Drug-induced extrapyramidal syndromes

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Thesis Utrecht University

ISBN: 90-393-2988-5

Cover design: René Marks

Printed by: Prima Print, Cologne

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Geneesmiddel-geïnduceerde extrapyramidale syndromen

(met een samenvatting in het Nederlands)

Proefschrift

Ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de Rector Magnificus Prof. Dr. W.H. Gispen
ingevolge het besluit van het College voor Promoties
in het openbaar te verdedigen
op donderdag 28 februari 2002 des middags te 12.45 uur

door

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This thesis was supported by the Utrecht Institute for Pharmaceutical Sciences (UIPS) and the Royal Dutch Organisation for the Advancement of Pharmacy (KNMP). Additional financial support was provided by Eli Lilly.

Aan mijn vader en moeder

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Chapter 1

Introduction

BACKGROUND

Extrapyramidal syndromes

Extrapyramidal syndromes (EPS) are a group of movement disorders that result from damage in the basal ganglia and certain related thalamic and brainstem nuclei [1]. Clinically, they can present as parkinsonism, dysthonia, akathisia, dyskinesia, hemiballism or chorea. EPS are either primary, i.e. due to a neurodegenerative disease, or secondary. Secondary forms can have different causes, including toxic, infectious, metabolic and vascular ones. However, by far the most important cause is the use of drugs.

Drug-induced extrapyramidal syndromes

EPS that are seen as a side effect of drug treatment include parkinsonism, dysthonia, akathisa and dyskinesia. Drug-induced parkinsonism, like idiopathic Parkinson's disease, is characterized by tremor, rigidity and bradykinesia [2]. Although the resting tremor and asymmetry of symptoms seen with Parkinson's disease were thought to be absent in drug-induced parkinsonism, both have been observed [3-5]. Dystonia refers to a briefly sustained abnormal posture caused by involuntary contractions of agonists and antagonist muscles. This may occur in the head/neck region, with eyes deviating to the side or upward (oculogyric crisis), tongue protrusion, jaw spasms (trismus), tightness or choking feelings in the throat (laryngeal-pharyngeal constriction) and the head pulling back or to the side (retrocollis, torticollis). Dystonia can also occur in the trunk and limbs, leading to bizarre positions or postures. Akathisia refers to a state of restlessness and a subjective need to move, presenting as pacing, rocking while sitting or standing, lifting the feet as if marching in place, crossing and uncrossing the legs while sitting or other purposeless repetitive actions. Features of tardive dyskinesia include repetitive, involuntary, hyperkinetic movements that include chewing, tongue protrusion, lip smacking and grimacing. Akathisia can begin within hours after drug intake, while dystonia most commonly occurs within 12 to 48 hours. Parkinsonism tends to develop after several days or weeks of continuous treatment. Tardive dyskinesias is generally not seen until after several months or years of treatment [6, 7].

Treatment of any drug-induced EPS first involves reducing the dose of the offending drug or switching to a drug less likely to cause these symptoms. If symptoms persist, pharmacological treatment is indicated. Drug-induced parkinsonism can be treated with anticholinergics or amantadine [8]. Levodopa or direct dopamine agonists are often not useful [9]. Anticholinergics (intramuscular) are also the mainstay for treatment of dystonia, though antihistamines can also be used [10]. Treatment options for akathisia include beta-blockers, anticholinergics, clonidine or benzodiazepines [11]. Several drugs have been used for treatment of tardive dyskinesia, including L-dopa and tiapride [12]. Anticholinergics may worsen symptoms and are contraindicated [2].

Numerous drugs have been reported to induce EPS [13, 14]. Epidemiologic studies showed that as much as one third to over one half of the cases of parkinsonism may be explained by the use of medication [14-16]. EPS is especially common during treatment with antipsychotic drugs (APDs) [15] and was reported as a side effect almost immediately after their introduction in the early 1950's [17]. Considering their disabling effect, clearly, drug-induced EPS have a strong negative impact on patients' well-being, compliance to treatment and as a result on treatment outcome [18-20]. Thus,

minimizing their frequency and severity is of clear clinical importance. This can be achieved either by prevention or by prompt diagnosis and treatment of symptoms. Both are greatly enhanced by knowing which drugs are implicated with EPS, to what extent, and which patients are most susceptible.

AIM OF THE THESIS

To be able to reduce the occurrence of drug-induced EPS in the general population, the aim of this thesis is to quantify the risk of drug-induced EPS for drugs commonly associated with this side effect and to quantify the influence of specific risk factors.

OUTLINE OF THE THESIS

In chapter two we will first review the current literature with regard to the epidemiology of drug-induced parkinsonism. This will be used to identify issues that require further study. Second, we will assess the validity of using antiparkinsonian medication as a way to identify drug-induced EPS in observational databases. Chapter three will focus specifically on EPS resulting from antipsychotic medication, since these drugs still are by far the most important cause of EPS. In chapter four, we will study risks and risk factors of EPS with drugs other than APDs. Laslty, chapter five will discuss the strengths and limitations of this thesis, the implications for medical and pharmaceutical practice, and suggestions for future research.

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Chapter 2

Background

CHAPTER 2.1

Epidemiology of drug-induced parkinsonism – a literature study

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ABSTRACT

Aim To give an overview of the drugs that have been reported to induce parkinsonism and review the frequency and risk factors of this side effect.

Methods Computerized search of the Medline from 1962 onwards on relevant keywords, and review of the bibliographies of the obtained articles.

Results The drugs that seem to be implicated with parkinsonism most often are antipsychotic drugs (APDs), selective serotonin reuptake inhibitors (SSRIs) and calciumantagonists (CAs). APD-induced parkinsonism has been widely studied. Possible risk factors include age, dose, smoking, drug type and cytochrome P450 activity, though especially these last two are still matter of debate. The incidence varies largely from 6% to 71%, possibly because of different distributions of risk factors among studied populations. So far, parkinsonism resulting from SSRIs and CAs has not been systematically studied. Therefore, frequency and risk factors are still largely unknown. In general, the occurrence of all drug-induced parkinsonism is thought to depend upon individual susceptibility, which may especially be related to the prescence of preclinical Parkinson's disease.

Conclusions Many epidemiological aspects of drug-induced parkinsonism have not yet been sufficiently studied. For SSRIs, CAs and the recently marketed APDs, the risk of parkinsonism still needs to be compared with drugs from the same pharmacotherapeutic class. Furthermore, the influence of several possible risk factors, especially genetic predisposition, needs further confirmation.

INTRODUCTION

Parkinsonism is usually caused by decreased dopaminergic activity within the striatum of the basal ganglia. In idiopathic parkinsonism –or Parkinson's disease (PD)- this impairment in neurotransmission results from neuronal loss in the substantia nigra and other pigmented nuclei, resulting in a loss of dopamine in the striatum and subsequent destruction of the nigrostriatal dopaminergic pathway. The typical symptoms of PD, including tremor at rest, rigidity, poverty or slowness of movement and loss of postural reflexes, do not appear until 80% of striatal dopamine is lost [2].

In addition to this idiopathic form of parkinsonism, the differential diagnosis also includes secondary forms with known causative or contributing factors [3, 4]. Probably the most common of these is medical prescription [5]: as much as one third to over one half of the cases of parkinsonism may be related to drug use [6-8]. With regard to the occurrence of drug-induced parkinsonism (DIP), three questions may be of particular importance to the clinician: which drugs are implicated, to what extent, and which patients are most susceptible?

To answer these questions, we reviewed the drugs that have been reported to induce parkinsonism, as well as the frequency and risk factors of this side effect.

METHODS

We conducted a computerized search of MEDLINE from 1963 to 2001 using relevant keywords to identify articles discussing drugs possibly inducing or aggravating parkinsonism. Additional references were obtained from a manual search of the bibliographies of these articles. We also included chapters of major neurologic and psychiatric textbooks. This literature search was last updated in August 2001. From these data we assessed which drugs are associated with parkinsonism most often. In addition, we reviewed the literature on frequency and risk factors of parkinsonism caused by these drugs, using the same literature search strategy.

RESULTS

Reports of parkinsonism resulting from drug use can be found in the literature as early as 1954 [9]. Since then, a vast number of drugs has been reported to induce parkinsonism (table 1), though the severity of symptoms may differ between them. Disregarding outliers [10, 11], the prevalence of drug-induced parkinsonism in the general population ranges from 11,8/100.000 - 35,2/100.000 [12-14]. Review of published case reports as well as studies from neurologic and pharmacovigilance centers showed that antipsychotic drugs (APDs), selective serotonin reuptake inhibitors (SSRIs) and calciumantagonists (CAs) are the drug groups most often associated with this side effect [7, 8, 15, 16].

Table 1 Reports and studies of drug-induced parkinsonism

Drug	De novo parkinsonism	Aggravation of parkinsonism	Epidemiologic studies
antipsychotic drugs			
conventional			see table 2 [6]
clozapine	[161]		
risperidone	[19, 162-166]	[19, 167, 168]	
olanzapine	[169, 170]	[171-176]	
calciumantagonists			
amlodipine	[177]		
cinnarizine	[8, 16, 126, 131, 133, 134, 138, 142-144, 152, 155]	[145, 178, 179]	
diltiazem	[8, 144, 180, 181]		
flunarizine	[8, 16, 126, 131-134, 138, 143, 155, 182-187]	[145, 186, 188]	
manidipine		[189]	
nifedipine	[188]	[188]	
verapamil	[8, 144, 190-193]		
antidepressants			
SSRI's			
fluvoxamine	[153, 194]	[195]	
fluoxetine	[8, 16, 81, 82, 144, 196-200]	[200-206]	
paroxetine	[8, 207, 208]	[202, 209]	
sertraline	[210-217]	[204]	
citalopram	[218]	[219]	
non-SSRIs			
amoxapine	[220-222]		
clomipramine	[223]		
phenelzine	[224]		
anti-arithmics			
amiodarone	[144, 225-227]		[228]
aprindine	[229]		
anticonvulsants			
phenytoin	[230]		
valproic acid	[231-234]		[235]
antihypertensives			
captopril	[236]		
methyldopa	[8, 16, 144]	[237, 238]	
anxiolytics			
chlordiazepoxide			[239]
diazepam			[240]
lorazepam	[8]		
buspiron	[241]		
NSAIDs			
flurbiprofen		[242]	
naproxen			[243]
sulindac		[244]	
oncolytics			
fluorouracil	[245]		
vincristine	[246]		
adriamycin	[246]		
CHOP	[247]		

Table 1 (continued) Reports and studies of drug-induced parkinsonism

Drug	De novo parkinsonism	Aggravation of parkinsonism	Epidemiologic studies
parasympathomimetics			
bethanechol	[248]		
pyridostygmine	[249]		
other drugs			
amphotericin B	[250, 251]		
buphormine	[229]		
cephaloridine	[252]		
cyclosporin	[253]		
cisapride	[254]	[254]	
clebopride	[8, 144, 229, 255-258]		
contrast agent	[259]		
diphenhydramine	[16]		
disulfiram	[260, 261]		
domperidone	[16]	[262]	
lithium	[8, 199, 263]		
manganese	[264]		
meperidine (pethidine)	[265, 266]		
metoclopramide	[8, 15, 16, 144, 231, 267-272]	[270]	[273-275]
oral contraceptives	[276]		
prochlorperazine	[150, 277, 278]		[55, 279]
tetrabenazine	[280]		
veralipride	[16, 144]		

Antipsychotic drugs

Since all APDs share the ability to block postsynaptic dopamine D_2-receptors in the basal ganglia [17], this is thought to be the mechanism responsible for their induction of parkinsonism [18]. Parkinsonism can occur within days after the start of APD treatment [19], but usually takes longer to develop. Some found that over 90% of the APD-induced parkinsonism cases occur within the first three months of treatment [20, 21], though others observed a longer latency period [22].

Frequency

Estimates of incidences of drug-induced parkinsonism among APD users range from 11% to 71% (table 2a). A similar large variation is seen for prevalence estimates (table 2b). This might be explained by differences in the definition of parkinsonism, sensitivity of the case-finding procedure or the presence of risk factors. Studies comparing the risk of parkinsonism between users and non-users of APDs found an increased relative risk [6, 23].

Risk factors

A large number of treatment- and patient-related factors may influence a patient's chance to develop parkinsonism during APD treatment. With regard to the first, both increased dose [6, 23-26] and prolonged use [25, 27-29] have been found to increase the risk. Furthermore, not all APDs have the same risk for inducing parkinsonism. Low potency APDs (i.e. those with low affinity for postsynaptic D_2-receptors like chlorpromazine and thioridazine) and atypical APDs (e.g. clozapine,

risperidone, olanzapine, quetiapine) are known to induce less parkinsonism than high potency drugs [26, 30-33]. While this can be explained by differences in receptor-affinities [34-36], others suggest these observations are artificial and result from non-equivalent dose comparisons [37]. Indeed, both low potency APDs [38-44] and atypical drugs [45-47] are often prescribed or tested in lower doses than high potency drugs.

Table 2a Incidence of drug-induced parkinsonism

Country, year, reference*	Study design	Setting	Age	Population size	Follow-up time	Incidence
US, 1959 [55]	not stated	inpatient	not stated	422	not stated	15-46%†
US, 1961 [279]	not stated	inpatient	not stated	>5,000	not stated	6-38%†
US, 1961 [21]	retrospective follow-up	not stated	4-88	3,775	variable	15%
US, 1976 [281]	not stated	inpatient	not stated	175	not stated	29%
US, 1981 [70]	prospective follow-up	inpatient	>18	80	2 weeks	31% ¥
US, 1983 [57]	retrospective follow-up	not stated	2-90	5,000	variable	13%
US, 1983 [24]	retrospective follow-up	inpatient	10-59	135	3 weeks	33%
EU, 1986 [54]	retrospective follow-up	inpatient	<20 - >69	230	variable	44% ¥
EU, 1990 [282]	prospective follow-up	inpatient	<30 - >60	1,107	not stated	17%
US, 1991 [25]	prospective follow-up	inpatient	60-96 mean: 77	17	4 weeks	71%
US, 1997 [22]	prospective follow-up	inpatient	mean: 46	35	1 year	37%
US, 1999 [53]	prospective follow-up	outpatient	>45 mean: 70‡	56	1 month	29%

abbreviations: US = United States (including Canada); EU = Europe (including Israel); APD = antipsychotic drug

* year of publication

† depending on the APD

‡ only stated for subgroup of patients

¥ only patients using haloperidol

Important patient-related risk factors may include age, gender, metabolic activity and smoking. Since normal striatal dopamine loss is age-related [48], older people are likely to be more vulnerable to the antidopaminergic effect of APDs. This has been confirmed by several studies [21, 22, 27, 29, 49-53], though some found an inverse association between age and incidence [24, 54]. Several studies observed a higher frequency of APD-induced parkinsonism among women [21, 55-57].

While this observation may be explained by an antidopaminergic effect of estrogens [58, 59], other studies found no difference between men and women [25, 27, 49, 54, 60-63] or even observed a higher risk among men [24]. In studies employing multivariate analysis, the higher frequency among women was shown to be secondary to differences in smoking [51] or other factors between men and women [29].

Since APD-induced parkinsonism is dose-dependent, factors that influence plasma levels may also affect the risk of this side effect. One such factor is the activity of the cytochrome P450 2D6 enzyme

Table 2b Prevalence of drug-induced parkinsonism

Country, year, reference*	Setting	Age	Population size	Prevalence
US, 1970 [60]	inpatient	18-64	350	73%
US, 1974 [27]	inpatient	not stated	669	36%
EU, 1976 [56]	inpatient	<40 - >51	66	66%
US, 1985 [283]	inpatient	>55	57	51%
US, 1987 [99]	inpatient + outpatient	55-78	21	76%
US, 1987 [284]	inpatient	mean: 27	48	60%
US, 1988 [62]	inpatient	<40 - >81	315	13%
US, 1990 [51]	inpatient	>45	130	27%
US, 1991 [28]	inpatient	9-18	61	34%
US, 1992 [285]	inpatient	not stated	101	26%
US, 1993 [90]	inpatient	mean: 63	111	25%
US, 1994 [23]	inpatient	>65	111	67%
EU, 1997 [52]	inpatient + outpatient	mean: 50	100	38%

abbreviations: US = United States (including Canada); EU = Europe (including Israel);

APD = antipsychotic drug

* year of publication

(CYP2D6), responsible for the metabolic elimination of several APDs [64]. This activity may vary substantially between patients. Up to ten percent of the European Caucasian population has one or more mutations at the locus coding for CYP2D6, leading to a defective enzyme [65]. While indeed these "poor metabolizers" are more prone to higher plasma levels of APDs [66], studies investigating the association between such mutations and the occurrence of parkinsonism have yielded conflicting results [64]. This may be explained by the limited sample size of some studies and by the fact that several studies included APDs for which the metabolic elimination of the active compound is not mediated by the CYP2D6 genotype.

In addition to "random" genetic variation, CYP2D6-activity also differs between ethnic groups. Asians have a lower CYP2D6-activity than Caucasians and Blacks [67, 68]. In accordance with this, they were found to have higher APD serum levels [69] and a higher risk for parkinsonism [41, 70, 71]. CYP2D6 activity can also be influenced by external factors. Several drugs can either induce or inhibit CYP2D6 activity [72] and thus cause metabolic drug-drug interactions with APDs [73]. In particular, SSRIs can inhibit CYP2D6 [74-77] and as a result increase APD serum levels [77-80]. There are several reports of parkinsonism after the addition of SSRIs to APD treatment [81-83].

Smoking has been associated with lower APD serum levels [84-86], a need for higher APD doses [87, 88] and a decreased risk of APD-induced parkinsonism [51, 89, 90]. This may be explained by enhanced central dopaminergic transmission or by inducing the activity of hepatic microsomal enzymes [51, 91], including CYP2D6 [92].

Other possible risk factors for APD-induced parkinsonism include a family history of PD [93, 94], pretreatment motor dysfunction [22, 53, 95, 96], previous APD-induced parkinsonism [97], early age at onset of schizophrenia [98], negative symptoms of schizophrenia [99-102], cognitive dysfunction [103], severity of dementia [53], increased ventricle/brain ratio [99, 104], organic brain pathology [56], diabetes mellitus [103] and presence of the Human Leukocyte Antigen (HLA) B44 [105]. Whether psychopathology is a predisposing factor is uncertain [22, 53, 63]. It was suggested that psychopathology is associated with APD-induced parkinsonism only in patients with more severe psychopathology [22]. Psychiatric diagnosis does not seem to affect the risk of APD-induced parkinsonism [62, 63, 96].

Selective serotonin reuptake inhibitors

The large number of published case reports indicates that SSRIs (i.e. fluoxetine, paroxetine, fluvoxamine, sertraline and citalopram) are capable of inducing or aggravating parkinsonism (table 1), even though some reports suggested otherwise [106-112]. Post-marketing study showed that symptoms occurred after a median time interval of two weeks (range: 1 day - 1 month) [115]. The mechanism underlying SSRI-induced parkinsonism is poorly understood, but may involve inhibition of striatal dopaminergic function by serotonergic neurons projecting from the dorsal raphe nucleus. Since the striatum is involved in the modulation of motor function, drugs with pro-serotonergic activity like SSRIs may enhance the inhibition of the dopamine system and thus induce parkinsonism [45]. The hypothesis of an antidopaminergic effect of SSRIs is supported by an increased prolactine-level observed after fluoxetine use [113]. However, since depression is a prodrome of PD [2, 114], patients with depression may also be inherently more likely to develop

parkinsonism, irrespective of their medication. To rule out this non-causal explanation, comparisons between SSRIs and other antidepressants are warranted.

Frequency

So far, epidemiological data on SSRI-induced parkinonism is scanty. A British pharmacovigilance study showed an incidence of all extrapyramidal syndromes (EPS) –also including dystonia, akathisia and tardive dyskinesia- of 2.4 per 1,000 for fluoxetine, 1,7 per 1,000 for paroxetine and 0,9 per 1,000 for fluvoxamine [116]. In another study the incidence of EPS with fluoxetine was estimated to be 1.3 per 1,000 (95% C.I. 0.5-2.6) [117]. However, in a small group of 67 elderly patients treated with SSRIs, 4 were found to have EPS, yielding a much higher incidence of 60 per 1,000 [118]. Recent comparative studies showed conflicting results. While an observational study suggested that existing parkinsonism is more likely to deteriorate during treatment with SSRIs than with tricyclic antidepressants [119], a randomized controlled trial found no difference in ratings of EPS between paroxetine and nortriptyline in a small group of elderly patients [120].

Risk factors

Since epidemiological studies are lacking, risk factors for SSRI-induced parkinsonism have not been systematically studied. However, based on the published case reports, several risk factors have been suggested. The majority of cases of SSRI-induced parkinsonism involved fluoxetine (table 1). While this may reflect its high market share, causal explanations may include its long half life [121]. Furthermore, fluoxetine lacks the relative potency for dopamine reuptake inhibition that sertraline has [122]. Whether dose and duration of use affect the risk is unknown. Reported cases of SSRI-induced parkinsonism tended to be older patients and included more women than men [123, 124]. While these observations suggest age and gender are risk factors for SSRI-induced parkinsonism, they can also merely result from increased use of SSRIs among these groups. Indeed, depression and antidepressant drug use are more prevalent among women and elderly [125]

Calciumantagonists

Numerous reports of parkinsonism associated with CAs have been published (table 1). These mainly include cinnarizine (Cz) and its difluorinated derivative flunarizine (Fz), calcium overload blockers used for vertigo, migraine and cerebrovascular purposes. However, parkinsonism has also been reported with CAs of the calcium channel blocker type, including diltiazem, verapamil, nifedipine, manidipine and amlodipine (table 1). Both Cz and Fz show structural similarity with some phenothiazine-like APDs [126], suggesting a common mechanism of inducing EPS. Indeed, SPECT study showed that -as with APDs- Cz/Fz-induced EPS is most likely to result from striatal D2 receptor blockade [127], which may also be the case for other CAs [128]. However, other mechanisms have also been suggested [129, 130]. Cz/Fz-induced parkinsonism can occur as soon as two days after the start of medication [131], but usually takes several weeks or months to develop [132-134].

Frequency

Although case reports are numerous, there are very few systematic studies that have estimated the absolute or relative frequency of CA-induced parkinsonism. Based on their personal experiences, Agnoli and Nappi suggested an overall incidence of EPS or depression with Cz/Fz use of 0.5%

[135]. In contrast with the large number of case reports, comparative studies –relying on either prescription analysis or postmarketing surveillance- found no association between Fz use and parkinsonism [136, 137]. However, in both studies the sample size is likely to have been too small, given the age of the study population (mean age 56 and 51 years, respectively) and the estimated low incidence of Fz-induced EPS in these younger patients [135].

Risk factors

Parkinsonism seems to be more frequent with Fz than with Cz [138], which is likely to be explained by its fluorination. Because of this, Fz is more lipophilic than Cz, resulting in easy crossing of the blood-brain barrier and a consequently higher concentration in the CNS [139] and in a much longer half-life (19 days [140], versus 3 hours for Cz [141]). The observation that patients with Cz/Fz-induced parkinsonism are relatively old led some to conclude that age is a risk factor [142-144]. However, this may also be explained by the fact that these drugs are especially used by elderly [126, 145]. The higher incidence of Fz-induced parkinsonism in elderly patients suggested by Agnoli and Nappi provides stronger evidence for an age preponderance [135]. Some studies observed more women than men with CA-induced parkinsonism [134, 144], but here too, this may be explained by higher use rather than increased risk.

