deelnemende oude patiënt en andere bewoners of medepatiënten, en tussen de deelnemende patiënt en zorgverleners. Tenslotte bleek dat patiënten met door antipsychotica geïnduceerd parkinsonisme minder om handen hadden en minder in staat bleken tot het uitvoeren van handelingen zonder de begeleiding van zorgverleners.

In eerdere studies wordt gesuggereerd dat behandeling met antipsychotica het risico op sterfte verhoogt bij ouderen. Cardiovasculaire aandoeningen of infecties (longontsteking) worden als mogelijk oorzaken voor deze extra sterfte beschouwd. De relatie tussen longontsteking en gebruik van antipsychotica is echter onduidelijk. In **hoofdstuk 4.2** onderzochten we de associatie tussen antipsychotica gebruik en longontsteking in een case-control studie opzet waarbij de cases en de controls uit een cohort met ouderen werd gerekruteerd. Voor deze studie hebben we gebruik gemaakt van een grote database met daarin afleverdata van verschillende apotheken aan een groot aantal inwoners van Nederland en hun gegevens van ziekenhuisopnames (PHARMO). In totaal werden 22.944 ouderen gevolgd vanaf hun eerste prescriptie voor antipsychotica tot aan een ziekenhuisopname vanwege een longontsteking of tot aan het einde van registratie in de database. Na correctie voor verstorende variabelen was gebruik van een antipsychoticum significant geassocieerd met een verhoogd risico op longontsteking (gecorrigeerde OR 1,6; 95% BI 1,3–2,1). Het risico was het hoogst in de eerste week van gebruik. Atypische antipsychotica bleken niet veiliger te zijn dan klassieke antipsychotica.
Hoe antipsychotica een longontsteking veroorzaken is nog niet opgehelderd. Verstoring van verplaatsing van gekauwd voedsel door een droge mond en/of keel (=anticholinerg effect), overmatige sufheid (=antihistaminerg effect) of verandering van spierspanning van mond en keel (=extrapiramidaal effect) resulterend in aspiratie zijn mogelijke onderliggende mechanismen. Aangezien atypische antipsychotica een hoger risico geven op longontsteking dan klassieke antipsychotica lijkt de laatste hypothese minder waarschijnlijk. Op basis van de bevindingen in deze studie is bij oude patiënten nauwlettende observatie van slikproblemen en sufheid aan te bevelen, vooral in de eerste week na voorschrijven van een antipsychoticum.

Tenslotte omvat **hoofdstuk 5** een algemene discussie waarbij de resultaten van de individuele onderzoeken in dit proefschrift in een breder perspectief worden plaatst. Drie onderwerpen worden besproken: de balans tussen beperkt wetenschappelijk bewijs voor werkzaamheid van antipsychotica en toenemend bewijs voor ernstige bijwerkingen bij ouderen; gevoeligheid voor door haloperidol geïnduceerd parkinsonisme bij ouderen en de hiaten in de veronderstelde pathofysiologische mechanismen; methodologische overwegingen bij het uitvoeren van onderzoek bij ouderen. Tot slot worden klinische implicaties en mogelijkheden voor toekomstig onderzoek besproken. Voorzetting van onderzoek bij ouderen is nodig voordat de hoopvolle verwachtingen van psychofarmacotherapie op maat voor de individuele oudere patiënt ingelost kunnen worden.

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Co-authors of manuscripts presented in this thesis
Affiliations during the conductance of the research

Asmar F.Y. Al Hadithy
Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, the Netherlands

Svetlana V. Belitser
Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, the Netherlands

Toine C.G. Egberts
Department of Clinical Pharmacy, University Medical Centre Utrecht, the Netherlands

Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, the Netherlands

Paul A.F. Jansen
Department of Geriatric Medicine, University Medical Centre Utrecht, the Netherlands

Carolina J.P.W. Keijsers
Department of Geriatric Medicine, University Medical Centre Utrecht, the Netherlands

Rob J. van Marum
Department of Geriatric Medicine, University Medical Centre Utrecht, the Netherlands

Department of Geriatric Medicine, Jeroen Bosch Ziekenhuis, 's-Hertogenbosch, the Netherlands

Roel A. Ophoff
Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, the Netherlands

Center for Neurobehavioral Genetics, University of California Los Angeles, California, United States of America

Alfred F.A.M. Schobben
Department of Clinical Pharmacy, University Medical Centre Utrecht, the Netherlands

Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, the Netherlands

Henrike J. Schouten
Department of Geriatric Medicine, University Medical Centre Utrecht, the Netherlands

Patrick C. Souverein
Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, the Netherlands

Eric Strengman
Department of Medical Genetics, University Medical Centre Utrecht, the Netherlands

Bob Wilffert
Department of Pharmacotherapy and Pharmaceutical Care, University of Groningen, the Netherlands

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About the author

Wilma Knol was born in Hasselt, the Netherlands, on February 21th 1973. In 1992 she graduated from the Carolus Clusius College in Zwolle. Subsequently, she studied Medicine at the VU University of Amsterdam. After obtaining her medical degree in 1999 she worked in the VU Medical Centre for 8 months at the Department of Geriatric Medicine. In 2000 she started her training as a geriatrician. She fulfilled her residency in internal medicine at the Kennemer Gasthuis in Haarlem, in geriatric medicine at the University Medical Centre Utrecht and at the Slotervaart Ziekenhuis in Amsterdam, and in old age psychiatry at Altrecht Institute for Mental Health Care in Zeist. The first preparations for the research presented in this thesis were made in 2005. Since august 2006 this research was combined with a position as geriatrician in Tergooiziekenhuizen in Hilversum and Blaricum. She has a special interest in gerontopharmacology. After a fellowship program at the University Medical Centre Utrecht she was registered as clinical pharmacologist in 2008.