DISCUSSION

Our results show that a very large number of drugs may induce parkinsonism. Based on the number of published reports, APDs, SSRIs and CAs seem to be the drugs most often associated with this side effect. Parkinsonism occurs frequently during APD use, though incidence and prevalence measures may differ largely between studies. This may be explained by the definition of parkinsonism, sensitivity of the case-finding procedure and the presence of risk factors. Possibly, with the expanding use of atypical APDs and the trend toward lower dosing of classical APDs, the frequency of APD-induced parkinsonism may decline. Because of these changes in APD-treatment, continuing epidemiological investigation of this side effect is warranted. Parkinsonism appears to be much less common with SSRIs and CAs then with APDs, though good epidemiological data is lacking. To assess the clinical relevance and public health impact of parkinsonism induced by different drugs, both absolute and relative risk estimates are needed, as well as the number of patients exposed to these drugs.

Numerous risk factors for drug-induced parkinsonism have been identified or suggested. Nevertheless, it still remains largely unexplained why some persons develop this side effect while others do not. Thus, it is clear that the occurrence of parkinsonism depends upon individual susceptibility. As much as twenty years ago it has been suggested that this individual susceptibility is due to an already decreased dopamine level in the brain, i.e. a latent or preclinical PD [2, 146]. This hypothesis is supported by several findings. 1) Autopsy on two patients who had suffered from drug-induced parkinsonism during life revealed Lewy bodies in their substantia nigra [147], inclusion cells typically seen in PD. 2) PET-scans showed a reduced putamen 18F-dopa uptake in nearly one-third of a group of patients suffering from drug-induced parkinsonism [148], indicating a dopaminergic nigrostriatal dysfunction as seen in PD. 3) Some patients suffering from drug-induced

parkinsonism developed true PD later on in their life, suggesting that the drug precipitated an already present preclinical PD [144, 149-153]. Indeed, patients with a prior history of drug-induced parkinsonism are at increased risk of developing PD later in life [154]. 4) Patients suffering from drug-induced parkinsonism more often have a family history of PD or essential tremor [93, 94, 142, 143, 155]. Taken together, these observations suggest that, instead of being a syndrome distinct from PD, drug-induced parkinsonism represents a worsening of a preexisting preclinical PD, at least in a proportion of the cases. PD is thought to be multifactorial, with genetic and environmental risk factors interacting [156, 157]. These risk factors –including drugs- may only precipitate parkinsonism in patients with an inherited PD susceptibility [158].

Notwithstanding their association with parkinsonism, the drugs we discussed are of clear therapeutic importance. Studying frequency and risk factors should contribute to selecting the appropriate medication for each individual patient and help prevent the occurrence of parkinsonism. In addition, since symptoms of drug-induced parkinsonism can be indistinguishable from those of idiopathic PD [150], knowing which drugs are capable of inducing these symptoms may often be the only way of differentiating these syndromes. This distinction is of particular importance with regard to treatment: in contrast with PD, treatment of drug-induced parkinsonism is relatively easy and consists of either withdrawing the inducing agent or the use of anticholinergic antiparkinsonian medication [159, 160].

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CHAPTER 2.2

Identifying patients with extrapyramidal syndromes using pharmacy records

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ABSTRACT

Aim To assess the validity of antiparkinsonian medication as a marker for antipsychotic-induced extrapyramidal syndromes (EPS).

Method Data was obtained from the Integrated Primary Care Information (IPCI) database containing all data on consultations, morbidity, prescriptions and other interventions of over 420.000 community-dwelling people in the Netherlands from January 1, 1995 through January 16, 2001. We defined a cohort of patients aged 15-54 who were newly treated with antipsychotic drugs (APDs), according to their outpatient prescription records. From them, we identified possible cases of EPS by reviewing patients' computerized medical charts for a priori selected terms and diagnostic codes indicative of EPS. Charts of selected patients were subsequently reviewed by an expert panel to verify the diagnosis of EPS. From the prescription files, we assessed the use of antiparkinsonian medication. From these data, we calculated the positive predictive value (PPV), sensitivity and specificity of antiparkinsonian medication as a marker for EPS.

Results From the 563 patients newly treated with APDs, we identified 28 (5.0%) cases of EPS. Twentytwo patients in the population (3.9%) were treated with antiparkinsonian medication, ten of which had an indication for treatment recorded in the medical charts. Of these, nine had EPS, yielding a PPV of 0.90. The majority of patients with EPS had no record of antiparkinsonian drug treatment, resulting in a low sensitivity: 0.32. Specificity was 0.98.

Conclusion Our results suggest that antiparkinsonian medication is mostly used for treatment of EPS and thus can be validly used in an uncontrolled setting to identify EPS in non-elderly APD users. However, this marker may induce considerable underestimation when used to study the frequency of these symptoms.

INTRODUCTION

One of the most important side effects of antipsychotic drugs (APDs) are extrapyramidal syndromes (EPS, i.e. parkinsonism, akathisia, dystonia and tardive dyskinesia). EPS can adversely affect a patient's well-being, compliance to treatment and as a result treatment outcome [1]. Therefore, many studies that compare new (atypical) APDs with conventional ones focus on the frequency of these symptoms.

In randomized clinical trials, EPS is often assessed both through clinical rating scales and by gauging the use of antiparkinsonian medication [2, 3]. While the first may also identify minor symptoms that may go unnoticed in daily practice, assessing the use of antiparkinsonian medication only identifies patients with symptoms that were considered severe enough by either the treating physician or the patient to warrant treatment. Since antiparkinsonian medication can easily be traced in medical care databases, several observational studies have used this marker to assess the occurrence of drug-induced EPS in daily clinical practice [4-6]. However, in such uncontrolled settings antiparkinsonian medication may also be prescribed for other reasons than treatment of EPS [7]. Furthermore, in addition to antiparkinsonian medication, there are several other treatment options to reduce drug-induced EPS, including dose reduction, discontinuation or switching of the offending medication or the use of other drugs such as benzodiazepines or propranolol [8].

Therefore, we assessed the validity of antiparkinsonian medication in an automated prescription database as a marker for EPS, using stored electronic medical records from a large outpatient population.

METHOD

Setting

Data was obtained from the Integrated Primary Care Information (IPCI) system, a database containing information from computerized patient records of Dutch general practioners (GPs). The database was initiated in 1992 and includes data on demographics, patient complaints, symptoms, laboratory tests, diagnoses, discharge and consultant letters and prescribed drugs, as well as all GPs' notes, recorded as free text. Prescriptions are written directly from the computer, thus ensuring automatic recording of dispensing date, drug name, dosage form, amount dispensed, prescribed dose regimen and indication. Patient complaints, diagnoses and indications are coded through a modified version of the International Classification of Primary Care (ICPC) [9], but can also be recorded in the GP's notes. The IPCI system has previously been used to study various types of drug-related morbidity [10-12]. For this study we used all available data from January 1, 1995 till January 16, 2001, incorporating data on 427,386 patients from 82 general practices.

Patients

We defined a cohort of patients who received antipsychotic medication for the first time, according to their outpatient prescription records, and who were enrolled in the IPCI database for at least one year and were between the age of 15 and 54 on the day APDs were first prescribed. Patients were followed until transferring out of the general practice or death, whichever came first.

Outcome definition

To assess the validity of antiparkinsonian medication as a marker for EPS, we first identified patients with EPS. Given the retrospective nature of this study, we were not able to actually examine patients for the occurrence of EPS during APD treatment. Therefore, we had to rely on the clinical observations and diagnoses made by the GPs or made available to the GP by means of referral or discharge letters. We identified possible cases of EPS by looking for ICPC codes and descriptions in GPs' notes that might refer to EPS, including any of the codes and terms listed in appendix 1 and 2, respectively. All recorded data of these cases –except information on antiparkinsonian medication and type of APD- was subsequently independently reviewed by two of us (R.A.C.R. and P.A.F.J.). Patients were defined as probable cases of EPS when, based on the chart review, the presence of EPS was considered likely by both reviewers. Discrepancies between the two reviewers were discussed until consensus was reached. Second, for each patient we assessed the first use of any drug indicated in the Netherlands for treatment of EPS, including both anticholinergic and dopaminergic drugs. Although most dopaminergic agents are not indicated for treatment of drug-induced EPS, they may be used as such when these symptoms are misdiagnosed with idiopathic Parkinson's disease [4].

Statistical analysis

We calculated the positive predictive value (PPV), sensitivity and specificity of antiparkinsonian medication as a marker for EPS. Patients prescribed antiparkinsonian medication and patients with EPS before or on the day of cohort entry were not included in the analysis.

RESULTS

We identified 563 patients who fulfilled the inclusion criteria for our study. Most of them started with haloperidol (18.5%), followed by pipamperon (14.2%) and pimozide (9.9%). Mean age of the study population was 37 years; 48.0% was female. Based on the ICPC codes and GP notes, we identified 28 probable cases of EPS (5.0%). In addition, we identified 22 patients in the whole population (3.9%) who received antiparkinsonian medication, all of which were anticholinergic drugs (table 1). Only ten of these patients had an indication for treatment recorded in their medical chart, nine of which were EPS. This yielded a PPV of 0.90. For the remaining patient the GP's notes showed antiparkinsonian medication was used prophylactically after an increase in APD dose. Of the twelve patients for which we could not find a reason for antiparkinsonian drug treatment in the medical charts, nine had been treated by a psychiatrist. Assuming all twelve patients had received antiparkinsonian medication for reasons other than treatment of EPS resultsed in a PPV of 0.41.

Of the 28 patients with EPS, nineteen (67.9%) had no record of outpatient antiparkinsonian drug treatment, yielding a sensitivity of 0.32. Ten of them had their symptoms treated by dose reduction, switching or stopping of the offending medication. For the remaining eight, we could not identify any EPS treatment from the GPs' notes. Including the 12 patients for which no indication of antiparkinsonian drug treatment was recorded, the specificity of antiparkinsonian medication as a marker for EPS was 0.98 (table 1).

Table 1 Number of patients prescribed antiparkinsonian medication and fulfilling the definition of possible and probable EPS (see text for definitions)

	Probable EPS		Total
	yes	no	
prescription of antiparkinsonian medication	9	13*	22
no prescription of antiparkinsonian medication	19	522	541
Total	28	535	563

* Only for one of these could an indication of antiparkinsonian drug treatment be identified from the GP notes, being prophylactic use after an increase of APD dosage. For the remaining 12 patients the presence or absence of EPS is uncertain

DISCUSSION

We found that in a cohort of new outpatient APD users, for many patients the reason for antiparkinsonian medication could not be retrieved from their medical charts. This is likely to be related to the fact that many of them were also seen by a psychiatrist: if antiparkinsonian medication was initiated by a psychiatrist and continued by the GP, the initial reason for prescribing is unlikely to be recorded in the outpatient medical charts. Of those who did have an indication for treatment recorded, ninety percent received antiparkinsonian medication for treatment of EPS. While the specificity was also high, this marker had a poor sensitivity: 68% of the patients with EPS were not treated with antiparkinsonian drugs. The majority of them had their EPS treated by either dose reduction, switching or discontinuation of the offfending medication. In addition to this, by definition, antiparkinsonian medication can only be a marker for EPS that has been recognized in the first place. Thus, the sensitivity may be lower when some cases of EPS were not diagnosed by the treating physician. However, patients with EPS that were not diagnosed as such or were not treated with antiparkinsonian medication are likely to represent milder cases [13].

We are not aware of other studies that assessed the use of antiparkinsonian medication as a marker for antipsychotic-induced EPS. Van de Vijver et al. studied the use of antiparkinsonian medication to identify patients with idiopathic Parkinson's disease [14]. As in our study, they found a high positive predictive value and specificity, while sensitivity was low.

Our results suggest that antiparkinsonian medication is mostly used for treatment of EPS and thus can be validly used in an uncontrolled setting to identify EPS in non-elderly APD users. However, this result is likely to apply only to settings where prescription data is (near-)complete. Furthermore, these results not necessairily apply to elderly patients or to EPS induced by drugs other than APDs. The use of antiparkinsonian medication showed a low sensitivity to identify antipsychotic-induced EPS. Thus, this marker may induce considerable underestimation when used to study the frequency of these symptoms.

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Appendix 1 ICPC codes searched for to identify possible cases of extrapyramidal syndromes

ICPC code		Symptom / diagnosis
D20		symptom / complaint mouth / tongue / lip
	D20.1	symptom / complaint mouth
	D20.2	symptom / complaint tongue
	D20.3	symptom / complaint lip
D21		swallowing problem
F14		eye movements abnormal
	F14.2	other abnormal eye movements
F15		eye appearance abnormal
	F15.3	other abnormal eye appearance
L01		neck symptom / complaint
L99		musculoskeletal disease other
	L99.9	musculoskeletal disease other
N04		restless legs
N06		sensation disturbance other
	N06.2	sensation disturbance other / unspecified
N29		neurological symptom / complaint other
	N29.1	movement disorder
N87		parkinsonism
	N87.1	Parkinson's disease
	N87.2	other parkinsonism
N99		neurological disease other
	N99.1	extrapyramidal disorder
R21		throat symptom / complaint
	R21.2	throat symptom / complaint
R23		voice symptom / complaint
	R23.3	other voice symptom / complaint

Appendix 2 Terms searched for in GP notes to identify possible cases of extrapyramidal syndromes

- parkinsonism, masked facies, coghweel rigidity, bradykinesia, shuffling gait, tremor, worsening of pre-existing parkinsonism
- akathisia, restless legs, restlessness
- dystonia, trismus, jaw spasms, oculogyric spasms, torticollis, opisthotonus
- dyskinesia, lingual-facial-buccal dyskinesia, limb-truncal dyskinesia, choreatic movements, athetosis
- extrapyramidal syndrome

CHAPTER 3

Extrapyramidal syndromes due to antipsychotic drugs

CHAPTER 3.1

Antipsychotic-induced extrapyramidal syndromes in psychiatric practice

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ABSTRACT

Aim To compare the risk of extrapyramidal syndromes (EPS) between specific subgroups of antipsychotics.

Method Using the automated dispensing histories of a large psychiatric hospital in the Netherlands, we defined cases as first-time users of anticholinergic antiparkinsonian drugs. Controls were patients with no recorded use of such medication. Cases and controls were compared with regard to previous use of antipsychotics and relevant co-factors.

Results Out of 1,403 patients, we identified 105 cases and 330 controls. Compared to non-users, antipsychotic-users were 10 times more likely to start with anticholinergic antiparkinsonian medication (adjusted odds ratio: 10.1; 95% confidence interval 4.6-22.3). Conventional and atypical antipsychotics showed comparable odds ratios (10.0, 95% CI 4.4-22.5 vs. 8.0, 95% CI 2.6-24.5). The occurrence of EPS was lower with low potency than with high potency antipsychotics (3.0, 95% CI 0.9-10.3 vs. 10.8, 95% CI 4.7-25.1). While low potency antipsychotics were given in lower doses than high potency drugs, prescribed doses of conventional and atypical antipsychotic drugs were equivalent. Furthermore, they were much lower than those used in previous clincial trials.

Conclusions We could not corroborate the reduced risk with atypical antipsychotics previously observed in several clinical trials. This discrepancy may be explained by the use of high and non-equivalent doses of conventional antipsychotics in many of these trials. However, we can not exclude that in our study population atypical antipsychotics were more often prescribed to patients susceptible to EPS.

INTRODUCTION

Since the introduction of chlorpromazine in the early 1950's, antipsychotics are the drugs of choice in the treatment of schizophrenia and other psychotic disorders. A drawback in their use is the induction of extrapyramidal syndromes (EPS), a group of movement disorders that include parkinsonism, akathisia, dystonia and tardive dyskinesia. Not all antipsychotics, however, induce EPS to the same extent. Low potency antipsychotics (i.e. those with low affinity for postsynaptic D_2-receptors) like chlorpromazine are thought to have a lower risk of EPS than high potency drugs like haloperidol [1]. However, their application is limited by the high incidence of cardiovascular and anticholinergic side effects [2].

In the 1960's clozapine was introduced, which combined a unique antipsychotic efficacy with a low risk of EPS. In recent years, several new antipsychotics have been marketed which tried to mimic this effect, including risperidone, olanzapine, sertindole and quetiapine. A number of clinical trials have indeed shown them to be at least as effective as haloperidol, but with considerably less EPS [3-5]. This group of antipsychotics has consequently been classified as atypical. However, their reduced risk of EPS is not undisputed and several other studies observed no difference in risk between atypical and conventional antipsychotics [6-9].

We studied whether differences in the occurrence of EPS between subgroups of antipsychotics could be observed in daily clinical practice. In a large population of institutionalized and semi-ambulant psychiatric patients in the Netherlands, we compared the risk of starting with anticholinergic antiparkinsonian medication between conventional and atypical, low and high potency and also between depot and non-depot antipsychotics.

METHOD

Setting

For this study we used dispensing histories from 1992 till 1997 stored in a central computer in a large psychiatric clinic in the Netherlands. The clinic consists of a large group (total 1,200 beds) of treatment centers responsible for institutionalized and semi-ambulant psychiatric care in the Netherlands. Three main departments are discerned: adult short stay and medium stay care, long stay care and elderly care, containing all types of psychiatric disorders, most commonly schizophrenia and other psychotic disorders, depressions, bipolar disorders, anxiety disorders and personality disorders. Departments have been automated with respect to dispensing of drugs consecutively since 1992. Therefore, dispensing histories and thus follow-up may differ in length per department and thus per patient.

Selection of cases and controls

Included as cases in our study were patients who used an anticholinergic antiparkinsonian drug (benzatropine, biperiden, dexetimide, orphenadrine, procyclidine, trihexyphenidyl) for the first time in their recorded automated dispensing history and who had an automated dispensing history of at least 180 days preceding that first use. Hence, all included patients were free from use of antiparkinsonian drugs for at least 180 days. Excluded were patients who used dopaminergic

antiparkinsonian drugs (i.e. levodopa, selegiline, bromocriptine, lisuride, pergolide and amantadine), since these drugs are not specifically indicated for treatment of antipsychotic-induced EPS [10]. We also excluded patients who started with antiparkinsonian and antipsychotic medication simultaneously, since this is likely to reflect prophylactic use of the antiparkinsonian drug. All remaining cases were assigned an index-date, being the date of first use of the antiparkinsonian drug. Controls were all patients with no recorded use of antiparkinsonian drugs who had an automated dispensing history of at least 180 days prior to their randomly assigned index date.

Exposure definition

Cases and controls were compared with regard to exposure to antipsychotic drugs within a period of 180 days before the index date. We divided antipsychotic drugs into conventional and atypical. Based on the division used by the Dutch Pharmacotherapeutic Guidelines and the British National Formulary [11], clozapine, sulpiride, risperidone, olanzapine and sertindole were classified as atypical; all other antipsychotics were classified as conventional. Conventional antipsychotics were further subdivided according to potency (low vs. high potency) and duration of action (depot vs. non-depot) (see table 2 for definitions). To evaluate a dose-response relationship, we converted the prescribed daily dose at or closest to the index-date of each patient into chlorpromazine equivalents (CPZeq), which were derived from the WHO dose recommendations [12]. Excluded from the dose calculations were patients using any injectable formula of antipsychotics. Since meta-analysis showed that conventional antipsychotics have no additional clinical effect at doses exceeding 375 mg chlorpromazine equivalents [13], standardized doses were stratified into <375 and ≥375 chlorpromazine equivalents.

Statistical analysis

To estimate the association between antipsychotic use and starting with antiparkinsonian therapy, crude and adjusted odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated using unconditional logistic regression (SPSS for Windows, version 7.5.2). We assessed several factors for a potential confounding effect, namely age, gender, index year, hospital department, use of other psychoactive drugs (tricyclic antidepressants, benzodiazepines) and use of other drugs associated with EPS [14]: calciumantagonists, selective serotonin reuptake inhibitors, metoclopramide, anticonvulsants (valproic acid, phenytoin), lithium and methyldopa. Included in the final logistic regression model were those factors that either caused a change of the crude odds ratio of at least 10%, had an odds ratio of more than 1.5 or less than 0.67 for starting with antiparkinsonian medication or were significantly associated with the use of antiparkinsonian medication [15]. The resulting multivariate model was also used for all subgroup analyses. Doses were compared using a Mann-Whitney U test.

RESULTS

From 1992 till 1997, the prescription-database contained dispensing records of a total of 1,403 patients. Of these, 44.0% (n=617) had used an anticholinergic antiparkinsonian drug at some time. Five hundred and twelve patients had dispensing histories of less than 180 days, leaving 105

patients who met our inclusion criteria. Controls were selected from the 786 patients who had never used an anticholinergic drug. This yielded 330 control patients who had a dispensing history of at least 180 days after random assignment of the index-date. Patient characteristics are summarized in table 1. The mean age was comparable for cases and controls (50 and 52 years respectively). Antipsychotics prescribed most often were zuclopenthixol and haloperidol, used by 14.0% (n=61) and 11.0% (n=48), respectively.

In the half year preceding the index-date, 91.4% of the cases and 50.0% of the controls were exposed to antipsychotics, which yielded crude and adjusted odds ratios of 10.7 (95% CI: 5.0-23.4) and 10.1 (95% CI: 4.6-22.3) respectively (table 2). This risk seemed to be higher with high dose than with low dose treatment (odds ratios: 9.9, 95% CI 3.5-27.5 vs. 6.2, 95% CI 2.8-15.0).

Most commonly used atypical antipsychotics were clozapine and risperidone, used by 5.7% (n=25) and 5.1% (n=22) respectively. Both conventional and atypical antipsychotics had a significantly increased risk of starting with anticholinergic drugs compared to patients who did not use antipsychotics: 10.0 (95% CI: 4.4-22.5) and 8.0 (95% CI: 2.6-24.5) respectively (table 2). A direct comparison showed an odds ratio of 0.7 for atypical versus conventional antipsychotics (95% CI: 0.3-1.8). Prescribed doses of conventional and atypical antipsychotics were not significantly different (median: 150 vs. 213 CPZeq per day, respectively; P=0.19).

Table 1 Demographic characteristics of cases and controls

Characteristic	Cases (N=105)	Controls (N=330)
Age (%)		
<45	46 (43.8)	120 (36.4)
45-64	34 (32.4)	109 (33.0)
>65	25 (23.8)	101 (30.6)
Sex (%)		
Male	44 (41.9)	142 (43.0)
Female	61 (58.1)	188 (57.0)
Index year (%)		
1996-1997	45 (42.9)	271 (82.1)
1994-1995	60 (57.1)	59 (17.9)
Department (%)		
Adult care	23 (21.9)	81 (24.5)
Long care	51 (48.6)	101 (30.6)
Elderly care	29 (27.6)	91 (27.6)
Other*	2 (1.9)	57 (17.3)

* recovery care, patients in stage of discharge or moving to another department

Median absolute doses were 20.1 mg for zuclopenthixol (range 3.9 - 120), 6 mg for haloperidol (range 0.5 – 22.1), 300 mg for clozapine (range 75 mg – 600 mg) and 3.0 mg for risperidone (range 1.0 mg – 8.0 mg). All of the most widely used conventional and atypical antipsychotics were associated with an increased risk of starting with anticholinergic antiparkinsonian medication; not

Table 2 Exposure to antipsychotics among new users of antiparkinsonian medication (n=105) and control patients (n=330)

Exposure category	Cases/controls	Crude OR (95% CI)	Adjusted OR (95% CI)*
any APD	96/165	10.7 (5.0-23.4)	10.1 (4.6-22.3)
conventional vs. atypical APD†			
conventional APD	75/131	10.5 (4.9-23.4)	10.0 (4.4-22.5)
atypical APD	10/20	9.2 (3.0-28.4)	8.0 (2.6-24.5)
both conventional and atypical APD	11/14	14.4 (4.6-46.4)	16.0 (4.9-52.1)
low potency vs. high potency APD‡§			
low potency APD	6/36	3.1 (0.8-10.3)	3.0 (0.9-10.3)
high potency APD	56/86	11.9 (5.4-27.3)	10.8 (4.7-25.1)
both low and high potency APD	13/9	26.5 (8.0-91.5)	31.0 (8.9-108.1)
depot vs. non-depot APD‡¥			
depot APD	16/16	18.3 (6.4-54.3)	10.9 (3.7-32.6)
non-depot APD	48/109	8.2 (3.7-18.8)	8.8 (3.8-20.4)
both depot and non-depot APD	11/6	33.6 (8.9-135.4)	47.8 (11.5-197.9)

abbrevations: OR = odds ratio, CI = confidence interval, APD = antipsychotic drug

* model included age, gender, index-year, hospital department and use of anticonvulsants, benzodiazepines, calciumantagonists and lithium in the 180 days preceding the index-date

† atypical antipsychotics include clozapine, risperidone, olanzapine, sertindole and sulpiride [11]

‡ depot vs. non-depot and low vs. high potency are subdivisions of conventional antipsychotics only

§ low potency antipsychotics are defined as drugs less than five times as potent as chlorpromazine and include chlorpromazine, thioridazine, pipamperone, chlorprotixen, trifluprom azine and levomepromazine. Potencies were derived from a variety of published data [23-26]

¥ antipsychotics available as depot include bromperidol, flupenthixol, fluphenazine, fluspirilene, haloperidol, perphenazine and zuclopenthixol

taking into account depot-preparations, odds ratios were in close range: 9.7 (95% CI: 2.9-32.6) for zuclopenthixol, 7.4 (95% CI: 1.7-33.2) for haloperidol, 7.2 (95% CI: 1.5-33.8) for clozapine and 11.7 (95% CI: 2.8-48.7) for risperidone.

Conventional antipsychotics were subdivided into high potency and low potency drugs. Users of low potency antipsychotics had a lower risk than users of high potency drugs: 3.0 (95% CI: 0.9-10.3) versus 10.8 (95% CI: 4.7-25.1) (table 2). A direct test showed an odds ratio of 0.2 for low potency versus high potency antipsychotics (95% CI: 0.1-0.6). The prescribed dose of low potency and high potency antipsychotics differed significantly (120 vs. 195 CPZeq; P=0.01). Depot and non-depot preparations had adjusted odds ratios of 10.9 (95% CI: 3.7-32.6) and 8.8 (95% CI: 3.8-20.4) respectively (table 2).

DISCUSSION

We found that in a psychiatric setting use of antipsychotic drugs is associated with a ten-fold increased risk to develop EPS, independent of several potential risk factors. An earlier study among outpatients showed a similar odds ratio of 8.5 for starting with anticholinergic antiparkinsonian drugs [16], suggesting that the risk of EPS is independent of treatment setting. Furthermore, the risk was dose-dependent, which has also been observed in previous studies [16, 17].

When comparing subgroups of antipsychotics, low potency agents showed a significantly lower risk of starting with anticholinergic antiparkinsonian medication than the high potency ones. While this may be explained by their intrinsic anticholinergic activity [18], it can also have resulted from the lower dosing of low potency antipsychotics in the study population. Unfortunately, due to the limited number of patients with available dose information, we were not able to compare antipsychotic drugs within strata of equivalent dose.

In contrast with previous clinical trials, we observed no difference in risk between conventional and atypical antipsychotics. This may be explained by a difference in dosing pattern. Meta-analysis showed that conventional antipsychotics have no additional clinical effect at doses exceeding 375 mg chlorpromazine equivalents (comparable to approximately 8 mg haloperidol), with higher doses only resulting in more side effects like EPS [13]. However, many trials have used 10-20 mg haloperidol as comparison for atypical antipsychotics. Furthermore, in many cases these doses were much higher than those of the atypical antipsychotic [3, 4, 19]. In contrast, in our study doses of conventional antipsychotics were low and more equivalent to those of atypical drugs. With such dose comparisons, differences in risk between these groups are expected to be much less pronounced or even absent, as has been observed in previous studies [6-9].

However, an alternative explanation for the discrepancy between results from our study and previous trials could be a bias in the first, in particular a difference in prognostic characteristics between patients using conventional and atypical antipsychotics. Due to their claim of a reduced risk of EPS, atypical antipsychotics may have especially been prescribed to patients who developed EPS during previous antipsychotic drug treatment. Users of atypical antipsychotics then represent patients with a predetermined increased risk of EPS, a phenomenon also known as confounding by

indication [20] or confounding by prognosis [21, 22]. Unfortunately, we had no information on patients' treatment history prior to admission to the clinic, making it difficult to assess such selective prescribing.

This study used prescriptions of anticholinergic antiparkinsonian medication to identify occurrences of EPS. Although these drugs are unlikely to be prescribed for other reasons than EPS in patients using antipsychotic drugs, this marker will not have identified all patients with EPS. First, this side effect may have gone unnoticed by the treating physician. Second, if correctly diagnosed, EPS may also have been treated by reducing the dosage of the antipsychotic drug or by switching to another antipsychotic. Thus, the occurrence of EPS may be underestimated. However, assuming the degree of misclassification is similar between subgroups of antipsychotics, the main results of our study will not be influenced.

In conclusion, this study showed that the beneficial effect of atypical antipsychotics found in randomized clinical trials may not be observed in clinical practice. Future study will have to assess whether this discrepancy is explained by differences in prognostic factors, dosing or some other factor. Clearly, the occurrence of EPS with atypical antipsychotics in clinical practice needs further study.

ACKNOWLEDGMENT

The authors wish to acknowledge Lucy Kutikova, MSc, for her assistance in data gathering.

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CHAPTER 3.2

Antipsychotic-induced extrapyramidal syndromes

Risperidone compared with low and high potency conventional antipsychotic drugs

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Euopean Journal of Clinical Pharmacology, 2001. 57(4): 327-31

ABSTRACT

Aim To compare the risk of extrapyramidal syndromes (EPS) between patients using risperidone and those using low potency conventional antipsychotic drugs (APDs) in clinical practice, as measured by the use of anticholinergic medication. Second, we tried to replicate results from previous clinical trials that compared risperidone with high potency APDs.

Method Data was obtained from the PHARMO-database containing filled prescriptions of 450.000 community-dwelling people in the Netherlands from 1986 through 1998. From the patients aged 15-54 who were newly treated with APDs, we defined mutually exclusive cohorts according to the APD first prescribed to a patient. APD exposure was followed until the first prescription of anticholinergic medication and was censored when APD prescribing was interrupted or switched. We estimated relative risks between risperidone and commonly used low potency and high potency APDs using Cox proportional hazards models, adjusting for age, gender, dose and other potential confounders.

Results In 4,094 patients who were newly prescribed antipsychotic drugs, the overall incidence rate of anticholinergic drug therapy was 556 per 1,000 person-years, which was dose dependent. Prescribed doses of all antipsychotics were low. While in accordance with previous trials risperidone showed a lower risk of EPS compared to the high potency APDs such as haloperidol (RR 0.26; 95% CI 0.10-0.64), we did not observe a lower EPS rate compared to low potency APDs (risperidone vs. thioridazine: RR 1.73; 95% CI 0.49-6.13; risperidone vs. pipamperone: RR 2.50; 95% CI 0.78-8.04).

Conclusion The reduced EPS rates observed when comparing risperidone with high potency antipsychotics like haloperidol may not apply to comparisons with low potency drugs.

INTRODUCTION

Extrapyramidal syndromes (EPS, i.e. parkinsonism, dystonia, akathisia and dyskinesia) is a group of movement disorders often seen as side effect of antipsychotic drugs (APDs). EPS can adversely affect a patient's well-being, compliance to treatment and as a result treatment outcome [1]. Atypical antipsychotics are a new generation of antipsychotic drugs known to have a lower tendency to cause EPS than the older generation of APDs. One of the most widely studied atypical antipsychotics is risperidone. Many clinical trials showed that patients treated with risperidone have a reduced frequency of EPS and anticholinergic drug use compared to those using high potency conventional antipsychotic drugs [2]. However, in non-elderly patients risperidone has not yet been compared with low potency antipsychotics, known to have a lower EPS liability than high potency drugs [3]. Most widely prescribed low potency APDs in the Netherlands include thioridazine and pipamperone (available in a limited number of European countries), where they accounted for nearly 30% of all antipsychotic drug prescriptions in outpatient practice in 1998 [4]. Thus, it is relevant to know how risperidone relates to this group of antipsychotic drugs in terms of EPS.

We conducted a study which aim was to compare the risk of extrapyramidal syndromes between patients prescribed risperidone and those receiving low potency conventional antipsychotic drugs in outpatient clinical practice, using anticholinergic medication as a marker for the occurrence of EPS. To assess the validity of the study method, we also tried to replicate the findings from previous clinical trials comparing risperidone with high potency APDs.

METHOD

Setting

Data were obtained from the PHARMO system, a database that includes information of drug-dispensing records for all 450.000 residents of 11 Dutch cities. The computerized drug-dispensing records are obtained from outpatient pharmacy files. Since virtually all patients in the Netherlands designate a single pharmacy to fill prescriptions from GPs or medical specialists, the PHARMO system provides a complete record of the prescription history of outpatients. In the Netherlands, prescription records are a reliable source for drug exposure measurement [5]. For every dispensed prescription drug the database contains information on the sex and date of birth of the patient, the dispensed drug, prescriber, dispensing date, amount dispensed and the prescribed dose regimen. All patients and prescribers in the database are anonymous. The duration of use of each dispensed drug is estimated by dividing the number of dispensed tablets by the prescribed number of tablets to be used per day. Thus, for each patient in the system drug exposure can be ascertained on a day-to-day basis [6]. The PHARMO database has previously been used to study various types of drug-induced morbidity [7, 8]. For this study we used all available data from January 1, 1986 till June 30, 1998.

Patients

We defined a cohort of patients aged 15-54 who were prescribed an oral antipsychotic drug for the first time since their enrollment in the PHARMO system. Excluded were: a) patients enrolled in the PHARMO system for less than one year prior to the initial APD prescription, b) patients already

using anticholinergic drugs before the day of cohort entry, c) patients receiving more than one APD at cohort entry, and d) patients who used APDs for less than 15 days. Follow-up was censored when a patient's exposure to antipsychotic drugs was interrupted for more than 30 days, when a patient switched to other antipsychotic treatment or after 90 days of follow-up, whichever of these came first. The selection procedure resulted in mutually exclusive cohorts of newly treated patients for each individual antipsychotic drug. In this study we focussed on patients who were initiated on risperidone, the low potency drugs thioridazine, pipamperone or chlorpromazine or on one of the high potency APDs previously studied in clinical trials, namely haloperidol, zuclopenthixol and perphenazine.

Previous trials comparing risperidone with haloperidol found a relative risk of 0.54 for starting with anticholinergic medication [2]. Sample size calculation showed that we needed to include at least 70 patients using risperidone and the same number of patients using a conventional APD to detect such a relative risk in our study with 80% power, given a type I error probability of 0.05.

Outcome definition

The outcome of the study was first use of any drug indicated for treatment of drug-induced extrapyramidal syndromes, which was taken as a measure for the occurrence of EPS. These included the anticholinergic drugs benzatropine, biperiden, dexetimide, orphenadrine, procyclidine and trihexyphenidyl. The risk for developing extrapyramidal syndromes was considered to be instantaneous, meaning that new use of anticholinergic medication was assessed from day 1 after initiation of antipsychotic-treatment till the end of follow-up. Patients who started the antipsychotic and anticholinergic drugs on the same day were excluded because such prescribing practice is likely to represent prophylactic use.

Statistical analysis

For each antipsychotic in the study, we calculated the incidence rate of anticholinergic medication by dividing the total number of events by the total number of exposed person-time. We evaluated the effect of dose for all antipsychotics taken together by calculating the incidence rate in separate dose strata. For each patient the mean daily dose during follow-up was expressed in chlorpromazine equivalents. This was done by multiplying the ratio of the mean daily dose and the defined daily dose (DDD) of the prescribed drug by the defined daily dose of chlorpromazine. One DDD, a technical unit for measurement and comparison of drug use defined by the World Health Organization, also equals the recommended adult daily dose of antipsychotic drugs in the Netherlands [9, 10].

We calculated crude and adjusted relative risks (RR) and 95% confidence intervals (95% CI) of starting with anticholinergic medication for risperidone compared to the different conventional APDs using a Cox proportional hazards model. All multivariate Cox models included age at cohort entry, gender, calendar year of cohort entry and prescriber (general practitioner, psychiatrist or other) as covariates, as well as terms for the use of benzodiazepines, lithium, tricyclic antidepressants and selective serotonin reuptake inhibitors in the 30 days prior to cohort entry or during follow-up. Furthermore, to control for possible differences in dosing between antipsychotic drugs, we adjusted for mean prescribed dose during follow-up, expressed in chlorpromazine

equivalents.

RESULTS

We identified 4,094 patients who met all the inclusion criteria of our study. Sixty-six percent of them started with one of the seven antipsychotic drugs under study. Characteristics of the treatment groups are presented in table 1. Patients treated with risperidone were younger and were more often treated by a psychiatrist than patients receiving other APDs. Prescribed doses of all antipsychotics were considerably lower than their defined daily dose (DDD). Median prescribed dose of risperidone was 99 chlorpromazine equivalents (2.0 mg), which was higher than that of other APDs we studied (table 1). Nevertheless, since the cohorts of conventional APDs were relatively large, for all conventional drugs but chlorpromazine there were at least as many patients prescribed more than 100 chlorpromazine-equivalents per day as in the risperidone group.

Table 1 Characteristics of antipsychotic drugs and their users

Exposure	Market share (%)†	Class‡	Patients (No.)	Mean age	Men (%)	Treated by psychiatrist (%)	Daily Dose, median	
							mg/day	CPZeq/day¶
Any APD*	100	-	4,094	36	45.9	29.3	-	-
Risperidone	7.6	A	77	31	48.1	58.4	2.0	99
Haloperidol	14.1	H	744	37§	44.6	10.3§	2.2	84§
Zuclopenthixol	10.8	H	353	37§	41.6	42.5§	6.0	60§
Perphenazine	4.1	H	343	38§	43.1	35.5§	5.3	66§
Thioridazine	9.2	L	625	36§	40.0	29.6§	48.0	48§
Pipamperone	17.2	L	498	35§	53.6	45.0§	40.0	60§
Chlorpromazine	0.4	L	61	41§	68.9§	1.6§	63.0	63§
Other APDs	36.6	-	1,393	36§	47.2	28.5§	-	-

* Abbreviations: N = number of patients; APD = antipsychotic drug

† Market share, as estimated from prescriptions filled in outpatient pharmacies in 1998 in the catchment area of the PHARMO system, standardized to the Dutch population in 1998 on age and sex [4]

‡ Classification of antipsychtotics: H = high potency, L = low potency, A = atypical

¶ Chlorpromazine equivalents per day

§ $p<0.05$, compared to risperidone (Student's t-test for continuous data, Chi-square test for categorical data)

We observed 284 patients who received anticholinergic medication during follow-up, which yielded an overall incidence rate of 556 per 1,000 person-years. The incidence rate was highest in the age-group 20-24 years (1,287 per 1,000 person years) and steadily decreased thereafter, until 328 per 1,000 person-years in the agegroup 50-54 years. Women had a lower risk for receiving anticholinergic medication than men (adjusted RR 0.74; 95% CI 0.58-0.93). The incidence rate showed a steady increase with increasing dose (figure 1), which was also observed for individual antipsychotics (data not shown). We observed no difference in the risk of anticholinergic medication between patients treated by psychiatrists and those treated by GPs (adjusted RR 1.20; 95% CI 0.89-1.62).

The Cox proportional hazards model showed that there was no difference in the risk of receiving anticholinergic medication between patients using risperidone and those using the low potency antipsychotics thioridazine or pipamperone (table 2). The number of patients using chlorpromazine was too small to estimate a relative risk. With respect to the high potency APDs, we observed that risperidone gave lower EPS rates compared to haloperidol and zuclopenthixol, though the latter was not statistically significant. Risperidone had a similar EPS rate compared to perphenazine. All these relative risk estimates were similar when we restricted the analysis to patients treated by psychiatrists (data not shown).

Figure 1 Association between antipsychotic dose (expressed in chlorpromazine equivalents) and the incidence rate of anticholinergic medication in all 4,094 outpatient first-time antipsychotic users

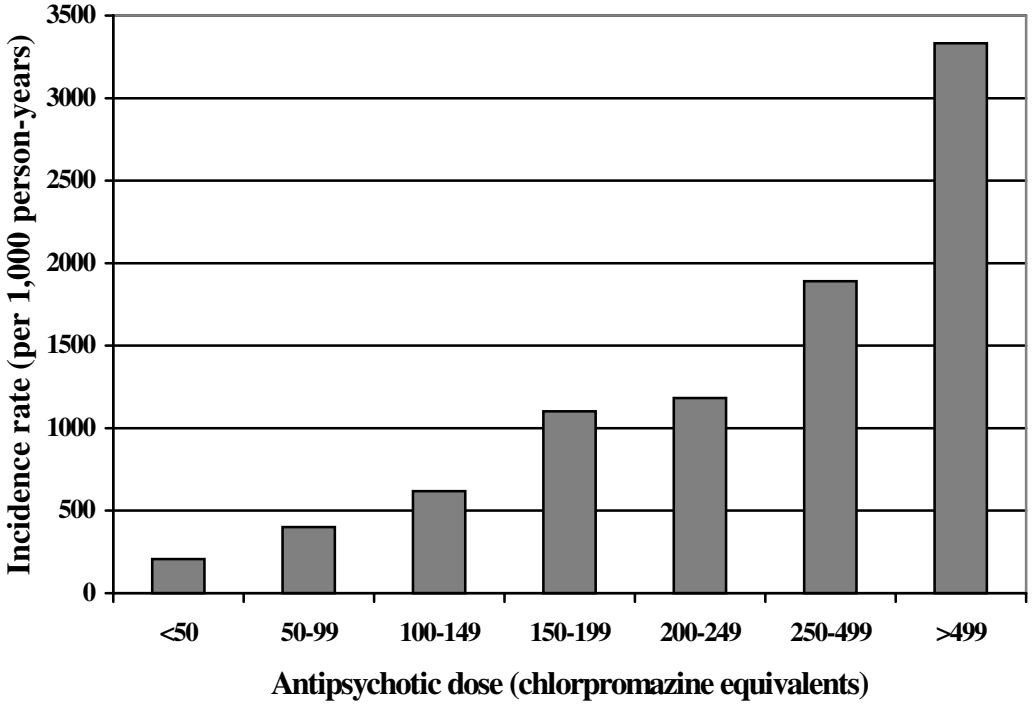

Table 2 Incidence rates and relative risk estimates of anticholinergic medication for risperidone compared to conventional antipsychotic drugs

Exposure	Person-time (years)	Events† (No.)	Incidence/ 1,000 py.	Crude relative risk (95% CI)‡	Adjusted relative risk (95% CI)‡ §
Risperidone	10.1	6	593.5	-	-
• vs. haloperidol	68.7	107	1,557.3	0.44 (0.20-1.01)	0.26 (0.10-0.64)
• vs. zuclopenthixol	40.0	51	1,275.0	0.49 (0.21-1.13)	0.43 (0.17-1.09)
• vs. perphenazine	48.1	14	291.3	1.92 (0.74-5.01)	0.91 (0.21-3.93)
• vs. thioridazine	81.8	15	183.4	3.12 (1.21-8.04)	1.73 (0.49-6.13)
• vs. pipamperone	76.3	10	131.0	4.25 (1.54-11.72)	2.50 (0.78-8.04)
• vs. chlorpromazine	4.4	1	225.7	2.97 (0.35-24.97)	-

† Event of extrapyramidal syndromes, as defined by the first prescribing of anticholinergic medication

‡ Calculated using a Cox proportional hazards model

§ Adjusted for age, sex, year of cohort entry, prescriber (general practitioner, psychiatrist or other), use of benzodiazepines, lithium, tricyclic antidepressants and selective serotonin reuptake inhibitors in the 30 days prior to cohort entry or during follow-up and mean dose during follow-up, expressed in chlorpromazine equivalents

Instead of adding an anticholinergic drug, in practice the occurrence of EPS may also be followed by changing the antipsychotic drug. Switching of antipsychotic medication during follow-up occurred in 7.8% of the patients in the total cohort. Except for chlorpromazine, relative risks did not substantially change when both switching of antipsychotic drug and the addition of anticholinergic medication was considered a marker for EPS.

DISCUSSION

We found no difference in anticholinergic drug use between patients prescribed risperidone and patients using the low potency APDs thioridazine and pipamperone. In contrast, we and others observed a reduced need for anticholinergic medication with risperidone compared to the high potency APDs haloperidol and zuclopenthixol. The number of patients prescribed chlorpromazine was too small to draw any conclusions.

Antipsychotic-induced anticholinergic medication was lower among older people and women, which was also found in previous observational studies [11, 12]. Since age and gender were adjusted for in the multivariate model, these factors could not explain any of the observed relative risks of risperidone versus other APDs. Unfortunately, we had no information on psychiatric

diagnosis or disease severity of our study population. However, previous studies found that in patients with mild impairment, the severity of psychopathology as such is not associated with the risk of extrapyramidal syndromes [13, 14]. Although disease severity may affect antipsychotic dosing and thus indirectly influence EPS rates, dosing was adjusted for in the analysis. Despite the dosing differences between conventional APDs and risperidone, there was still a sufficient number of patients prescribed conventional drugs in the higher dose range to allow for these dose adjustments. Thus, any differences in severity of psychopathology between patients using different APDs are unlikely to have biased the results of our study.

The study outcome was a first prescription of anticholinergic medication, which was used to classify absence or presence of extrapyramidal syndromes. Although anticholinergic drugs are unlikely to be prescribed for other reasons than EPS in a non-elderly population using antipsychotic drugs, this marker will not have identified all patients with EPS. First, symptoms of EPS may have gone unnoticed by the treating physician. Second, if correctly diagnosed, EPS may also have been treated by reducing the dosage of the antipsychotic drug or by switching to another APD. Relative risk estimates may have been biased when this underestimation of EPS occurrence differs between different antipsychotics. Difference in assessment, diagnosis or treatment of EPS may especially result from the observed difference in type of prescriber between risperidone and other APDs. However, our data showed similar degrees of anticholinergic drug prescribing between psychiatrists and GPs. Furthermore, main results of our study did not change when switching of antipsychotic medication was taken as a marker for EPS. While these observations argue against such a bias, it can not be completely ruled out.

Our results may also have been influenced by treatment noncompliance, which is known to be substantial with antipsychotic medication [15]. Apart from EPS, other side effects of APD treatment such as sedation, weight gain or sexual dysfunction may also contribute to noncompliance. As a result, the frequency of EPS in our study would most likely have been higher if all APD medication had been taken as prescribed. However, since we have no information on the relative frequency of side effects of risperidone versus low potency APDs, it is difficult to speculate on their effect on our study results and we can not exclude any differences in noncompliance.

How generalizable are our findings to other treatment settings? Our study population is characterized by outpatient treatment with low doses of antipsychotic drugs, suggesting that patients had only mild psychopathology. In many other settings however dosing is likely to be higher, especially when patients are more severely ill. Based on its pharmacological properties, Kapur and Remington argued that risperidone's superiority in terms of EPS diminishes as dosing increases [16]. Consistent with the higher doses of APDs, clinical trials comparing risperidone with haloperidol showed less favourable relative risks of EPS than our study (RR 0.54, 95% CI 0.42-0.70 [2]). However, trials of risperidone versus zuclopenthixol and perphenazine gave results comparable to our findings (RR 0.52, 95% CI 0.30-0.89 [17] and 0.83, 95% CI 0.47-1.49 [18], respectively). We are aware of only one study that compared risperidone with low potency APDs. In line with the presumed association between dosing and relative EPS liability, low dose risperidone (1 mg/day) showed a trend towards a lower EPS rate compared to thioridazine in a

retrospective study among demented elderly patients [19]. Taken together, in settings where dosing is higher than in our study, relative risk estimates for risperidone are likely to be similar or less favourable than those we observed, both compared to low and high potency APDs.

Concern about extrapyramidal syndromes is an important aspect in choosing between different antipsychotic drugs, considering its possible impact on compliance and treatment outcome. Recent guidelines for treatment of schizophrenia recommend atypical antipsychotics when avoidance of EPS is an important treatment goal [20]. Our study suggests that low potency conventional APDs may also be prescribed for this purpose in non-elderly patients. Given the low costs of these drugs, this is a relevant expansion. With regard to future research, our findings indicate that results from studies with high potency drugs like haloperidol not necessarily apply to all conventional APDs. Thus, complete assessment of the added value of new antipsychotic drugs over the existing arsenal of low cost conventional APDs requires comparative studies with both high and low potency antipsychotic drugs.

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CHAPTER 3.3

Risk of extrapyramidal syndromes with haloperidol, risperidone or olanzapine

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Annals of Pharmacotherapy, 2001. 35(12): 1517-22

ABSTRACT

Aim To compare the risk of extrapyramidal syndromes (EPS) between risperidone, olanzapine and haloperidol, taking into account patients' past antipsychotic drug use and past EPS.

Method Data was obtained from the PHARMO-database, containing filled prescriptions of 450.000 community-dwelling people in the Netherlands from 1986 through 1999. We defined cohorts of first-time users of haloperidol, risperidone or olanzapine aged 15-54. In the first 90 days of treatment, we assessed the occurrence of EPS, defined as first use of any antiparkinsonian agent. We estimated relative risks of EPS for risperidone and olanzapine versus haloperidol using a Cox proportional hazards model. Patients were subdivided according to prior use of antipsychotic and antiparkinsonian drugs.

Results We identified 424 patients starting with haloperidol, 243 with risperidone and 181 with olanzapine. Prior use of antipsychotic plus antiparkinsonian medication was significantly more frequent among users of risperidone and olanzapine than in those using haloperidol (36.2%, 40.3% and 4.5%, respectively; P<0.001). Within most subgroups of comparable treatment history, both users of risperidone and olanzapine showed reduced risks of EPS compared to haloperidol, though some did not reach statistical significance (relative risks between 0.03 and 0.22). However, this was not observed for risperidone users who had experienced EPS in the past (RR: 1.30; 95% CI: 0.24-7.18).

Conclusion In general, we observed strongly reduced risks of EPS for risperidone and olanzapine compared to haloperidol within subgroups of relevant disease history. However, the added value of risperidone in patients who have experienced EPS in the past needs further study.

INTRODUCTION

One of the most important side effects of conventional antipsychotic drugs (APDs) are the extrapyramidal syndromes (EPS), a group of movement disorders that include parkinsonism, akathisia, dystonia and tardive dyskinesia. Although these symptoms were initially thought to be a prerequisite for the therapeutic effect of antipsychotic drugs, this view was radically altered with the introduction of clozapine in the 1960's. This drug combines an increased antipsychotic efficacy with a very low risk of neurological side effects and for this reason was called "atypical" [1]. Based on these observations, several other "atypical" antipsychotics have been developed and marketed in recent years. Of these, risperidone and olanzapine are currently the most widely used. Recent meta-analysis of randomized clinical trials indicated that while atypical APDs may not be more efficacious than conventional drugs, they do show fewer extrapyramidal side effects [2].

A general limitation of randomized trials is that patients and treatment methods may differ largely from those seen in clinical practice, making generalization of results difficult. Trials comparing atypical APDs with conventional drugs generally included chronically ill hospitalized schizophrenic patients. In contrast, in clinical practice users of APDs are much more heterogeneous and include patients who are less severely ill, are treated in an outpatient setting and receive APDs in other doses than those applied in clinical trials [3]. Thus, results from trials need to be confirmed in the everyday clinical setting using observational studies. However, a traditional concern with observational studies regards their potential bias due to the nonrandomized treatment assignment. In the first few years of marketing, new drugs are apt to be prescribed to patients who do not tolerate or who do not respond adequately to older drugs labelled for the same indication [4]. Thus, atypical APDs are likely to be selectively prescribed to patients with an overt susceptibility for EPS, i.e. those who developed EPS during previous treatment with APDs. When comparing the risk of EPS between atypical and classical APDs in observational studies, such imbalance in prognostic factors needs to be accounted for. In previous observational studies regarding antipsychotic-induced EPS this issue was either not addressed [5] or circumvented by limiting the study to newly treated patients [6].

We performed a study to compare the risk of extrapyramidal syndromes between patients using risperidone or olanzapine and those using haloperidol in clinical practice. To account for possible selective precribing of atypical antipsychotics to patients more susceptible for EPS, patients were stratified according to their prior use of antipsychotic drugs and prior EPS.

METHOD

Setting

Data were obtained from the PHARMO system, a database that includes information of drug-dispensing records for all 450.000 residents of 11 Dutch cities. The computerized drug-dispensing records are obtained from outpatient pharmacy files. Since virtually all patients in the Netherlands designate a single pharmacy to fill prescriptions from GPs or medical specialists, the PHARMO system provides a complete record of the prescription history of outpatients. For every dispensed prescription drug the database contains information on the sex and date of birth of

the patient, the dispensed drug, prescriber, dispensing date, amount dispensed and the prescribed dose regimen. The duration of use of each dispensed drug is estimated by dividing the number of dispensed tablets by the prescribed number of tablets to be used per day. Thus, for each patient in the system drug exposure can be ascertained on a day-to-day basis [7]. The PHARMO database has previously been used to study various types of drug-induced morbidity [8, 9], including EPS [10]. For this study we used all available data from January 1, 1986 till June 30, 1999.

Patients

We defined a cohort of patients aged 15-54 who received oral haloperidol, risperidone or olanzapine for the first time ever according to their drug-dispensing records (i.e. "new users"). We only included patients whose first use of haloperidol, risperidone or olanzapine was in the period January 1st, 1994 till June 30th, 1999. Due to switching of antipsychotic medication, one patient could be a new user of more than one of the studied antipsychotic drugs. Excluded were patients who were enrolled in the PHARMO database for less than three years prior to their first use of the study drug and patients who filled prescriptions for more than one antipsychotic drug at cohort entry. Follow-up was censored when a patient stopped antipsychotic medication for more than 60 days, when a patient switched to other antipsychotic medication or after 90 days of follow-up.

Outcome definition

The outcome of the study was first use of any drug indicated for treatment of drug-induced extrapyramidal syndromes, which was taken as a measure for the occurrence of EPS. These included the anticholinergic antiparkinsonian drugs benzatropine, biperiden, dexetimide, orphenadrine, procyclidine and trihexyphenidyl. The risk for developing extrapyramidal syndromes was considered to be instantaneous, meaning that new use of antiparkinsonian medication was assessed from day 1 after initiation of antipsychotic-treatment till the end of follow-up. Patients who started the antipsychotic and antiparkinsonian drugs on the same day were excluded because such prescribing practice represents prophylactic use of antiparkinsonian medication.

Statistical analysis

Crude and adjusted relative risks of EPS for risperidone and olanzapine were calculated using a Cox proportional hazards model, taking users of haloperidol as the reference group. All multivariate Cox models included age at cohort entry, gender, year of cohort entry and prescriber (general practitioner, psychiatrist or other/unknown) as covariates, as well as terms for the use of benzodiazepines, lithium, tricyclic antidepressants and selective serotonin reuptake inhibitors during follow-up. Furthermore, to control for possible differences in dosing between antipsychotic drugs, we adjusted for mean prescribed dose during follow-up, expressed in chlorpromazine equivalents. Chlorpromazine equivalents were calculated by multiplying the ratio of the mean prescribed daily dose and the recommended daily dose of the prescribed drug by the recommended dose of chlorpromazine. Recommended doses of antipsychotic drugs were adopted from the World Health Organization (WHO) [11].

We assessed possible differences in susceptibility for EPS between users of haloperidol, risperidone and olanzapine by comparing their prior use of antipsychotic and antiparkinsonian drugs. We distinguished three strata of increasing complexity of prior antipsychotic drug use: 1) patients with

no history of antipsychotic drug use in the three years prior to cohort entry, 2) patients with a history of antipsychotic drug use, but with no use of antiparkinsonian medication in this three year period, and 3) patients who had used both antipsychotic and antiparkinsonian medication in the three years prior to cohort entry. For convenience, we shall refer to these strata as "no complexity", "intermediate complexity" and "severe complexity" respectively. To account for differences in susceptibility for EPS between patients using different APDs, we calculated relative risks of EPS within each of these strata of complexity. Among patients with severe complexity, residual imbalance in EPS susceptibility was adjusted for by adding an additional term to the multivariate Cox model representing the number of prescriptions for antiparkinsonian drugs in the three years prior to cohort entry. Furthermore, among patients with a history of APD use (intermediate and severe complexity strata) we also adjusted for whether or not patients were free from APDs on the day before cohort entry. Continuous data were compared using a Student's t-test; a Chi-square test was used to compare categorical data.

RESULTS

We identified 424 patients who started for the first time with haloperidol and met all the inclusion criteria of our study, 243 who started with risperidone and 181 who started with olanzapine. Table 1 shows characteristics regarding their demographics and medication. Especially for haloperidol and risperidone, the prescribed daily dose was lower than recommended by WHO and the Dutch Pharmacotherapeutic Guidelines. Patients receiving haloperidol were generally treated by a general practitioner, while patients using risperidone or olanzapine were more often treated by a psychiatrist. Sixty-seven patients were a new user of more than one of the studied antipsychotic drugs and contributed to more than one of the cohorts. Most of them first used haloperidol (59.7%).

Patients using risperidone or olanzapine had a significantly higher frequency of prior use of antipsychotic drugs (i.e. intermediate and severe complexity) than patients using haloperidol (table 1). However, while the portion of antipsychotic-naïve patients (i.e. those with "no complexity") remained more or less constant over time among haloperidol users (1994: 74.0%; 1996: 64.7%; 1999: 82.9%), it increased steadily in patients using risperidone (1994: 0.0%; 1996; 19.2%; 1999: 55.6%) and olanzapine (1996: 0.0%; 1999: 25.0%). For those who had a history of APD use, the median time between cohort entry and the most recent previous APD prescription was 48 days. Based on the estimated duration of use of this most recent prescription, we inferred that on average 40.9% of these patients were exposed to an antipsychotic drug on the day before cohort entry. This number was lower for patients starting with haloperidol (28.0%) than for those using risperidone (48.1%, P=0.002) or olanzapine (41.0%; P=0.060). Among patients with severe complexity, those using risperidone or olanzapine had received significantly more prescriptions of antiparkinsonian drugs in the three years prior to cohort entry than those using haloperidol (on average 12, 11 and 5 prescriptions for users of risperidone, olanzapine and haloperidol, respectively; $P<0.05$). Except for haloperidol, patients with severe complexity tended to receive higher doses of antipsychotic drugs (2.3, 2.0 and 2.2 mg haloperidol; 2.0, 2.0 and 3.0 mg risperidone; 7.5, 8.7 and 9.9 mg olanzapine for patients with no, intermediate and severe complexity, respectively). In addition, they tended to be treated more often by a psychiatrist and more often receive concurrent lithium treatment (data not

Table 1 Characteristics of users of haloperidol, risperidone and olanzapine

	Haloperidol (N=424)[a]	Risperidone (N=243)	Olanzapine (N=181)
Age, mean	37	34[b]	35[b]
Gender (%)			
• male	195 (46.0)	114 (46.9)	96 (53.0)
• female	229 (54.0)	129 (53.1)	85 (47.0)
Duration of follow-up, mean (days)	32	54[b]	64[b]
Precribed dose [c], median (recommended dose [d]; mg/day)	2.2 (8.0)	2.0 (6.0)	9.0 (10.0)
Prescriber (%)			
• general practitioner	308 (72.6)	38 (15.6) [b]	21 (11.6) [b]
• psychiatrist	44 (10.4)	160 (65.8) [b]	130 (71.8) [b]
• other or unknown	72 (17.0)	45 (18.5)	30 (16.6)
Concurrent medication use (%)			
• benzodiazepines	240 (56.6)	125 (51.4)	95 (52.5)
• antidepressants, TCAs	38 (9.0)	28 (11.5)	30 (16.6) [b]
• antidepressants, SSRIs	57 (13.4)	48 (19.8) [b]	34 (18.8)
• lithium	8 (1.9)	18 (7.4) [b]	12 (6.6) [b]
Complexity of prior antipsychotic drug use (%) [e]			
• no complexity	331 (78.1)	81 (33.3) [b]	47 (26.0) [b]
• intermediate complexity	74 (17.5)	74 (30.5) [b]	61 (33.7) [b]
• severe complexity	19 (4.5)	88 (36.2) [b]	73 (40.3) [b]

[a] Reference group

[b] P<0.05, compared to the reference group (Student's t-test for continuous data, Chi-square test for categorical data)

[c] Mean prescribed dose of antipsychotic drug treatment during follow-up

[d] Recommended dose for treatment of psychosis, according to the World Health Organization and the Dutch Pharmacotherapeutic guidelines [11, 25]

[e] no complexity = no prior antipsychotic drug use in the three year period prior to cohort entry; intermediate complexity = prior antipsychotic drug use without prior antiparkinsonian drug use in the three year period prior to cohort entry; severe complexity = prior antipsychotic drug use and prior antiparkinsonian drug use in the three year period prior to cohort entry

Table 2 Percentage of patients starting with antiparkinsonian medication and adjusted relative risk of starting with antiparkinsonian medication for risperidone and olanzapine compared to haloperidol, stratified according to complexity of prior antipsychotic drug use

Complexity of prior APD use [a]	Haloperidol [b]		Risperidone		Olanzapine	
	events (%)	relative risk	events (%)	relative risk [c]	events (%)	relative risk [c]
all patients	56 (13.2)	1.0	29 (11.9)	0.57 (0.31-1.04)	9 (5.0)	0.19 (0.08-0.48)
• no complexity	42 (12.7)	1.0	4 (4.9)	0.22 (0.06-0.77)	2 (4.3)	0.22 (0.04-1.14)
• intermediate complexity	12 (16.2)	1.0	5 (6.7)	0.20 (0.05-0.72)	1 (1.6)	0.03 (0.00-0.42)
• severe complexity	2 (10.5)	1.0	20 (22.7)	1.30 (0.24-7.18)	6 (8.2)	0.14 (0.02-1.15)[d]

abbrevations: APD = antipsychotic drug

[a] no complexity = no prior antipsychotic drug use; intermediate complexity = prior antipsychotic drug use without prior antiparkinsonian drug use; severe complexity = prior antipsychotic drug use and prior antiparkinsonian drug use, in the three year period prior to cohort entry

[b] Reference group

[c] Calculated using a Cox proportional hazards model, adjusted for age, gender, year of cohort entry, prescriber, concurrent use of benzodiazepines, lithium, tricyclic antidepressants and selective serotonin reuptake inhibitors, mean antipsychotic dose during follow-up, whether or not patients were free from APD use immediately before precribing of the study drug (intermediate and severe complexity strata only) and number of prescriptions for antiparkinsonian drugs prior to cohort entry (severe complexity stratum only)

[d] Because of the small number of events in this comparison, the adjusted Cox model was reduced to include only terms for age, gender, mean antipsychotic dose during follow-up, whether or not patients were free from APD use immediately before precribing of the study drug and number of prescriptions for antiparkinsonian drugs prior to cohort entry

shown).

After cohort entry, antiparkinsonian medication was started in 13.2% of the patients using haloperidol, 11.9% of the patients using risperidone and 5.0% of those using olanzapine. This

yielded an adjusted relative risk of 0.57 (95% CI: 0.31-1.04) for risperidone and 0.19 (95% CI: 0.08-0.48) for olanzapine compared to haloperidol (table 2). We then stratified patients according to their complexity of prior antipsychotic drug use. For patients using risperidone, we observed significantly reduced risks of EPS compared to haloperidol among those with no and those with intermediate complexity of prior antipsychotic drug use. However, risperidone showed a slight but non-significant increase in risk among patients with severe complexity. Patients receiving olanzapine had a reduced risk of EPS in all three strata, although in the no complexity and severe complexity subgroup this reduced risk did not reach statistical significance. We observed no difference in the degree of anticholinergic drug use between patients treated by psychiatrists and those treated by GPs in the study population (adjusted RR 1.30; 95% CI 0.71-2.39).

DISCUSSION

Not taking into account any differences in prior medication use between patients, we found that those prescribed risperidone or olanzapine had a lower risk of extrapyramidal syndromes than patients receiving haloperidol. We also found that users of these atypical antipsychotic drugs more often had a history of antipsychotic and antiparkinsonian drug use than patients prescribed haloperidol. This indicates that atypical drugs are selectively prescibed to patients who had EPS in the past and thus are likely to be susceptible for future EPS [12]. We subsequently accounted for this difference in susceptibility by stratifying patients according to their prior use of antipsychotic and antiparkinsonian drugs. With the exception of risperidone-users who have a history of both antipsychotic and antiparkinsonian drug use, we observed reduced risks of antiparkinsonian drug use for the atypical APDs in each of these strata. These relative risks were similar or somewhat lower than those found in previous randomized controlled trials. Meta-analyses of these trials showed relative risks of antiparkinsonian drug use of 0.47 (95% CI 0.38-0.59) for risperidone [3] and 0.17 (95% CI 0.14-0.21) for olanzapine [13] compared to conventional APDs.

Among patients with a history of both antipsychotic and antiparkinsonian medication we found no difference in antiparkinsonian drug use between users of risperidone and haloperidol. A similar result was observed in a previous randomized controlled study among patients who had disturbing EPS during prior neuroleptic treatment [14]. The absence of such a reduced risk for risperidone in our study may have several explanations. First, it may be related to dosing. While antipsychotic-induced extrapyramidal syndromes are caused by blockade of central dopamine D_2 receptors, risperidone also antagonizes 5-HT_2 receptors [15]. This can counterbalance the antidopaminergic effect by disinhibition of the dopamine system. However, this compensatory mechanism is thought to diminish as dosing increases [16]. Indeed, we observed that patients in the severe complexity stratum received higher doses of risperidone than those in the other strata (3.0 mg vs. 2.0 mg per day). Second, the absence of a reduced risk may also be explained by an underlying pathology. Patients who have experienced EPS in the past are likely to have an inherent susceptibility [12] which is thought to result from a preexisting nigrostriatal dopamine deficiency, i.e. preclinical Parkinson's disease [17, 18]. Possibly, risperidones 5-HT_2 antagonism can not compensate for D_2 blockade in patients with an already impaired dopaminergic function. Contrary to risperidone, olanzapine did show a reduced prescribing of antiparkinsonian medication among "severe

complexity" patients. This may be explained by their different pharmacological profiles. In addition to 5-HT_2 antagonism, olanzapine also blocks muscarinic receptors [19], which is known to reduce EPS liability [20].

Notwithstanding these biological explanations, we must also consider non-causal explanations. In light of the limited number of patients, the absence of a reduced risk among those with a history of both antipsychotic and antiparkinsonian drug use may be due to random error. Furthermore, results may have been affected by misclassification of the study outcome or by uncontrolled confounding.

We used prescriptions of anticholinergic antiparkinsonian medication to identify events of extrapyramidal syndromes in our study population. Although anticholinergic drugs are unlikely to be prescribed for other reasons than EPS in a non-elderly population using antipsychotic drugs, this marker will not have identified all patients with EPS. First, symptoms of EPS may have gone unnoticed by the treating physician. Second, if correctly diagnosed, EPS may also have been treated by reducing the dosage of the antipsychotic drug or by switching to another APD. Relative risk estimates may have been biased when this underestimation of EPS occurrence differs between different antipsychotics. Difference in assessment, diagnosis or treatment of EPS may especially result from the observed difference in type of prescriber between atypical APDs and haloperidol. However, we observed similar degrees of anticholinergic drug prescribing between psychiatrists and GPs. Furthermore, main results of our study did not change when switching of antipsychotic medication was taken as a marker for EPS (data not shown). These observations argue against such a bias.

In our study the recency of prior use of antipsychotic drugs varied between patients. According to the prescription data, a substantial number of patients were exposed to antipsychotic drugs on the day before starting with haloperidol, risperidone or olanzapine. Such an acute switch from one APD to another can cause several problems in assessing the occurrence of EPS. First, some patients may have been exposed to the old and the new APD simultaneously, either because an overlap approach was used in switching individuals from one drug to the other or because the prior antipsychotic drug was not completely washed out at the time the new drug was started [21]. Second, any extrapyramidal syndromes that existed prior to switching may have persisted while receiving the new treatment. Taken together, APD use immediately before cohort entry may have increased the risk of EPS. This problem also occurs in many randomized clinical trials, explaining why often increased EPS rates are observed among patients receiving placebo [22]. To control for this potential confounding effect, in our study relative risk estimates were adjusted for whether or not patients were free from APDs in the period immediately before cohort entry.

We had no information on psychiatric diagnosis or disease severity of our study population. However, previous studies found that severity of psychopathology is not associated with the risk of extrapyramidal syndromes [23, 24]. Although disease severity may affect antipsychotic dosing and thus indirectly influence EPS rates, dosing was adjusted for in the analysis. Thus, any differences in severity of psychopathology between patients using different APDs are unlikely to have biased the results of our study.

From our study we can conclude that, since atypical antipsychotics tend to be selectively prescribed to patients with a history of EPS, a patient's disease history should be taken into account when comparing the risk of future EPS between atypical and conventional APDs. Stratifying on prior use of antipsychotic and antiparkinsonian drugs, we found that patients using olanzapine have a strongly reduced risk for EPS compared to haloperidol. This was also observed for risperidone, except in the subgroup of patients who had experienced EPS in the past. The added value of risperidone in this patient group needs further study.

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CHAPTER 3.4

Antipsychotic-induced extrapyramidal syndromes and Cytochrome P450-2D6 genotype

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Pharmacogenetics (in press)

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ABSTRACT

Aim To study the association between polymorphism of the cytochrome P450 2D6 gene (CYP2D6) and the risk of antipsychotic-induced extrapyramidal syndromes (EPS), as measured by the use of antiparkinsonian medication.

Method Data were obtained from a psychiatric hospital where newly admitted patients are routinely screened for several CYP2D6 mutant alleles. Cases were those prescribed antiparkinsonian medication during oral antipsychotic drug (APD) treatment in the period September 1994 till August 2000. They were divided into those using an APD whose metabolic elimination depends on the activity of the CYP2D6 enzyme ("CYP2D6-dependent") and those using other APDs. We formed a control group of APD users for both case groups using a matching ratio of 3:1 (controls:cases). Controls were matched on whether or not their prescribed APD is CYP2D6-dependent. Odds ratios (OR) for slow versus extensive metabolizers were calculated using conditional logistic regression and were adjusted for age, gender, dose and other potential confounding factors.

Results We identified 77 cases prescribed an APD that is CYP2D6-dependent and 54 prescribed APDs not CYP2D6-dependent. Among patients using a CYP2D6-dependent APD, the poor metabolizers were more than four times more likely to start with antiparkinsonian medication than extensive metabolizers (OR: 4.44; 95% CI 1.11-17.68). An increased risk was not observed for patients using APDs not CYP2D6-dependent (OR: 1.20; 95% CI 0.21-6.79).

Conclusion Genetically impaired CYP2D6 activity can increase the risk of antipsychotic-induced EPS. Poor metabolizers should have their APD dosage reduced when the metabolism of the prescribed APD depends on CYP2D6 activity or receive an APD not CYP2D6-dependent.

INTRODUCTION

Antipsychotic drugs (APDs) are widely used for treatment of schizophrenia and other psychotic disorders. However, a great limitation of their use are extrapyramidal syndromes (EPS, i.e. parkinsonism, dystonia, akathisia and dyskinesia), a group of movement disorders that can adversely affect patients' well-being, compliance to treatment and as a result treatment outcome. Since EPS is dose-dependent, factors that influence plasma levels of APDs may also affect the risk of developing EPS. One such factor is the activity of the cytochrome P450 2D6 enzyme (CYP2D6), responsible for the metabolic elimination of several APDs [1]. Up to ten percent of the European Caucasian population has a defective CYP2D6 enzyme due to one or more mutations at the locus coding for CYP2D6 and are classified as poor metabolizers [2]. Several studies have investigated the association between such mutations and the occurrence of EPS, but results have been conflicting [1]. This may be explained by the limited sample size of some studies or by the fact that several studies included APDs for which the metabolic elimination of the active compound does not depend on CYP2D6 activity [3-6].

We studied the association between the CYP2D6 genotype and the occurrence of EPS as measured by the use of antiparkinsonian medication in a large population of APD users. To help explain previous conflicting results, we distinguished between patients using APDs that are CYP2D6-dependent and those using other APDs.

METHODS

Setting

Data for this nested case-control study was obtained from GGz "Meerkanten", a psychiatric institution in the Netherlands of approximately 700 beds responsible for institutionalized and semi-ambulant psychiatric care. Since 1994 this hospital uses several computerized databases to collect and store information on patients' demographics, psychiatric diagnoses, laboratory test results, medication use and other administrative data from hospitalized patients. The study protocol was reviewed and approved by the hospital's Ethics Committee.

Case definition

The study population consisted of all patients who had been hospitalized between September 1994 and August 2000 and during that time had received at least one prescription for an antipsychotic drug. From them, we identified cases of extrapyramidal syndromes as inpatients with a first recorded prescription of any drug indicated for treatment of extrapyramidal syndromes while using antipsychotic medication. These include the antiparkinsonian drugs benzatropine, biperidene, dexetimide, orphenadrine, procyclidine, trihexyphenidyl, levodopa, carbidopa/levodopa, amantadine, bromocriptine, pergolide and selegiline. Excluded were cases who were prescribed parenteral antipsychotic medication on the day antiparkinsonian medication was first prescribed (index date) or who started with antipsychotic and antiparkinsonian medication on the same day, since this represents prophylactic use of antiparkinsonian drugs.

Cases were divided into two mutually exclusive groups. The first consisted of all patients who on

the index date used an APD whose metabolic elimination depends on the activity of the CYP2D6 enzyme (i.e. "CYP2D6-dependent"). These include chlorpromazine, haloperidol, perphenazine, sertindole, thioridazine and zuclopenthixol [1]. Although metabolized by CYP2D6, risperidone was not included in this group. Since its metabolite 9-hydroxyrisperidone is equally active as the parent compound, the impact of CYP2D6 polymorphism on the pharmacologic effect of risperidone is likely to be minimal [7]. The second case group consisted of cases who exclusively used any of the remaining antipsychotic drugs on the index date, including risperidone.

Controls

From the study cohort of antipsychotic drug users we selected a control group for each of the two case groups using risk-set sampling [8]. This first entails identifying all eligible controls for each case, being all cohort members who on the index date of the corresponding case 1) were hospitalized and prescribed antipsychotic medication; 2) had not yet received antiparkinsonian medication; 3) were not prescribed parenteral antipsychotic medication and 4) met the matching criteria. Controls were matched to cases according to whether or not the prescribed APD is CYP2D6-dependent. From this set of eligible controls we randomly selected three controls for each case.

Exposure definition

Starting in July 1995, hospitalized patients are routinely genotyped for several mutations in the cytochrome P450 genes upon first admission. For CYP2D6, these mutations include the defect gene variants CYP2D6*3 and CYP2D6*4, which allow for identification of approximately 90% of the poor metabolizers in the Caucasian population [9]. Patients' DNA was isolated from peripheral leucocytes using the GenomicPrep Blood DNA Isolation Kit (Amersham Pharmacia Biotech, Piscataway N.J. USA). Genotyping for the mutant alleles was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analyses as described elsewhere [10-12], with some slight modifications. For identification of the CYP2D6*3 allele, amplification of a 270 bp fragment was carried out using a single base mismatch primer. This primer introduces an extra MspI restriction site in case of the CYP2D6*3 variant but not in the wildtype allele. The CYP2D6*4 allele was detected by amplification of a 460 bp fragment, including four *Bst*NI restriction sites in the wildtype allele, but only three in the CYP2D6*4 variant. After restriction enzyme digestion, nucleotide fragments were separated and visualized by electrophoresis on an ethidium bromid containing 5.5% agarose gel. All samples were analyzed in duplicates. Alleles without the CYP2D6*3 and CYP2D6*4 mutations were classified as wild type (CYP2D6*1). Genotype data may not be available for patients who were already hospitalized prior to July 1995 and was missing for patients who did not donate blood samples. All patients included in our study were subdivided into poor metabolizers (PM), intermediate metabolizers (IM) and extensive metabolizers (EM) according to their genotype data. Subjects who are homozygous for the CYP2D6*3 allele or the CYP2D6*4 allele or who are heterozygous for both are classified as poor metabolizers. Those who are heterozygous for just one of these alleles are classified as intermediate metabolizers. All other subjects are classified as extensive metabolizers.

Statistical analysis

To estimate the association between CYP2D6 genotype and the occurrence of extrapyramidal

syndromes, we calculated crude and adjusted odds ratios (OR) and their 95% confidence intervals (95% CI) using conditional logistic regression (Egret for Windows, version 2.0.3, Cytel Software Corporation). All multivariate logistic regression models included age at the index date, gender, DSM-IV diagnosis and time since first recorded APD treatment in the hospital as covariates, as well as terms for the use of benzodiazepines, tricyclic antidepressants, selective serotonin reuptake inhibitors and lithium at the index date and the type of antipsychotic drug used. Furthermore, to control for possible differences in dosing between patients, we adjusted for the prescribed dose at the index date, expressed in chlorpromazine equivalents [13, 14]. Doses between subgroups of patients were compared using a Mann-Whitney U test.

We calculated the etiologic fraction, defined as the fraction of antiparkinsonian drug use attributable to the poor metabolizer genotype. This was calculated as 100 x [P(OR-1)]/[1+P(OR-1)] [15], where P is the proportion poor metabolizers in hospitalized patients and OR the odds ratio of antiparkinsonian drug use among poor metabolizers.

RESULTS

The study population consisted of 1,133 patients who were prescribed antipsychotic medication while hospitalized. In this cohort we identified 165 cases starting with antiparkinsonian medication during treatment with oral APDs. The majority of them (97%) started with an anticholinergic antiparkinsonian drug. We excluded 34 cases who had not been genotyped for CYP2D6. Of the 131 remaining cases, 77 used a CYP2D6-dependent APD (case group I), while 54 used other APDs (case group II). Most widely used APDs in case group I were haloperidol (n=39) and zuclopenthixol (n=34). In case group II these were pimozide (n=18), risperidone (n=13) and olanzapine (n=12).

Selecting controls from the cohort of 1,133 APD users by means of risk set sampling yielded 231 and 162 controls for case group I and II, respectively (table 1). Among patients using a CYP2D6-dependent APD (group I), cases were significantly younger than controls and received significantly higher APD doses. This was not observed in those using APDs that are not CYP2D6-dependent (group II). Furthermore, especially in group I, cases and controls differed with regard to psychiatric diagnoses (table 1). Adjusted for several potential confounding factors, in group I patients with the poor metabolizer genotype had a more than four times higher risk of being prescribed antiparkinsonian medication than extensive metabolizers (table 2). Prescribed APD doses of poor and extensive metabolizers in this group were similar (median: 180 vs. 156 chlorpromazine equivalents, respectively; P=0.92). No difference in the degree of antiparkinsonian medication between the PM and EM genotype was observed in group II (table 1). In this group we again observed no difference in prescribed dose between poor and extensive metabolizers (median: 420 vs. 399 chlorpromazine equivalents, respectively; P=0.39). Neither in group I nor group II did patients with the intermediate metabolizer genotype have an increased risk of receiving antiparkinsonian medication. The proportion of antiparkinsonian medication attributable to the poor metabolizer genotype in patients prescribed APDs metabolized by CYP2D6 was 19.2%.

Table 1 Characteristics of cases and controls

	Group I: patients using CYP2D6-dependent APDs*		Group II: patients using APDs not CYP2D6-dependent*	
	Cases (n=77)	Controls (n=231)	Cases (n=54)	Controls (n=162)
Age, mean (s.d.)	50.5 (17.5)	63.3 (16.4)	43.0 (21.0)	45.4 (17.8)
Gender (%)				
• male	37 (48.1)	101 (43.7)	20 (37.0)	79 (48.8)
• female	40 (51.9)	130 (56.3)	34 (63.0)	83 (51.2)
DSM IV diagnosis (%)				
• schizophrenia and other psychotic disorders	28 (36.4)	38 (16.5)	10 (18.5)	41 (25.3)
• bipolar disorders	14 (18.2)	9 (3.9)	5 (9.3)	13 (8.0)
• depressive disorders	10 (13.0)	26 (11.3)	16 (29.6)	21 (13.0)
• dementia	4 (5.2)	36 (15.6)	3 (5.6)	0 (0.0)
• other	11 (14.3)	62 (26.8)	9 (16.7)	29 (17.9)
• no diagnosis / missing	10 (13.0)	60 (26.0)	11 (20.4)	58 (35.8)
APD dose, median (CPZeq/day)	299	123	300	399
(10^{th}, 90^{th} percentile)	(60, 753)	(51, 921)	(107, 960)	(120, 1002)
Concurrent medication use (%)				
• benzodiazepines	58 (75.3)	133 (57.6)	40 (74.1)	94 (58.0)
• antidepressants, TCAs	12 (15.6)	24 (10.4)	9 (16.7)	34 (21.0)
• antidepressants, SSRIs	7 (9.1)	14 (6.1)	12 (22.1)	17 (10.5)
• lithium	17 (22.1)	25 (10.8)	10 (18.5)	15 (9.3)
CYP2D6 genotype				
• extensive metabolizer (homozygous: wt/wt)	39 (50.6)	161 (69.7)	32 (59.3)	88 (54.3)
• intermediate metabolizer (heterozygous: wt/mut)	27 (35.1)	47 (20.3)	19 (35.2)	66 (40.7)
• poor metabolizer (homozygous: mut/mut)	11 (14.3)	23 (10.0)	3 (5.6)	8 (4.9)

abbreviations: CYP2D6 = cytochrome-P450 2D6; APD = antipsychotic drug; CPZeq / day = chlorpromazine equivalents per day; TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor; wt = wildtype allele; mut = mutant, non functional allele (CYP2D6*3 or CYP2D6*4)

* CYP2D6-dependent APDs indicates antipsychotic drugs whose metabolic elimination is dependent on the activity of the CYP2D6 enzyme [1]

Table 2 Cytochrome P450-2D6 genotype among new users of antiparkinsonian medication and among control patients

CYP2D6 genotype	Cases / controls	Crude OR (95% CI)	Adjusted OR (95% CI)*
Group I: patients using CYP2D6-dependent APDs†			
• extensive metabolizer (homozygous: wt/wt)	39/161	1.00¥	1.00¥
• intermediate metabolizer (heterozygous: wt/mut)	27/47	2.42 (1.33-4.42)	0.90 (0.34-2.38)
• poor metabolizer (homozygous: mut/mut)	11/23	2.08 (0.93-4.63)	4.44 (1.11-17.68)
Group II: patients using APDs not CYP2D6-dependent†			
• extensive metabolizer (homozygous: wt/wt)	32/88	1.00¥	1.00¥
• intermediate metabolizer (heterozygous: wt/mut)	19/66	0.78 (0.40-1.52)	0.69 (0.29-1.66)
• poor metabolizer (homozygous: mut/mut)	3/8	1.03 (0.27-3.97)	1.20 (0.21-6.79)

abbreviations: CYP2D6 = cytochrome-P450 2D6; OR = odds ratio; CI = confidence interval; APD = antipsychotic drug; wt = wildtype allele; mut = mutant, non functional allele (CYP2D6*3 or CYP2D6*4)

* adjusted for age, gender, DSM-IV diagnosis, time since first recorded antipsychotic drug treatment, type of antipsychotic drug and the prescribed antipsychotic dose at the index date and concurrent use of benzodiazepines, lithium, tricyclic antidepressants and selective serotonin reuptake inhibitors at the index date

† CYP2D6-dependent APDs indicates antipsychotic drugs whose metabolic elimination is dependent on the activity of the CYP2D6 enzyme [1]

¥ reference group

DISCUSSION

We found that antipsychotic drug users who are poor metabolizer for CYP2D6 have a substantially increased risk for being prescribed antiparkinsonian medication, typically used for treatment of extrapyramidal syndromes. Not surprisingly, this was only observed in patients using an antipsychotic drug for which the metabolic elimination depends on the activity of the CYP2D6 enzyme. In our study population these drugs included haloperidol, zuclopenthixol, perphenazine and thioridazine. Indeed, previous studies found increased plasma levels of these APDs in poor

metabolizers [16-18]. Despite their impaired CYP2D6 activity, patients with the intermediate metabolizer genotype were not more likely to receive antiparkinsonian medication, regardless of the type of APD used. This might be explained by a large interindividual variability in APD plasma levels and resulting side effect risk within both EM and IM genotypes [7]

In the psychiatric hospital from which our study population was drawn, hospitalized patients are screened for mutations in the CYP2D6 gene upon admission with the purpose of optimizing their drug treatment. Although results from genotype testing may not come available to the prescribing physician until several days or even weeks after drug treatment has started, this calls for caution in the interpretation of our study results. In the hospital, prescribers are advised to reduce the dose of antipsychotic medication in patients with the poor metabolizer genotype. Such a dose reduction is likely to reduce the frequency of EPS and as a result will underestimate relative risks. However, we did not observe lower dosing of antipsychotic drugs among poor metabolizers, arguing against such a bias and indicating that the effect of a PM genotype on physicians' prescribing pattern is limited. As a result, we also expect other effects on treatment behaviour such as prophylactic treatment with antiparkinsonian medication or increased vigilance for symptoms of EPS to be small. This is reinforced by our observation that from the eleven poor metabolizers in the first case group, six had not yet been genotyped at the time antiparkinsonian medication was first prescribed.

We used prescriptions of antiparkinsonian medication to identify events of EPS in our study population. Although antiparkinsonian drugs are unlikely to be prescribed for other reasons than EPS, this marker will not have identified all patients with these side effects. First, symptoms of EPS may have gone unnoticed by the treating physician. Second, if correctly diagnosed, EPS may also have been treated by changing the antipsychotic drug treatment. However, assuming such underestimation of the study outcome occurs to the same extent for patients with different genotypes, it does not bias relative risk estimates, [19].

Especially among patients using CYP2D6-dependent APDs, cases and controls were not comparible with regard to DSM-IV diagnosis. This may have introduced bias when diagnosis is related to the occurence of EPS. However, despite an early report indicating a higher frequency of dystonia in manic patients [20], more recent studies observed no association between psychiatric diagnosis and EPS frequency [21-25]. Thus, differences in diagnosis between patients is unlikely to have affected the results of our study.

Several other studies have investigated the association between CYP2D6 genotype and the occurrence of EPS, but their results have been conflicting. While several found a statistically significant association [26-29], others did not [3-6, 30]. Since some studies identified only five or less poor metabolizers [3, 5, 6], the absence of an association may partly be explained by a limited sample size. In addition, several studies included APDs for which the elimination of the active moiety (parent compound plus active metabolite) does not depend on CYP2D6, including levomepromazine, flupenthixol, thiothixene, sulpiride, clozapine and risperidone [3-6]. Since our results confirm that CYP2D6 genotype does not affect the risk of EPS in patients using such APDs, the absence of an association when including these drugs is not surprising.

While being at least partly metabolized by CYP2D6, we classified risperidone and olanzapine as not-CYP2D6-dependent. For risperidone, this was done because of the fact that its main metabolite 9-hydroxyrisperidone has the same pharmacological activity as the parent compound [7]; neither the plasma concentration of the active moiety (parent drug plus metabolite) [7, 31, 32] nor the overall side effect rates [32] have been found to be associated with CYP2D6 phenotype or genotype. For olanzapine CYP2D6 offers only a minor route of metabolism [33]. Despite these observations, a recent study suggested CYP2D6 activity does have an effect on risperidone-induced side effects [34]. We can not explain the discrepancy between this observation and previous studies. However, if CYP2D6 genotype indeed would be associated with EPS in patients treated with risperidone or olanzapine, the risk estimate between the PM and EM genotype in the subgroup of patients using non-CYP2D6-dependent APDs (group II) may have been lower if these APDs were not included in this subgroup.

Taken together, the results of our study show that CYP2D6 genotype can affect the risk of extrapyramidal syndromes in patients using antipsychotic drugs. As a result, poor metabolizers who require antipsychotic drug treatment should have their dose reduced when the prescribed APD is metabolized by CYP2D6. Alternatively, the treating physician may choose to prescribe an antipsychotic not metabolized by CYP2D6. From a public health perspective, we found that the poor metabolizer genotype could explain 19.2% of all antiparkinsonian drug use in patients using APDs metabolized by CYP2D6. Thus, prior knowledge about a patients CYP2D6 genotype could prevent a substantial number of EPS cases if the antipsychotic drug treatment is appropriately adjusted. Future study will have to determine whether the additional costs of routine screening for CYP2D6 polymorphisms prior to antipsychotic drug treatment is offset by the gain in treatment outcome.

ACKNOWLEDGMENT

The contribution of Marga van Weelden, Annemiek Bosman, Kim Notenboom, Dirk van der Glind and Hendrik-Jan Luiting in data gathering is greatly acknowledged.

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CHAPTER 4

Extrapyramidal syndromes due to other drugs

CHAPTER 4.1

Extrapyramidal syndromes associated with selective serotonin reuptake inhibitors; a case-control study using spontaneous reports

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International Clinical Psychopharmacology (in press)

ABSTRACT

Aim To study whether use of selective serotonin reuptake inhibitors (SSRIs) is associated with extrapyramidal syndromes (EPS).

Method We analyzed the spontaneous reports of adverse drug reactions (ADRs) collected by the Netherlands Pharmacovigilance Foundation Lareb in the period 1985-1999 (N=24,263). The study population consisted of all patients using an antidepressant drug at the time the ADR occurred. We calculated ADR-reporting odds ratios (ADR-OR) to estimate the association between SSRI-use and EPS, relative to other antidepressants.

Results We identified 61 patients with EPS. SSRI-use was associated with spontaneous reporting of EPS relative to other antidepressants (adjusted ADR-OR: 2.2; 95% confidence interval: 1.2-3.9). This risk estimate seemed to be higher in patients concurrently using antipsychotic medication (6.9, 0.7-68.0), though the confidence interval was very wide.

Conclusion SSRI-use seems only moderately associated with EPS compared to other antidepressants. However, those concurrently using antipsychotic drugs or presenting with other risk factors may be more susceptible and should be closely monitored.

INTRODUCTION

Over the years, numerous case reports have described the occurence of extrapyramidal syndromes (EPS, i.e. parkinsonism, dystonia, akathisia and dyskinesia) in patients using antidepressant drugs (ADs) [1]. Based on the number of published reports and the antidopaminergic effect of serotonin in the striatum [2], selective serotonin reuptake inhibitors (SSRIs) are thought to induce EPS more often than other ADs. However, so far this hypothesis has not been tested in either experimental or observational studies. This may partly be explained by the low frequency of antidepressant-induced EPS. With an estimated incidence of 1 per 1,000 users of SSRIs or less [3, 4], a cohort study would need to include over 100,000 AD users to detect a two-fold increase in EPS with SSRIs relative to other ADs [5]. Even in a case-control design the required sample size may be difficult to achieve using classical medical registries.

In many countries adverse drug reactions (ADRs) are reported by health care professionals to regional or national pharmacovigilance centers. Despite considerable underreporting [6], this pharmacovigilance data is often used to compare the safety of two drugs from the same pharmacotherapeutic group, especially with regard to new or rare ADRs [7]. This is often done through "reaction proportion signalling", which assesses whether a drug has a disproportionate share in a certain ADR, relative to all other reported ADRs [8]. This methodology has previously been used to study various types of drug-induced morbidity [9-11].

In the absence of population-based pharmacoepidemiological studies, we evaluated whether SSRIs were associated with EPS relative to other antidepressants in a database of spontaneously reported adverse drug reactions.

METHOD

Source

Data for this nested case-control study was obtained from the Netherlands Pharmacovigilance Foundation Lareb. From 1985 onwards, Lareb collects reports of adverse drug reactions (ADRs) in the Netherlands. These reports are provided by health care professionals on a voluntary basis through a "yellow card" system. After being received by Lareb, each report is evaluated by a trained physician and/or pharmacist and filed in a database. Reports contain information about the patient, adverse drug reaction, medication used at the time of the event –both suspected drug and concomitant medication- and indication for use of the suspected drug, as well as the original description of the adverse drug reaction as provided by the reporter. ADRs are coded according to the adverse reaction terminology of the World Health Organization (WHO-ART) [12]. Between January 1st 1985 and June 30th 1999, Lareb has received 24,263 reports.

Selection of cases and non-cases

The study population consisted of all patients for whom an ADR has been reported to Lareb between January 1st 1985 and June 30th 1999 and who used an antidepressant drug at the time the ADR occurred, either recorded as suspected drug or as concomitant medication. From them we identified possible cases of EPS as patients whose ADR was assigned one or more of the following

WHO-ART terms: dystonia, torticollis, choreoathetosis, dyskinesia, extrapyramidal disorder, hyperkinesia, hypokinesia, oculogyric crisis, tremor, muscle contractions involuntary, dyskinesia tardive, parkinsonism aggravated or bradykinesia. From this first selection of patients, only those whose original description of the ADR contained one or more terms indicative of EPS (see table 1, legend) were selected as cases. All other patients in the study population (non-cases) were selected as controls.

Data analysis

We assessed the use of SSRIs (fluoxetine, paroxetine, sertraline, fluvoxamine and citalopram) and other antidepressant drugs -either recorded as suspected drug or as concomitant medication- among cases of EPS and control patients. To quantify the association between SSRI use and spontaneous reporting of EPS relative to other antidepressants, we calculated the ADR-reporting odds ratio (ADR-OR). The ADR-OR is defined as the ratio of two odds, namely the odds of exposure among reported cases of a certain suspected ADR relative to the odds of exposure among reported non-cases [9, 10]. Thus, the numerator of the ADR-OR is calculated by dividing the number of cases (i.e. patients with EPS) where SSRIs are used by the number of cases where other antidepressants were used; the denominator is calculated by dividing the number of controls (i.e. patients with other ADRs) where SSRIs are used by the number of controls where other antidepressants were used.

Crude and adjusted ADR-reporting odds ratios and their 95% confidence intervals were calculated using unconditional logistic regression (SPSS for Windows, version 7.5.2). Odds ratios were adjusted for age and gender of the patient, year and source of the report and the concurrent use of benzodiazepines, antipsychotic drugs and lithium. We also assessed odds ratios within strata of age, gender, calendar year and antipsychotic drug use.

RESULTS

The study population consisted of 2,476 patients in the Lareb database who were using an antidepressant drug at the time their adverse drug reaction occurred. Of them, 61 fulfilled our criteria of EPS and were selected as cases. The remaining 2,415 patients were selected as controls. Mean age of cases and controls was comparable (49 vs. 51, respectively; P=0.33). Sixty seven percent of the cases and 71% of the controls was female (P=0.63). Parkinsonism and dystonia were the most frequently reported extrapyramidal syndrome (59.0% and 21.3%, respectively) (table 1). However, tremor often was the only sign of parkinsonism (83.3%). Only one report described akathisia.

In patients with EPS, SSRIs were more often reported as suspected medication than other antidepressants (41 versus 14 times). In six of the patients with EPS, the antidepressant drug that was used was not the suspected medication (table 1). Not differentiating between suspected and concomitant medication, 41 (67.2%) of the cases and 1,264 (52.3%) of the control patients were using an SSRI. This yielded crude and adjusted ADR reporting odds ratios of 1.9 (95% confidence interval 1.1 to 3.4) and 2.2 (1.2-3.9), respectively, relative to other antidepressants (table 2).

The risk estimate was slightly higher for people 55 years or older and for male patients. Furthermore, the ADR-OR increased over time. Notably, the association between SSRI use and EPS seemed strongest in those concurrently using antipsychotic medication. However, in many of these subanalyses, confidence intervals were wide (table 2).

In this study, restless legs was not considered an extrapyramidal syndrome [13]. It was reported 14 times. The risk estimate did not change when these reports were included as cases (ADR-OR 2.1, 1.2-3.6). Furthermore, SSRI-use remained significantly associated with EPS when tremor was not regarded a symptom of EPS (ADR-OR 2.8, 1.2-6.7).

Table 1 Cases of drug-induced extrapyramidal syndromes (EPS), divided by suspected drug (as indicated by the reporter) and type of disorder

Drug (year of market introduction in the Netherlands)	Any EPS	Parkinsonism †‡	Akathisia §	Dystonia ‖	Dyskinesia ¶	Unspecified EPS ¥
Any drug	61	36 (30)	1	13	10	2
SSRIs	41**	20 (18)	1	11	8	2
• paroxetine (1991)	23**	9 (8)	-	9	6	-
• fluoxetine (1989)	9	7 (6)	-	1	1	-
• fluvoxamine (1985)	7	3 (3)	-	1	1	2
• citalopram (1997)	1	-	1	-	-	-
• sertraline (1994)	1	1 (1)	-	-	-	-
Other antidepressant drugs	14	11 (8)	-	1	2	-
• amitriptyline (1962)	3	3 (3)	-	-	-	-
• clomipramine (1970)	3	2 (2)	-	-	1	-
• dosulepin (1984)	2	2 (2)	-	-	-	-
• maprotiline (1975)	1	1 (1)	-	-	-	-
• mianserin (1982)	1	-	-	-	1	-
• mirtazapine (1994)	1	-	-	1	-	-
• nefazodone (1997)	2	2 (0)	-	-	-	-
• venlafaxine (1994)	1	1 (0)	-	-	-	-
No antidepressant drug	6	5 (4)	-	1	-	-

abbreviations: EPS = extrapyramidal syndrome; SSRI = selective serotonin reuptake inhibitor

† parkinsonism was identified in reports containing one or more of the following terms in the original text: parkinsonism, masked facies, coghweel rigidity, bradykinesia, shuffling gait, tremor, worsening of pre-existing parkinsonism

‡ in parentheses are the number of reports where tremor was the only sign of parkinsonism

§ akathisia was identified in reports containing the term akathisia in the original text

‖ dystonia was identified in reports containing one or more of the following terms in the original text: dystonia, trismus, jaw spasms, oculogyric spasms, torticollis, opisthotonus

¶ dyskinesia was identified in reports containing one or more of the following terms in the original text: lingual-facial-buccal dyskinesia, limb-truncal dyskinesia, choreatic movements, athetosis

¥ unspecified extrapyramidal syndrome was identified in reports containing the term “extrapyramidal syndrome” in the original text without any specification

** this total number of reports is less than the sum of individual extrapyramidal syndromes, since some reports described more than one different extrapyramidal syndromes

DISCUSSION

Our data shows that, relative to other antidepressant drugs, the use of selective serotonin reuptake inhibitors is associated with a two-fold increase in spontaneous reporting of EPS. While this might suggest that SSRIs are more likely to cause EPS than other antidepressants, the association is only moderate. Furthermore, several biases have to be considered.

The use of ADR reporting odds ratios to estimate relative risks may especially be biased by underreporting of ADRs [7]. Important factors that can influence reporting include the time a drug has been on the market and recent publications in the medical literature [14]. The former is unlikely to bias reporting odds ratios. The initial increase and subsequent decrease of the number of ADR reports for a given drug after marketing –known as the "Weber effect"- influences all ADRs of that drug and thus affects the numerator and denominator of the odds ratio to the same extent [9]. However, odds ratios could be affected by the latter. Case reports of antidepressant-induced EPS published during the study period –most of which involved SSRIs- may have selectively stimulated

Table 2 ADR-reporting odds ratios of extrapyramidal syndromes for selective serotonin reuptake inhibitors versus other antidepressant drugs (either suspected drug or concomitant medication)

	cases: reports of EPS (SSRIs / other ADs) †	controls: reports of other ADRs (SSRIs / other ADs) †	ADR-reporting OR (crude, 95% CI)	ADR-reporting OR (adjusted, 95% CI) ‡
overall	41 / 19	1,264 / 1,107	1.9 (1.1-3.4)	2.2 (1.2-3.9)
age				
• <55 years old	25 / 11	919 / 863	2.1 (1.0-4.6)	2.1 (0.9-4.5)
• ≥55 years old	16 / 8	345 / 444	2.6 (1.0-6.6)	2.9 (1.1-7.3)
gender				
• men	15 / 5	356 / 332	2.8 (0.9-8.9)	3.1 (1.0-9.5)
• women	26 / 14	908 / 775	1.6 (0.8-3.2)	1.9 (0.9-3.9)
year of reporting				
• 1985-1990	1 / 5	50 / 226	0.9 (0.0-8.3)	1.1 (0.1-10.8)
• 1991-1993	3 / 3	113 / 146	1.3 (0.2-9.8)	1.7 (0.3-9.3)
• 1994-1996	16 / 4	491 / 288	2.4 (0.7-8.4)	2.7 (0.9-8.2)
• 1997-1999	21 / 7	610 / 447	2.2 (0.9-6.2)	2.5 (1.1-6.2)
concurrent use of antipsychotic drugs				
• no	37 / 18	1,210 / 1,021	1.7 (1.0-3.2)	2.0 (1.1-3.6)
• yes	4 / 1	54 / 86	6.4 (0.6-317)	6.9 (0.7-68.0)

abbreviations: ADR = adverse drug reaction; OR = odds ratio; 95% CI = 95% confidence interval; EPS = extrapyramidal syndromes; SSRI = selective serotonin reuptake inhibitor; AD = antidepressant drug

† Excluding patients who used both an SSRI and another antidepressant drug were used (1 case, 44 controls)

‡ adjusted for age, gender, year or reporting, source and concurrent use of antipsychotic drugs, benzodiazepines or lithium

the reporting of SSRI-induced EPS, thus overestimating the true relative risk. This seems to be supported by the increasing ADR reporting odds ratio over time. Thus, the overall odds ratio of 2.2 is likely to be an upper bound estimate of the true relative risk.

Based on the antidopaminergic effect of serotonin in the striatum [2] and the large number of published case reports of SSRI-induced extrapyramidal syndromes [1], one might have expected a much stronger association between SSRI use and the occurrence of EPS. However, many of the published case reports involved patients also carrying other risk factors for EPS, such as advanced age, concomitant use of antipsychotic drugs, previous events of drug-induced EPS or presymptomatic Parkinson's. This may suggest that the effect of SSRIs on the development of EPS especially presents in those who are already vulnerable to this side effect. Indeed, while the number of patients were small, our results suggest that the association between SSRI-use and EPS is strongest in elderly and those concurrently using antipsychotic drugs.

In conclusion, our data indicate that SSRIs are only moderately associated with extrapyramidal syndromes relative to other antidepressant drugs. Especially those with an already compromised dopaminergic function due to for instance concurrent treatment with other antidopaminergic drugs or Parkinson's disease may be more susceptible and should be closely monitored.

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CHAPTER 4.2

Extrapyramidal syndromes associated with selective serotonin reuptake inhibitors; results from pharmacy data

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ABSTRACT

Aim To study whether use of selective serotonin reuptake inhibitors (SSRIs) is associated with extrapyramidal syndromes (EPS).

Method Data for a population-based case-control study was obtained from the PHARMO-database, containing filled prescriptions of 450.000 outpatients in the Netherlands from 1986 through 1998. We selected cases, being patients newly prescribed antiparkinsonian medication, and six matched controls per case.

Results From the 194 cases and 1,105 matched controls we identified, we observed that patients prescribed SSRIs had an increased risk of antiparkinsonian medication (odds ratio 5.9, 95% confidence interval 1.8-18.8). This was considerably lower for other antidepressants (1.6, 0.6-4.4).

Conclusion Unlike other antidepressants, SSRIs are strongly associated with EPS.

INTRODUCTION

Both selective serotonin reuptake inhibitors (SSRIs) and other antidepressants have been implicated with extrapyramidal syndromes (EPS, i.e. parkinsonism, dystonia, akathisia and dyskinesia) [1]. Based on the number of published reports and the antidopaminergic effect of serotonin in the striatum [2], SSRIs are thought to induce EPS more often than other antidepressants. However, especially for non-elderly patients this hypothesis has not been tested in controlled experimental or observational studies.

We studied the association between the use of SSRIs or other antidepressants and the occurrence of extrapyramidal syndromes, as measured by the start of antiparkinsonian medication.

METHOD

Source

Data for this population-based case-control study was obtained from the PHARMO system, a database that includes information of drug-dispensing records for all 450.000 residents of 11 Dutch cities. These records are obtained from outpatient pharmacy files and provide a virtually complete record of the prescription history of outpatients [3, 4]. The PHARMO database has previously been used to study various types of drug-induced morbidity [5, 6], including EPS [7]. For this study we used all available data from January 1, 1986 till December 31, 1998.

Case definition

Since antiparkinsonian medication is specifically indicated for treatment of EPS, these drugs are often used to identify patients with EPS in epidemiological studies [7, 8]. We identified incident cases of EPS as patients with a first recorded prescription of such medication. These included both anticholinergic and dopaminergic antiparkinsonian drugs. We did not include women prescribed bromocriptine alone (i.e. without other EPS medication), since this drug is also used for suppression of lactation, nor patients prescribed amantadine alone, since this drug may also be used for several other indications, including influenza prophylaxis, dementia or multiple sclerosis.

For each case patient we randomly selected six controls from the PHARMO database, matched on age, gender, pharmacy and calendar year. All patients were assigned an index-date, being the date of first recorded use of antiparkinsonian medication for cases and the same date for the matched controls. Excluded were patients younger than 15 or older than 54, patients who were enrolled in the PHARMO-system for less than one year prior to the index date and patients who had used antipsychotic medication or lithium at any time during their enrollment in the PHARMO system.

Exposure definition

We assessed the use of antidepressant drugs in cases and controls by examining all their drug-dispensings in the 365 days prior to the index date. Current users of antidepressants were patients who had filled a prescription for an antidepressant drug before the index date with a supply of drug that ended 90 days or less before the index date or after the index date. Past users were those whose most recent prescription ended somewhere between 90 and 365 days before the index date. All patients without antidepressant drug prescriptions in the 365 days prior to the index date were

classified as non-users. Current users were subdivided into patients prescribed SSRIs (i.e. fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram) and those using other antidepressants. Those who were current user of antidepressants from both groups were excluded.

Statistical analysis

To estimate the association between antidepressant drug use and starting with antiparkinsonian medication, we calculated crude and adjusted odds ratios using unconditional logistic regression (SPSS for Windows, release 9.0.0). For all risk estimates, no use of antidepressant drugs was taken as the reference exposure category. All models were adjusted for age, gender, pharmacy, calendar time, current use of benzodiazepines and current use of other drugs known to induce EPS, including cinnarizine, flunarizine and metoclopramide [9].

RESULTS

We identified 194 incident users of antiparkinsonian medication and 1,105 controls who fulfilled the inclusion criteria for our study. Mean age of cases and controls was 39 years (table 1). Most frequently prescribed antidepressant drugs in the 90 days before the index date were amitriptyline (9

Table 1 Characteristics of cases and controls

Exposure category	Cases (N=194)	Controls (N=1,105)
Age, mean (s.d.)	39.4 (10.4)	39.2 (10.4)
Gender (%)		
• male	92 (47.4)	525 (47.5)
• female	102 (52.6)	580 (52.5)
Treated by specialist*		
• psychiatrist	7 (3.6)	9 (0.8)
• neurologist	22 (11.3)	13 (1.2)
Concurrent medication use (%)†		
• benzodiazepines	42 (21.6)	95 (8.6)
• cinnarizine	2 (1.0)	2 (0.2)
• flunarizine	2 (1.0)	1 (0.1)
• metoclopramide	5 (2.6)	2 (0.2)

abbreviations: s.d. = standard deviation

* measured in the year prior to the index date

† measured in the 90 days prior to the index date

patients), clomipramine (8 patients) and fluoxetine (7 patients). Of the cases, 7 were current user of SSRIs (3.6%) and 6 were current user of other antidepressants (3.1%), compared to 6 (0.5%) and 17 (1.5%) of the control patients, respectively. This yielded that current users of SSRIs were nearly six times more likely to receive antiparkinsonian medication than people not using antidepressants (adjusted odds ratio 5.9, 95% confidence intervals 1.8-18.8). Current use of other antidepressants was not significantly associated with the use of antiparkinsonian drug treatment (odds ratio 1.6, 0.6-4.4). Past use of antidepressant drugs showed an odds ratio of 2.2 (0.9-5.3) (table 2).

DISCUSSION

We found that the use of SSRIs is significantly associated with an increased risk of starting with antiparkinsonian medication, which was not observed for other antidepressants. Furthermore, past use of antidepressant drugs also seemed to be associated with antiparkinsonian drug treatment. As suggested by previous studies, depression may be a prodrome of Parkinson's disease (PD) and thus inherently associated with future parkinsonian symptoms and antiparkinsonian drug treatment [10, 11]. In addition, symptoms of fatigue, often seen in PD, may have been mistaken for depression [12].

Table 2 Exposure to antidepressant drugs among users of antiparkinsonian medication (n=194) and control patients (n=1,105)

Exposure category	Cases / controls	Crude OR (95% CI)	Adjusted OR (95% CI)*
No antidepressant drug use†	169 / 1,063	1.0	1.0
Current use‡			
• selective serotonin reuptake inhibitor	7 / 6	7.3 (2.1-26.7)	5.9 (1.8-18.8)
• other antidepressants	6 / 17	2.2 (0.7-6.0)	1.6 (0.6-4.4)
Past use, any antidepressant drug	9 / 19	3.0 (1.2-7.1)	2.2 (0.9-5.3)

abbreviations: OR = odds ratio; 95% CI = 95% confidence interval

* adjusted for age, gender, pharmacy, calendar time and current use of benzodiazepines, cinnarizine, flunarizine and metoclopramide

† reference group

‡ excluding patients who were current users of both selective serotonin reuptake inhibitor and other antidepressants (3 cases)

The use of antiparkinsonian medication as a marker for symptoms of EPS will not have identified all patients with EPS: EPS may also have been treated by dose reduction, discontinuation or switching
of antidepressant medication or by the use of other drugs indicated for certain types of EPS, such as benzodiazepines or propranolol. Thus, the observed risk estimates are likely to be underestimates of the true relative risks. Physicians may have been more likely to use one of these alternatives than to prescribe anticholinergic antiparkinsonian medication in patients already receiving highly anticholinergic antidepressants such as the non-SSRIs amitriptyline, clomipramine and imipramine. If so, underestimation may be higher for other antidepressants than for SSRIs. While a previous study indicates that the anticholinergic potential of antidepressants has no effect on physicians' prescribing patterns [13], we can not completely rule out a difference in underestimation between SSRIs and other antidepressants.

Unfortunately, we had no information on psychiatric diagnoses or disease severity of patients prescribed antidepressants. While in the Netherlands more severely depressed patients are recommended to be treated with tricyclic antidepressants (non-SSRIs) [14], we have no reason to assume that disease severity is associated with the likeliness to develop EPS. If a positive association does exist, the difference in risk estimates between SSRIs and other antidepressants may in fact be higher than we observed.

So far, only a few studies have compared the risk of EPS between SSRIs and other antidepressants. These studies were focussed on elderly patients and yielded conflicting results [15, 16]. Our results from a non-elderly population are in line with the higher reporting of EPS with SSRIs compared to other antidepressants, both observed in the literature [1] and in a pharmacovigilance database (data on file). This higher risk may be explained by an indirect antidopaminergic effect of serotonin in the striatum [2].

In conclusion, our observation warrants increased caution when prescribing SSRIs. Especially those with an already compromised dopaminergic function due to for instance Parkinson's disease or concurrent treatment with other antidopaminergic drugs like antipsychotics should be closely monitored.

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CHAPTER 4.3

Extrapyramidal syndromes associated with cinnarizine and flunarizine

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ABSTRACT

Aim To evaluate the association between cinnarizine (Cz) and flunarizine (Fz) and extrapyramidal syndromes (EPS), as measured by the use of antiparkinsonian medication, and to study possible risk factors.

Method Data for this case-control study was obtained from the PHARMO-database, containing filled prescriptions of 450.000 outpatients in the Netherlands from 1986 through 1998. We selected cases, being patients newly prescribed antiparkinsonian medication, and three matched controls per case. We assessed the use of Cz and Fz in the 90 days prior to the index date and calculated odds ratios using logistic regression, adjusting for relevant cofactors.

Results We identified 1,330 cases prescribed antiparkinsonian medication and 3,942 matched controls. Patients using Cz or Fz were more likely to receive antiparkinsonian medication than non-users (odds ratio 3.0, 95% confidence interval 2.1-4.2 and 17.1, 9.5-30.8, respectively). The use of antiparkinsonian medication was already elevated with low doses of Cz/Fz, and increased with increasing dose and duration of use. Age and gender did not affect risk estimates.

Conclusion Fz more than Cz is associated with an increased risk of EPS, even when prescribed at low doses. Dose and duration of use are strong risk factors. These drugs should be used with caution.

INTRODUCTION

Parkinsonism and other extrapyramidal syndromes (EPS) are frequently encountered in neurologic, psychiatric and general practice. While EPS is often idiopathic, the differential diagnosis also includes secondary forms with known causing or contributing factors [1]. Probably the most common of these is medical prescription. As much as one third to over one half of the cases of parkinsonism may be related to drug use [2-4]. Antipsychotics are well-known for their potential to cause EPS, but many other drugs are also implicated. Among these are cinnarizine (Cz) and its difluorinated derivative flunarizine (Fz) [5], both calcium channel-entry blockers with structural similarity to some antipsychotic drugs. Cz and Fz are most commonly used for motion sickness, vascular disease (Cz), vertigo, dizziness (Cz and Fz) and migraine prophylaxis (Fz). The large number of case reports published from 1986 onwards seem to have established the causal relationship between the use of these drugs and the occurence of EPS [6]. However, considering that Cz and Fz are especially used by elderly patients who may also develop EPS without the use of such medication, it would be relevant to compare the risk of EPS between users and non-users of Cz/Fz. Surprisingly, such comparative studies –relying on either prescription analysis or postmarketing surveillance- found no association between Fz use and EPS [7, 8]. However, since especially in non-elderly patients this side effect is thought to be rare (<0.5%) [9], these results may be explained by limited sample sizes.

Therefore, we studied to what extent patients using Cz or Fz are more likely to develop EPS than patients not using these drugs -as measured by the start of antiparkinsonian medication- in a large outpatient population. Second, we studied whether this association was affected by certain patient or treatment characteristics.

METHODS

Source

Data for this population-based case-control study was obtained from the PHARMO system, a database that includes information on drug-dispensing records for all 450.000 residents of 11 Dutch cities. The computerized drug-dispensing records are obtained from outpatient pharmacy files. Since virtually all patients in the Netherlands designate a single pharmacy to fill prescriptions from GPs or medical specialists, the PHARMO system provides a complete record of the prescription history of outpatients. In the Netherlands, prescription records are a reliable source for drug exposure measurement [10]. For every dispensed prescription drug the database contains information on the sex and date of birth of the patient, the dispensed drug, prescriber, dispensing date, amount dispensed and the prescribed dose regimen. All patients and prescribers in the database are anonymous. The duration of use of each dispensed drug is estimated by dividing the number of dispensed tablets by the prescribed number of tablets to be used per day. Thus, for each patient in the system drug exposure can be ascertained on a day-to-day basis [11]. The PHARMO system has previously been used to study various types of drug-related morbidity [12, 13], including antipsychotic-induced EPS [14]. The latter yielded results comparable to randomized clinical trials. For this study we used all available data from January 1, 1986 till December 31, 1998.

Selection of cases and controls

Since antiparkinsonian medication is specifically indicated for treatment of EPS, these drugs are often used to identify patients with EPS in epidemiological studies [2, 14]. We identified incident cases of EPS as patients with a first recorded prescription of antiparkinsonian medication, either anticholinergic or dopaminergic. We did not include women prescribed bromocriptine alone (i.e. without other EPS medication), since this drug is also used for suppression of lactation, nor patients prescribed amantadine alone, since this drug may also be used for several other indications, including influenza prophylaxis, dementia or multiple sclerosis. For each case patient we randomly selected three controls from the PHARMO database, matched on age, gender, pharmacy and calendar time. All patients were assigned an index-date, being the date of first recorded use of antiparkinsonian medication for cases and the same date for the matched controls. We did not include patients younger than 15, patients who were enrolled in the PHARMO-system for less than one year prior to the index date or patients who had used antipsychotic medication or lithium at any time during their enrollment in the PHARMO system.

Exposure definition

We assessed the use of Cz and Fz among cases and controls by examining all their drug-dispensings in the 365 days prior to the index date. Furthermore, to study whether the underlying condition for which these drugs are being prescribed is associated with EPS-treatment, we also assessed the use of betahistine (Bh). Like Cz and Fz, Bh is used for treatment of dizziness/vertigo. However, Bh is not a calcium channel blocker, is structurally unrelated to antipsychotic drugs and is not known to be related to EPS.

We subdivided patients using Cz, Fz or Bh into “current users” and “past users”. Current users were patients who had filled a prescription of Cz, Fz or Bh before the index date with a supply of drug that ended 90 days or less before the index date or after the index date. Past users were those whose most recent prescription ended somewhere between 90 and 365 days before the index date. All patients without prescriptions for Cz, Fz or Bh in the 365 days prior to the index date were classified as non-users.

For current users of Cz and Fz we also studied the effects of dose and duration of use. To study whether the risk of Cz/Fz-induced EPS was dose-related, the prescribed daily dose (PDD) of the last prescription filled before the index date was expressed as a fraction of the defined daily dose (DDD), being 90 mg for Cz and 10 mg for Fz [15]. Users of Cz and Fz were grouped into low dose (PDD/DDD <0.50), medium dose ($0.50 \leq$ PDD/DDD < 1.00) and high dose (PDD/DDD ≥ 1.00). We estimated the duration of use by calculating the total days of supply of these drugs in the 365 days before the index date. Patients were categorized as having 30 or fewer days, 31 to 180 days, or 180 or more days of drug use in the year before the index date.

Statistical analysis

To estimate the association between the use of Cz, Fz and Bh and starting with antiparkinsonian medication, we calculated crude and adjusted odds ratios and their 95% confidence intervals using unconditional logistic regression (SPSS for Windows, release 9.0.0). For all risk estimates, patients not using Cz, Fz or Bh were taken as the reference category. All models were adjusted for age,

gender, pharmacy, calendar time and use of benzodiazepines, selective serotonin reuptake inhibitors, other antidepressants and metoclopramide within 90 days before the index date.

RESULTS

We identified 1,330 incident users of antiparkinsonian medication (cases) and 3,942 control patients who fulfilled the inclusion criteria for our study. Median age of cases and controls was 73 years. Of the cases, 64 were current users of Cz (4.8%) and 69 of Fz (5.2%), compared to 74 (1.9%) and 14 (0.4%) of the control patients, respectively. This yielded that current users of Cz were three times more likely to receive antiparkinsonian medication than non-users (adjusted odds ratio 3.0, 95% confidence interval 2.1-4.2). Users of Fz were more than seventeen times more likely to start EPS-medication (17.1, 9.5-30.8) (table 1). Current use of Bh was not associated with the start of antiparkinsonian medication (odds ratio 0.9, 0.5-1.5).

Table 1 Exposure to cinnarizine, flunarizine and betahistine among users of antiparkinsonian medication (n=1,330) and control patients (n=3,942)

Exposure category	Cases (n=1,330)	Controls (n=3,942)	Crude OR (95% CI)	Adjusted OR (95% CI)*
No use of cinnarizine, flunarizine or betahistine†	1,124	3,670	1.0	1.0
Current use¶				
• Cinnarizine	64	74	2.8 (2.0-4.0)	3.0 (2.1-4.2)
• Flunarizine	69	14	16.1 (8.8-30.0)	17.1 (9.5-30.8)
• Betahistine	16	62	0.8 (0.5-1.5)	0.9 (0.5-1.5)
Past use¶				
• cinnarizine	14	68	0.7 (0.4-1.2)	0.7 (0.4-1.2)
• flunarizine	10	9	3.6 (1.4-9.7)	4.0 (1.6-10.0)
• betahistine	17	36	1.5 (0.8-2.8)	1.5 (0.8-2.7)

Abbreviations: OR = odds ratio, CI = confidence interval

* adjusted for age, gender, pharmacy, calendar time, concurrent use of benzodiazepines, selective serotonin reuptake inhibitors, other antidepressants and metoclopramide

† reference group

¶ patients using a combination of cinnarizine, flunarizine or betahistine were excluded (current users: 14 cases, 7 controls; past users: 2 cases, 2 controls)

Past use of Cz did not show an increased risk (table 1). However, past use of Fz still was associated with initiation of antiparkinsonian therapy (odds ratio 4.0, 1.6-10.0). Within this subgroup, this association was strongest when the last prescription prior to the index date was more recent (i.e. 90-180 days before the index date, odds ratio 11.0, 2.2-54.9), but approached unity when this prescription ended longer ago (1.4, 0.3-7.3).

Age had no influence on the observed associations, neither for Cz (age <65: 3.8, 1.1-8.6; age 65-74: 3.2, 1.6-6.1; age ≥75: 3.1, 1.9-4.8) nor Fz (age <65: not estimable; age 65-74: 16.8, 5.6-50.4; age ≥75: 17.8, 8.8-36.2). Gender also had no clear effect on risk estimates of Cz (men: 4.1, 2.3-7.3; women: 2.5, 1.6-4.0) and Fz (men: 15.2, 4.3-53.7; women: 18.6, 9.6-36.3). The use of antiparkinsonian medication was already elevated with low doses of Cz and Fz, and increased with increasing dose and duration of use (table 2). However, while for Cz an increased use of antiparkinsonian medication only became apparent after 30 days of continuous use, Fz showed an increased use immediately after initiation of medication.

When looking at the antiparkinsonian drug treatment of current users of Cz and Fz, we observed this was chronic (i.e. ≥180 days in the first year) in 65.6.% and 66.7% of the cases, respectively. Fourty-four percent (43.8%) of the current users of Cz and 52.2% of Fz refilled a prescription for Cz/Fz in the first 90 days after starting antiparkinsonian medication, suggesting that in these cases prescribing of Cz/Fz was not or only temporarily discontinued after extrapyramidal syndromes occurred.

DISCUSSION

We found that both cinnarizine and flunarizine are associated with the occurence of extrapyramidal syndromes, as measured by the use of antiparkinsonian medication. This association was considerably stronger with Fz than with Cz (odds ratio 17.1 vs 3.0, respectively). While for Cz the increased prescribing of antiparkinsonian medication only became apparent after 30 days of use and disappeared shortly after discontinuation of medication, with Fz it was more acute and persisted longer after discontinuation. Risks were already elevated with low doses of Cz and Fz and increased with increasing dose and duration of use. Unlike suggested by previous case series, we observed no clear effect of age [16] or gender [17, 18] on risk estimates. In agreement with the persistence of symptoms found in other studies [17, 19], antiparkinsonian medication that was initiated during Cz/Fz-treatment often was chronic.

We used prescriptions of antiparkinsonian medication to identify extrapyramidal syndromes in our study population. While these drugs are unlikely to be prescribed for other reasons than EPS, this marker will not have identified all patients with these symptoms. First, EPS may have gone unnoticed by the treating physician. Second, if correctly diagnosed, EPS may also have been treated by dose reduction, switching or discontinuation of the offending medication. Thus, the observed effect measures may be underestimates of the true relative risks. While we could not assess the degree of underestimation, we have no reason to assume it differed between Cz and Fz or between different subgroups.

Table 2 Dose and duration of use of cinnarizine and flunarizine among users of antiparkinsonian medication (n=1,330) and control patients (n=3,942)

Exposure category	Cases (n=1,330)	Controls (n=3,942)	Crude OR (95% CI)	Adjusted OR (95% CI)*
No use of cinnarizine, flunarizine or betahistine†	1,124	3,670	1.0	1.0
Prescribed daily dose of cinnarizine (PDD/DDD) ¶¥				
• <0.50	10	13	2.5 (1.0-6.1)	2.7 (1.2-6.1)
• 0.50-0.99	44	55	2.6 (1.7-4.0)	2.7 (1.8-4.1)
• ≥1.00	10	3	10.9 (2.8-49.8)	12.2 (3.3-44.5)
Prescribed daily dose of flunarizine (PDD/DDD) ¶¥				
• <0.50	0	0	-	-
• 0.50-0.99	21	10	6.9 (3.1-15.6)	7.4 (3.4-15.8)
• ≥1.00	47	3	51.2 (15.3-206.1)	52.8 (16.6-167.5)
Duration of cinnarizine use¶				
• <30 days	9	22	1.3 (0.6-3.1)	1.3 (0.6-2.8)
• 30-179 days	20	19	3.4 (1.8-6.7)	3.8 (2.0-7.2)
• ≥180 days	35	33	3.5 (2.1-5.7)	3.7 (2.3-6.0)
Duration of flunarizine use¶				
• <30 days	2	1	6.5 (0.5-181.8)	6.9 (0.6-76.6)
• 30-179 days	8	2	13.1 (2.6-89.0)	12.9 (2.7-61.6)
• ≥180 days	59	11	17.5 (8.9-35.4)	18.9 (9.8-36.4)

Abbreviations: OR = odds ratio, CI = confidence interval, PDD = prescribed daily dose, DDD = defined daily dose [15]

* adjusted for age, gender, pharmacy, calendar time, concurrent use of benzodiazepines, selective serotonin reuptake inhibitors, other antidepressants and metoclopramide

† reference group

¶ current users only

¥ dosis information was not available for 3 users of cinnirazine and 2 users of flunarizine

Results may have been biased when the underlying disease for which patients were being treated with Cz or Fz is associated with the occurence of EPS. In the Netherlands, Cz is labelled for treatment of vertigo, motion sickness and allergic disorders, while Fz is indicated for treatment of vertigo and migraine prophylaxis. Previous study suggests dizziness is more frequent in patients

with Parkison's disease (PD) than in healthy controls [20]. Thus, patients presenting with dizziness may include some who are in an early stage of PD. In addition, initial symptoms of PD may also include postural instability, which could be misdiagnosed as vertigo or dizziness. However, we found no association between the use of Bh -also used in treatment of vertigo and dizziness- and antiparkinsonian drug treatment, indicating that vertigo/dizziness itself is not associated with EPS. Additional analysis also showed no association between the use of migraine drugs other than Fz and EPS (data not shown). Taken together, this kind of "confounding by indication" seemed unlikely.

Despite the many case reports of Cz/Fz-induced EPS, to our knowledge so far only two studies have tried to quantify the risk of EPS associated with these drugs. Within a group of 777 Fz recipients, Petri et al. compared the rate of antiparkinsonian drug prescribing during periods of use and non-use of Fz and observed no difference [7]. However, this study design may have introduced bias, since Fz-induced EPS may also be treated some time after discontinuation of Fz (i.e. during non-use of Fz), as indicated by our study. Second, a postmarketing study including over 1,600 Fz users only observed two cases of EPS [8]. In both studies the sample size is likely to have been too small, given the age of the study population (mean age 56 and 51 years, respectively) and the estimated low incidence of Fz-induced EPS in these younger patients (<0.5%) [9]. In our study population, mean age of current users of Cz/Fz was 76 years.

Cz and Fz belong to the group of calcium-entry blockers. Several lines of evidence suggest that this feature may contribute to the occurrence of EPS [6]. In addition, both Cz and Fz show structural similarity with some phenothiazine-like antipsychotic drugs [5], suggesting a common mechanism of inducing EPS. Indeed, SPECT-study showed that -as with antipsychotics- Cz/Fz-induced EPS is most likely to result from striatal D2 receptor blockade [21]. Because of its fluorination, Fz is more lipophilic than Cz, resulting in easy crossing of the blood-brain barrier and a consequently higher concentration in the CNS [22] and in a much longer half-life (19 days [23], versus 3 hours for Cz [24]). Together, these characteristics are likely to explain the more acute effect of Fz, the higher risk, and the persistence of an increased risk after discontinuation of treatment.

In conclusion, clinicians should be aware of extrapyramidal syndromes during both initial and maintenance treatment with Cz and Fz, even when prescribed at low doses. Furthermore, assessment of possible causes of EPS should include a thorough review of patients' drug use history. Whenever possible, the use of Cz or Fz should be discontinued upon appearance of EPS, though especially with Fz symptoms may not subside immediately. Prescribing of these drugs should be well-considered, since their potential to induce EPS is considerable and may be the start of long-term morbidity.

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CHAPTER 5

Summary and general discussion

BACKGROUND

Drug-induced extrapyramidal syndromes (EPS) are a group of movement disorders that include parkinsonism, dysthonia, akathisia and dyskinesia. One of the first documented reports of drug-induced EPS was published in 1954 and involved chlorpromazine [1]; similar observations were seen with all other antipsychotic drugs (APDs) thereafter. All these drugs share a striatal antidopaminergic activity, suggesting this to be the underlying mechanism. In addition to APDs, over the years several other drugs have been strongly implicated with EPS, including metoclopramide [2], prochlorperazine [3], cinnarizine [4] and flunarizine [5]. In addition, case reports have described the occurrence of EPS with numerous other drugs.

EPS can be severely disabling, limiting patients in their daily activities and affecting their well being. As a result, these side effects can have a substantial negative impact on treatment adherence and treatment outcome [6, 7]. Thus, minimizing the occurrence of drug-induced EPS is of clear importance. This can be achieved by increasing physicians' and pharmacists' awareness of drug-induced EPS and by identifying possibilities for prevention. This requires information about: 1) which drugs are implicated with EPS; 2) the frequency of occurrence with each of these drugs, and 3) which patients are most susceptible for drug-induced EPS. The aim of this thesis was to quantify the risk of drug-induced EPS for drugs commonly associated with this side effect and to quantify the influence of specific risk factors.

MAIN FINDINGS

Review of the literature

Literature review showed that of the large number of drugs that have been reported to induce parkinsonism, antipsychotic drugs (APDs), selective serotonin reuptake inhibitors (SSRIs) and calciumantagonists (CAs) seem to be implicated most often (chapter 2.1). However, for all three of these groups, several issues have remained unresolved. For APDs, this includes the effect of different risk factors, in particular type of drug and genetically impaired drug metabolism. For SSRIs and CAs, the causal relationship suggested by case reports had not yet been confirmed in controlled studies. As a result, both the strength of the association and risk factors were yet to be established. These issues were the focus of this thesis.

Use of antiparkinsonian medication as a marker for EPS

We used several large databases to study the epidemiology of drug-induced EPS, most of which are based on inpatient or outpatient pharmacy dispensing records. In the Netherlands, while such data sources generally provide accurate information on medication use, they often contain no data on clinical measures such as EPS. Therefore, the occurrence of EPS was derived from the use of antiparkinsonian medication, which in the Netherlands is specifically indicated for treatment of EPS. This method has been used previously in both randomized and observational studies [8, 9]. We evaluated the validity of this marker in an observational setting in the Netherlands by calculating its positive predictive value, sensitivity and specificity using the Integrated Primary Care Information (IPCI) database, containing both prescription and clinical data (chapter 2.2). This showed that, within a cohort of APD users, 90% of the patients treated with anticholinergic

antiparkinsonian medication had symptoms of EPS. While the specificity was also high (0.98), many patients with EPS did not receive antiparkinsonian medication, resulting in a low sensitivity (0.32). These results indicate that antiparkinsonian medication can be validly used to identify patients with EPS. However, a considerable proportion of patients with EPS will not be identified using this marker, making it inappropriate for estimating absolute frequencies. While extrapyramidal syndromes that go undiagnosed or untreated with antiparkinsonian medication are likely to represent milder cases [10], this underestimation requires careful consideration when comparing the risk of EPS between two drugs.

Risk factors for antipsychotic-induced EPS

1. Type of drug

While APDs are well-known for their potential to induce EPS, differences between drugs have been observed. In particular, numerous randomized controlled trials (RCTs) have shown that newer atypical APDs such as clozapine, risperidone and olanzapine are less likely to induce EPS than haloperidol, the standard of care [11-13]. Thus, type of drug is considered a strong risk factor for APD-induced EPS. However, several lines of evidence suggest this difference is artificial and results from non-equivalent dose comparisons that were made in these trials [14].

In this thesis, a series of studies compared the occurrence of EPS between atypical and conventional APDs in clinical practice. Since in clinical practice dosing will be based on therapeutic effect, it is likely to be less disproportionate than in previous RCTs. Any difference in dosing that might have existed (for instance due to differences in diagnoses) was adjusted for in the analysis. In the first of these studies we observed similar risks of EPS for atypical and conventional APDs among patients treated in a large psychiatric hospital (chapter 3.1). This suggested that results from previous trials have been strongly biased by non-equivalent dose comparisons. However, an alternative explanation for the discrepancy between results from our study and previous trials could be a bias in the first, in particular a difference in prognostic factors between the two treatment groups: due to their claim of a reduced risk of EPS, atypical APDs are likely to be selectively prescribed to patients more susceptible to this side effect, i.e. those who have experienced EPS before. This phenomenon is known as confounding by indication [15] or confounding by prognosis [16, 17]. Unfortunately, in this study we had no information on patients' treatment history prior to admission to the clinic, making it difficult to assess such selective prescribing. Nevertheless, confounding by indication has been observed for a wide number of drug groups [15-23] and is also likely to play a role with APDs. Indeed, this was confirmed in later study (chapter 3.3, table 1). Thus, further study had to focus on eliminating this potential confounding effect.

As with other confounders, confounding by indication can be dealt with either by restriction, matching, stratification or statistical adjustment. In the first of two subsequent studies, the study population was restricted to APD-naive patients. Here, selective prescribing is unlikely, since prior to APD treatment a patient's susceptibility to EPS is yet unknown. In this cohort we compared the occurrence of EPS between risperidone and several conventional APDs, both the high potency APDs studied in previous RCTs and the low potency APDs such as thioridazine, which are less likely to induce EPS than high potency drugs and had not been studied previously (chapter 3.2).

With regard to high potency APDs, results were very similar to trials, despite the difference in selected patients, drug dosing and treatment setting between our study and RCTs: risperidone showed a lower risk of EPS compared to haloperidol and zuclopenthixol (though not significant for the latter) but not compared to perphenazine. Interestingly, risperidone did not show fewer EPS than the low potency APDs thioridazine and pipamperone, both of which are still widely used in the Netherlands.

In addition to restriction, confounding by indication was also addressed by stratifying patients based on prognostic factors, defined as prior use of antiparkinsonian medication (chapter 3.3). Comparing the occurrence of EPS for both risperidone and olanzapine with haloperidol showed reduced risks similar to trial results in all strata but one. We did not observe a reduced risk with risperidone among patients who had received antiparkinsonian medication in the past. This suggests that, while risperidone is prescribed selectively to patients with a history of EPS, these are the patients least likely to benefit from it!

2. Past antipsychotic-induced EPS
While not studied in this thesis, we wish to emphasize the importance of past experience of APD-induced EPS. It has been identified as a risk factor for future EPS in a previous study [24], explaining why the observed difference in past EPS between users of conventional and atypical APDs can bias their comparison in observational studies. As described above, we observed that among patients with a history of EPS, the relative safety of the atypical APD risperidone compared to conventional drugs in terms of EPS might be different from that in patients without such history.

3. Cytochrome P450-2D6 (CYP2D6) genotype
This thesis, as well as previous studies found dosage to be a strong risk factor for antipsychotic-induced EPS (chapter 3.2) [9]. As a result, factors that influence plasma levels may also affect the risk of EPS. One such factor that received much attention in recent years is mutations in the gene coding for cytochrome P450 2D6 enzyme (CYP2D6), which is responsible for the metabolic elimination of several APDs [25]. While patients who are homozygous for non-functional CYP2D6 alleles (“poor metabolizers”, PMs) have higher plasma levels of APDs than those homozygous for the wildtype allele (“extensive metabolizers”, EMs) [26], studies that investigated the association between such mutations and the occurrence of EPS found conflicting results. We suggested this could partly be explained by the fact that several of these studies included APDs that are not metabolized by the CYP2D6 enzyme. Therefore, we compared the occurrence of APD-induced EPS between poor and extensive metabolizers, stratifying on whether the prescribed APD is metabolized by CYP2D6 or not. We observed that among patients using an APD metabolized by CYP2D6, poor metabolizers were more than four times more likely to start with antiparkinsonian medication than extensive metabolizers, while an increased risk was not observed for patients using APDs not metabolized by CYP2D6 (chapter 3.4). Thus, CYP2D6 genotype is a clear risk factor for APD-induced EPS.

Other drugs associated with EPS
Of the numerous published case reports on drug-induced EPS, selective serotonin reuptake inhibitors (SSRIs) and the calciumantagonists cinnarizine (Cz) and flunarizine (Fz) seem to be

implicated most often. While case reports generally are not suitable for making causal inferences, especially for Cz and Fz their potential to induce EPS seems to be well established. Nevertheless, controlled studies are needed to quantify the risk and to assess non-causal explanations for the presumed association (i.e. confounding).

1. Selective Serotonin Reuptake Inhibitors

With regard to the association between SSRIs and EPS, two issues are of particular importance. The first question is whether SSRIs are more likely to induce EPS than other antidepressants, some of which have also been implicated with EPS [27]. Second, since depression can be a prodrome of Parkinson's disease, the underlying disease may partly explain the association between SSRIs and EPS. We used data of spontaneously reported adverse drug reactions (ADRs) as well as prescription data to address these issues. In the first study we observed that, relative to other antidepressants, the use of SSRIs was two times more frequent in reports of EPS than in reports of other ADRs (chapter 4.1). Since published case reports may have selectively stimulated reporting of SSRI-induced EPS, we hypothesized this risk is likely to be an upper bound estimate of the true relative risk. However, analysis of prescription data yielded a somewhat stronger effect of SSRI-use: while SSRI-users were six times more likely to start antiparkinsonian treatment than non-users, patients using other antidepressants showed a (non-significant) relative risk of 1.6 (chapter 4.2). In addition, a two fold increase in risk was observed with past use of antidepressants (though not significantly), suggesting that the underlying disease (i.e. depression) is associated with EPS.

2. Cinnarizine and Flunarizine

While from 1985 onwards the association between the calciumantagonists Cz and Fz and the occurrence of EPS has been widely described in the literature, the presumed association could not be corroborated in two previous controlled studies among non-elderly patients [28, 29]. As a result, neither risk estimates nor risk factors have been established. Studying an elderly population, we observed that Cz and especially Fz is strongly associated with EPS compared to people not using such medication (odds ratio 3.0 and 17.1, respectively) (chapter 4.3). Although age and gender were suggested to be risk factors based on case series, this was not observed in our study. However, the risk strongly increased with increasing dose and duration of use. Interesting, while Cz and Fz only differ from each other structurally in their fluorination, this results in considerable pharmacokinetic and pharmacodynamic differences [30, 31] that are closely reflected by markedly different risk profiles, both in terms of onset, magnitude and duration of effect.

METHODOLOGICAL CONSIDERATIONS

The main question in interpreting the results of observational studies is to what extent results have been affected by bias. In general, three types of biases can be distinguished: selection bias, information bias and confounding. We will discuss the effect each of these may have had on the main results of this thesis.

Selection bias

Selection bias occurs when selection of the study population is not independent of the outcome (in cohort studies) or the exposure (in case control studies) [32]. As a result, when considering a case-

control study, the exposure in the study population will be different from that in the source population from which the study population was drawn. For example, in this thesis the relative use of SSRIs may have been higher in spontaneouly reported cases of EPS than in EPS cases in the general population, because published case reports may have selectively stimulated reporting of SSRI-associated EPS. However, since in other studies data was obtained from population-based registries, the study population comprises all patients in the source population, rather than a selection thereof. Thus, selection bias is unlikely.

Information bias

Information bias can be defined as error that arises from systematic differences in the way information on exposure, disease or confounders is collected [32]. In this thesis, data was obtained mainly from automated prescription databases. While such data collecting proces may not be very susceptible to bias, this does not guarantee the validity of the data being collected. In the Netherlands, prescription records have been found to be a reliable source for drug exposure measurement [33], allowing ascertainment of patients' prescribed drug use on a day-to-day basis. Nevertheless, both exposure and outcome may have been misclassified.

Especially in patients using APDs, a likely cause of exposure misclassification is an alternating outpatient and hospitalized treatment. Since in the studies described in this thesis, data was obtained from either community or hospital pharmacies, prescription data will be incomplete for patients receiving both inpatient and outpatient treatment. This problem is most relevant in chapter 3.2 and 3.3, where different APDs were compared in an outpatient setting. Here, follow-up was censored when a patient did not refill an APD prescription for more than 30 days (chapter 3.2) or 60 days (chapter 3.3), since in that case exposure to medication could no longer be measured. Such censoring is accounted for in the Cox proportional hazards model, provided that it is independent of the study outcome. Assuming that the major causes of censoring are hospitalization and termination of treatment, this requirement is likely to be met.

A second problem in these studies was that patients who were identified as newly treated may in fact have received their initial medication during prior hospitalization, which was then continued by the GP. Since the PHARMO database does not contain information on inpatient drug prescriptions, such prior treatment would go unnoticed in our study. In this initial treatment phase, patients may already have been selected towards certain APD medication based on the occurrence of EPS. Unfortunately, the nature of our data did not allow us to assess whether such selection occurred more frequently with certain APDs than with others, thus introducing bias.

Another problem with measuring exposure is treatment noncompliance, which especially with chronic medication can be substantial [34] and may have reduced the occurrence of EPS. While we had no information on the compliance in our datasources, external data indicates a slightly higher compliance rate with SSRIs than with other antidepressant drugs [35, 36], suggesting the occurrence of EPS with SSRIs relative to other antidepressants may have been overestimated in our studies. Unfortunately, such external data is not available for low dose APDs, and we can not exclude any differences in noncompliance between the drugs compared in our studies.

In this thesis the occurrence of EPS was inferred from the prescribing of antiparkinsonian medication. Given the complexity and diversity of these symptoms, using this antiparkinsonian medication as the outcome measure in our studies may be seen as an oversimplification of a patients disease state. The use of this measure was dictated by the constraints of our datasources. However, even in studies where a more detailed measure of EPS is available, this is often dichotomized for ease of analysis and interpretation [37, 38].

The validation study in chapter 2.2 showed that 90% of the patients who received antiparkinsonian medication during APD treatment indeed had EPS. However, only a small percentage of all the patients with EPS receive antiparkinsonian drugs. The majority of patients is treated either by dose reduction, switching or stopping of the drug causing the symptoms, or are not treated at all, and will not be identified by this marker. In addition, although not observed in the small sample of this validation study, akathisia may also be treated with beta-blockers or benzodiazepines [39]. Furthermore, antiparkinsonian medication is contraindicated for treatment of tardive dyskinesia [40] and therefore is unlikely to be a marker for this type of EPS. As a result of all these factors, the occurrence of EPS is most likely to be underestimated in our studies. By definition, antiparkinsonian medication will only have identified those occurrences of acute EPS that were considered severe enough –either by the patient or the physician- to warrant treatment. Thus, our results are likely to reflect only more severe cases of EPS. Sensitivity analysis in our studies comparing individual APDs showed that results do not change when switching was taken as a marker for EPS. While this observation argues against bias due to underestimation of EPS, it cannot be completely ruled out.

Confounding

Confounding can be defined as a bias in the crude measure of association that is due to a factor that is associated with the exposure, is an independent risk factor for the outcome and is not in their causal pathway [32]. Of particular importance in observational studies on known side effects is confounding by indication, a bias resulting from differences in prognostic characteristics between the compared treatment groups [16]. Since many RCTs showed that atypical APDs are less likely to cause EPS, in practice these drugs may be prescribed particularly to patients most susceptible to this side effect. This prescribing pattern is confirmed in one of our studies (chapter 3.3, tabel 1). As a result of this, drugs that have been shown beneficial in RCTs may appear less so in clinical practice. This may partly explain why we observed similar risks of EPS between atypical and conventional APDs in our initial study (chapter 3.1).

In general, confounding can be controlled in the design of the study -through randomization, restriction or matching- or in the analysis of the study –through standardization, stratification or multivariate analysis. We used both restriction and stratification to account for confounding by indication: since selective prescribing of atypical APDs is likely to be triggered by a patient's past EPS, the study population was either restricted to APD-naive patients (chapter 3.2) –who are unlikely to have experienced EPS previously- or stratified based on prior antiparkinsonian drug use (chapter 3.3).

IMPLICATIONS OF THE STUDY RESULTS

Implications for practice

This thesis showed that type of drug, drug dosage and a genetically impaired CYP2D6 activity are strong risk factors for drug-induced EPS. From this we can derive several recommendations to reduce the occurrence of these adverse effects.

1. Among patients who have not previously been treated with APDs, risperidone and olanzapine are clearly preferred over the high potency drugs haloperidol and zuclopenthixol when avoidance of EPS is an important treatment goal. Most importantly however, several low cost conventional APDs, including perphenazine, thioridazine and pipamperone, have an EPS profile similar to risperidone and should be included in the list of treatment options.
2. Patients who have experienced APD-induced EPS in the past are at greater risk for future EPS [24]. Thus, preventive measures should be considered, in particular the use of APDs that are less likely to induce EPS. However, whether risperidone offers an advantage over haloperidol in terms of EPS in this patient population is uncertain. Olanzapine does induce less EPS and may be preferred.
3. A genetically impaired CYP2D6 activity is a strong risk factor for APD-induced EPS that accounts for a substantial number of EPS cases. Thus, from a clinical perspective, genotyping all patients who require APD medication for CYP2D6 polymorphisms prior to treatment is worthwhile. Those who are tested to be homozygous for a non-active CYP2D6 mutant allele (i.e. poor metabolizers) should either have their APD dosage reduced when the metabolism of the APD depends on CYP2D6 activity or should receive an APD that is not CYP2D6-dependent.
4. Although SSRIs were found to have a higher risk of EPS than other antidepressant drugs, whether or not this should affect the choice of treatment may depend on the type of patient. Since in non-elderly uncomplicated patients the absolute risk of SSRI-induced EPS is estimated to be low (approximately 1 per 1,000 [41, 42]), only few cases will be prevented when SSRIs are substituted with other antidepressants. However, many more patients are likely to benefit in populations with a higher background risk, such as patients using antipsychotic medication and the elderly. Thus, increased vigilance for EPS is warranted in patients carrying these and other risk factors, and replacing SSRIs with other antidepressants should be considered. This also applies to patients suffering from Parkinson's disease, for whom SSRIs may be similarly detrimental [43].
5. In elderly patients, cinnarizine and especially flunarizine were found to strongly increase the risk of EPS. Since in the Netherlands these drugs are not considered first line treatment for any of their registered indications, they may well be substituted for drugs less likely to cause EPS. These include scopolamine or meclozine for motion sickness, betahistine for vertigo and propranolol for migraine prophylaxis. We were not able to assess the risk of EPS with cinnarizine and flunarizine in non-elderly patients, since the use of these drugs in this population was very low. However, external data showed that the absolute risk among flunarizine-users younger than 55 is low (0.5 per 1,000 [44]). Therefore, EPS does not need to be an important determinant of drug choice.

Implications for research

The results of this thesis raise several new issues. A first important question is whether our finding that risperidone has no advantage over the conventional APDs perphenazine, thioridazine and pipamperone in terms of EPS also applies to other atypical APDs, such as olanzapine, quetiapine and ziprasidone. Second, future studies may assess whether interventions proposed in this thesis to reduce the occurrence of EPS, in particular routine screening for CYP2D6 polymorphisms, are cost-effective. A more general issue regards confounding by indication. As observed in this thesis with risperidone, the relative effectiveness (or safety) of a drug may depend on patients' disease severity. Thus, while in observational studies differences in disease severity between patients using new and older treatments are typically dealt with by statistical adjustment, a stratified analysis may be more appropriate.

The results of this thesis also extend to the field of randomized controlled trials. Our results once more stretch the importance of dosage in the occurrence of drug-induced EPS, and with that, the need for equivalent dosing when comparing APDs. In the past, several RCTs failed to meet this requirement and compared atypical APDs with high dose haloperidol [45, 46]. Such trials both expose patients to sub-optimal treatment, putting them at risk for serious morbidity, and will not be able to validly assess the added value of new treatment.

In conclusion, settings with accurate and detailed prescription data are suitable for studying drug-induced EPS. This can be further improved when patients can be continuously followed during both inpatient and outpatient treatment and when there is access to relevant clinical data. While we only addressed a small number of drugs, the methods described in this thesis can also be applied to other drugs or drug groups that have been implicated with EPS in the literature. Studying frequency and risk factors for drug-induced EPS can identify high-risk patients. This should contribute to selecting the appropriate medication for each individual patient and help prevent the occurrence of this side effect, thus improving treatment adherence and treatment outcome.

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Chapter 6

Samenvatting

In *hoofdstuk 1* van dit proefschrift wordt een beschrijving gegeven van geneesmiddel-geïnduceerde extrapyramidale stoornissen en wordt het doel van het proefschrift uiteengezet. Extrapyramidale stoornissen (EPS) is een verzamelnaam voor een groep bewegingsstoonissen die worden veroorzaakt door schade in de basale kernen in de hersenen en in andere gerelateerde kernen. Hoewel deze bewegingsstoornissen vaak het gevolg zijn van een neurodegeneratieve aandoening, kunnen ze ook ontstaan door het gebruik van bepaalde geneesmiddelen. Onder deze geneesmiddel-geïnduceerde extrapyramidale stoornissen wordt verstaan parkinsonisme, dystonie, akathisie en dyskinesie. Parkinsonisme kenmerkt zich door tremoren, rigiditeit en/of bradykinesie (bewegingsarmoede). Dystonie is een kortdurende abnormale houding die veroorzaakt wordt door onwillekeurige contracties van agonistische en antagonistische spieren. Dit kan leiden tot een abnormale stand van de nek, ogen, tong, gezicht, ledematen en romp. Bij akathisie is er sprake van rusteloosheid en subjectieve bewegingsdrang. Patienten ervaren het als onmogelijk om lange tijd achter elkaar te kunnen blijven staan of zitten, wat zich kan uiten als ijsberen, heen en weer schommelen op een stoel, continu de benen kruisen etcetera. Tardieve dyskinesie omvat herhalende onvrijwillige hyperkinetische bewegingen waaronder kauwen, tong-bewegingen, smakken en grimassen.

Uit onderzoek blijkt dat eenderde tot de helft van de gevallen van parkinsonisme het gevolg is van geneesmiddel-gebruik. EPS komt met name voor bij het gebruik van antipsychotica. Er zijn echter nog vele andere geneesmiddelen die EPS kunnen veroorzaken. Extrapyramidale stoornissen hebben een sterk negatieve invloed op de kwaliteit van leven van patienten. Ze zijn niet alleen geinvalideerd, maar kunnen ook in een sociaal isolement raken. Patienten bij wie deze bijwerking optreedt zijn tevens vaak minder therapie-trouw. Dit kan het klinische effect van een behandeling sterk reduceren. Het verminderen van de ernst en frequentie van EPS is dan ook van groot belang voor het slagen van een medicamenteuze behandeling waarbij EPS als bijwerking kan optreden. Dit kan worden bereikt door preventie of door tijdige herkenning en behandeling van de symptomen. Voor beide geldt dat kennis omtrent de geneesmiddelen die EPS kunnen veroorzaken, de mate waarin ze dat doen en de risicofactoren essentieel zijn. Het doel van dit proefschrift is dan ook om het risico van verschillende middelen op EPS en de invloed van bepaalde risicofactoren te kwantificeren.

In *hoofdstuk 2* komt de achtergrond van dit proefschrift aan de orde. *Hoofdstuk 2.1* beschrijft een literatuurstudie waarin wordt bekeken welke geneesmiddelen de belangrijkste veroorzakers van EPS zijn, wat de frequentie van deze bijwerking is en wat de risicofactoren zijn. Antipsychotica, selectieve serotonine heropname remmers (SSRIs) en calciumantagonisten komen in de literatuur het vaakst naar voren als veroorzakers van EPS. Verschillende epidemiologische aspecten zijn echter nog niet of niet voldoende onderzocht. Voor antipsychotica betreft dit onder andere de invloed van het type antipsychoticum op het ontstaan van EPS en het effect van een genetische afwijking in het enzym cytochroom P450-2D6. Voor zowel SSRIs als calciumantagonisten geldt dat de diverse case reports van EPS nog niet gevolgd zijn door epidemiologisch onderzoek om de sterkte van de associatie en de risicofactoren te bepalen. Deze aspecten komen in dit proefschrift aan de orde.

Om de epidemiologie van geneesmiddel-geinduceerde EPS te bestuderen. wordt in dit proefschrift gebruik gemaakt van diverse grote medische gegevensbestanden. Het merendeel hiervan betreft medicatiegegevens van openbare apotheken of ziekenhuis-apotheken. Dergelijke informatie is bij uitstek geschikt om het gebruik van specifieke geneesmiddelen door individuele patienten te bepalen. Deze gegevensbestanden bevatten echter veelal geen diagnoses en andere klinische informatie. Om deze reden wordt in dit proefschrift het optreden van EPS afgeleid van het gebruik van antiparkinson-medicatie, welke in Nederland specifiek geindiceerd is voor de behandeling van EPS. Deze methode is eerder in verschillende andere studies gebruikt. In *hoofdstuk 2.2* wordt de validiteit van het gebruik van deze marker onderzocht met behulp van gegevens uit de Integrated Primary Care Information (IPCI) database. Deze database bevat zowel prescriptie als klinische gegevens. Uit deze validatie blijkt dat binnen een cohort van antipsychotica-gebruikers 90% van de patienten die met anticholinerge antiparkinson-medicatie behandeld werden EPS had. Hoewel de specificiteit ook hoog was (0.98), werden veel mensen met EPS niet met antiparkinson-medicatie behandeld, met tot gevolg een lage sensitiviteit (0.32). Deze resultaten laten zien dat antiparkinson medicatie een valide marker is om patienten met EPS te identificeren (vanwege de hoge positief voorspellende waarde), maar niet geschikt is om bijvoorbeeld de frequentie van EPS te bepalen (vanwege de lage sensitiviteit). Deze onderschatting van EPS betreft waarschijnlijk met name mildere gevallen van EPS. Hier dient in de interpreatie van de verschillende onderzoeken rekening mee gehouden te worden.

Antipsychotica zijn de bekendste veroorzakers van EPS. Verschillende gerandomiseerde onderzoeken hebben aangetoond dat nieuwere –atypische- middelen zoals clozapine, risperidon en olanzapine minder vaak EPS geven dan de “standaard-therapie” haloperidol. Het type antipsychoticum is dus een sterke risicofactor voor het optreden van antipsychotica-geïnduceeerde EPS. Er zijn echter verschillende aanwijzingen dat dit verschil in EPS ten minste ten dele te verklaren is door niet-equivalente doserings-vergelijkingen in deze gerandomiseerde onderzoeken: in verscheidene studies wordt een atypisch antipsychoticum vergeleken met een relatief hoge dosering haloperidol, met als gevolg een hoge frequentie van EPS in de controlegroep .

In *hoofdstuk 3* worden in een drietal studies atypische en klassieke antipsychotica vergeleken voor wat betreft het optreden van EPS in de klinische praktijk. Aangezien hier de dosis veelal getitreerd wordt op basis van het klinische effect (of op basis van het optreden van bijwerkingen), zullen de verschillen in dosering tussen middelen naar verwachting minder zijn dan in veel van de eerdere gerandomiseerde studies. Voor verschillen die er desondanks zijn –bijvoorbeeld als gevolg van verschillen in de diagnose van patienten- wordt in de analyse gecorrigeerd. In *hoofdstuk 3.1* is het optreden van antipsychotica-geinduceerde EPS onderzocht bij patienten die behandeld werden in een groot psychiatrisch ziekenhuis. In tegenstelling tot de resultaten van gerandomiseerde onderzoeken worden in deze studie vergelijkbare risico’s op EPS gevonden voor patienten die atypische en patienten die klassieke antipsychotica gebruikten. Een mogelijke verklaring voor dit verschil is dat de resultaten van gerandomiseerde studies vertekend zijn door de niet-equivalente doserings-vergelijkingen. Een geheel andere verklaring is echter dat in ons onderzoek gebruikers van atypische antipsychotica van zichzelf al een hoger risico op EPS hadden, los van het gebruikte antipsychoticum. Vanwege de claim van met name de farmaceutische industrie dat atypische

middelen minder EPS geven dan oudere antipsychotica, worden atypische middelen mogelijk selectief voorgeschreven aan patienten met een verhoogd risico op EPS, te weten patienten die deze bijwerking al eerder gehad hebben. Dit fenomeen van selectief voorschrijven staat bekend als “confounding by indication” of “confounding by prognosis”, oftewel vertekening als gevolg van een verschil in prognose tussen de groepen die vergeleken worden. Omdat in dit onderzoek geen informatie beschikbaar is over het geneesmiddel-gebruik van patienten voorafgaand aan hun opname, is het niet mogelijk deze hypothese te testen. “Confounding by indication” is echter waargenomen voor een groot aantal andere geneesmiddel-groepen en zal waarschijnlijk ook bij antipsychotica een rol spelen. Verdere studies in dit proefschrift moeten dan ook trachten deze vertekening te elimineren.

Net zoals bij andere vormen van confounding kan “confounding by indication” voorkomen of gecorrigeerd worden door middel van restrictie, matching, stratificatie of statistische correctie. In *hoofdstuk 3.2* is de onderzoeks-populatie beperkt tot patienten die –voor zover in de medicatie-gegevens was na te gaan- voor het eerst met een antipsychoticum behandeld werden. In deze situatie is selectief voorschrijven van atypische antipsychotica onwaarschijnlijk, aangezien voorafgaand aan behandeling onbekend is of een patient gevoelig is voor EPS. In dit cohort wordt het optreden van EPS vergeleken tussen risperidon en verschillende hoog- en laag-potente klassieke antipsychotica. Met name de vergelijking met laag-potente middelen is van belang, aangezien hier nog geen gegevens over zijn en ze minder EPS geven dan de hoog-potente. Voor hoog potente antipsychotica blijken de resultaten van dit onderzoek vergelijkbaar met die van eerdere gerandomiseerde studies: risperidon heeft een lager risico op EPS vergeleken met haloperidol (RR 0.26; 95% BI 0.10-0.64) en zuclopentixol (RR 0.43; 95% BI 0.17-1.09), maar niet vergeleken met perfenazine (RR 0.91; 95% BI 0.21-3.93). Een relevante nieuwe bevinding is dat risperidon geen lager risico op EPS laat zien ten opzichte van de laag potente antipsychotica thioridazine (RR 1.73; 95% BI 0.49-6.13) en pipamperone (RR 2.50; 95% BI 0.78-8.04), welke beide nog veelvuldig voorgeschreven worden in Nederland.

In *hoofdstuk 3.3* is het optreden van EPS vergeleken tussen de atypische antipsychotica risperidon en olanzapine enerzijds en haloperidol anderzijds. Ditmaal is de onderzoekspopulatie niet beperkt tot nieuwe gebruikers van antipsychotica. Uit dit onderzoek komt allereerst naar voren dat atypische antipsychotica inderdaad vaker worden voorgeschreven aan patienten met een verleden van antipsychotica-gebruik en EPS. De vertekening die hier het gevolg van kan zijn wordt getracht te voorkomen door patienten te stratificeren op basis van deze prognostische factor. In patienten zonder verleden van EPS laten zowel risperidon als olanzapine een verlaagd risico op EPS zien ten opzichte van haloperidol. Bij patienten met een verleden van EPS is voor risperidon echter geen verlaagd risico op EPS waarneembaar (RR 1.30; 95% BI 0.24-7.18). Dit onderzoek laat zien dat, hoewel risperidon relatief veel wordt voorgeschreven aan patienten met een verleden van EPS, juist bij hen de minste reductie in EPS te verwachten is ten opzichte van bijvoorbeeld haloperidol.

Zowel uit dit proefschrift als uit andere onderzoeken blijkt dat dosis een sterke risicofactor is voor het ontstaan van EPS tijdens antipsychotica-gebruik. Factoren die van invloed zijn op de bloedspiegel zullen daarom waarschijnlijk ook het risico op EPS beinvloeden. Een onderwerp dat

de laatste jaren veel aandacht heeft gehad is de rol van het cytochroom P450 2D6 enzym (CYP2D6), wat verantwoordelijk is voor de eliminatie van verschillende antipsychotica. Mutaties in het gen dat codeert voor dit enzym kunnen leiden tot een verminderd actieve of inactieve vorm van CYP2D6. Onderzoek heeft aangetoond dat mensen die homozygoot zijn voor het niet-functionele CYP2D6 allel (zogenaamde "poor metabolizers") hogere bloedspiegels hebben dan mensen die homozygoot zijn voor het wild-type allel ("extensive metabolizers"). Desondanks hebben studies naar het verband tussen dergelijke mutaties en het optreden van EPS tegenstrijdige resultaten opgeleverd. Dit zou deels verklaard kunnen worden door het feit dat verscheidene van deze studies ook patienten hebben geïncludeerd die antipsychotica gebruiken die niet via dit enzym worden afgebroken. In *hoofdstuk 3.4* is het optreden van EPS tijdens antipsychotica-gebruik vergeleken tussen "poor metabolizers" en "extensive metabolizers". Hierbij is de patienten-populatie onderverdeeld in patienten met een middel dat wel en patienten met een middel dat niet via CYP2D6 wordt afgebroken. Dit onderzoek laat zien dat in de groep patienten die een antipsychoticum gebruiken dat wordt afgebroken door CYP2D6, "poor metabolizers" een meer dan vier maal zo hoge kans hebben op EPS dan "extensive metabolizers" (RR 4.44; 95% BI 1.11-17.68). In de patienten die een antipsychoticum gebruiken dat niet wordt afgebroken door CYP2D6 is geen verschil in risico te zien (RR 1.20; 95% BI 0.21-6.79). Hieruit blijkt dat het CYP2D6 genotype een duidelijke risicofactor kan zijn voor antipsychotica-geïnduceerde EPS.

Naast antipsychotica zijn er nog zeer veel andere middelen die EPS kunnen veroorzaken. Voor het merendeel van deze middelen is dit alleen bekend uit case reports en is geen epidemiologisch onderzoek gedaan. Selectieve serotonine heropname remmers (SSRIs) en calciumantagonisten zijn het vaakst met EPS in verband gebracht. In *hoofdstuk 4* wordt getracht voor deze middelen het risico op EPS te kwantificeren.

Voor wat betreft SSRIs is het van belang te weten of deze middelen vaker EPS veroorzaken dan andere antidepressiva. Daarnaast rijst de vraag in welke mate de associatie tussen SSRIs en EPS verklaard kan worden door het feit dat depressie een prodromen van de ziekte van Parkinson kan zijn. In *hoofdstuk 4.1* is de associatie tussen SSRIs en EPS bestudeerd in een landelijke database van spontaan gemelde bijwerkingen. Hieruit blijkt dat SSRIs ten opzichte van andere antidepressiva geassocieerd zijn met rapportage van EPS (OR 2.2; 95% BI 1.2-3.9). Dit resultaat kan echter vertekend zijn: door de diverse publicaties in de medische literatuur over het optreden van EPS tijdens SSRI gebruik is deze bijwerking mogelijk selectief meer gemeld dan EPS als gevolg van andere antidepressiva. Het gevonden risico is dan ook mogelijk een overschatting van het werkelijke risico. In *hoofdstuk 4.2* is echter op basis van prescriptie-gegevens een sterker effect van SSRIs gevonden: SSRI-gebruikers hadden een 6 maal hogere kans om antiparkinson-medicatie voorgeschreven te krijgen dan mensen die geen antidepressiva gebruikten (OR 5.9; 95% BI 1.8-18.8). Patienten die andere antidepressiva gebruikten hadden een 1.6 maal verhoogde kans (OR 1.6; 95% BI 0.6-4.4). Verder werd een tweemaal verhoogd risico gevonden bij mensen die in het verleden met antidepressiva zijn behandeld (OR 2.2; 95% BI 0.9-5.3). Dit suggereert dat de onderliggende aandoening (i.e. depressie) geassocieerd is met EPS en een deel van de associatie tussen SSRIs en EPS kan verklaren.

Cinnarizine en flunarizine zijn sinds 1985 bekende veroorzakers van EPS. Sinds die tijd is er een groot aantal case reports van deze bijwerking gepubliceerd. Cinnarizine is geïndiceerd voor de behandeling van vertigo, reisziekte en allergische aandoeningen; flunarizine wordt gebruikt bij vertigo en als migraine profylaxe. Flunarizine is een analogon van cinnarizine, met als enig verschil in chemische structuur twee fluor-atomen. Ondanks het grote aantal case reports zijn er vooralsnog geen epidemiologische studies geweest die de associatie tussen deze middelen en EPS hebben kunnen bevestigen. Er is tot op heden dan ook geen informatie beschikbaar geweest over hoe sterk deze middelen met EPS geassocieerd zijn en wat de risicofactoren zijn. Dit wordt in *hoofdstuk 4.3* van dit proefschrift onderzocht. Hierin blijkt dat in een populatie van ouderen zowel cinnarizine als flunarizine geassocieerd zijn met EPS. Hoewel in de gepubliceerde case reports leeftijd en geslacht als mogelijke risicofactor geidentificeerd werden, komt dat in dit onderzoek niet naar voren. Wel neemt het risico op EPS sterk toe met toemende dosering en gebruiksduur. Cinnarizine en flunarizine hebben een duidelijk verschillend risico-profiel ten aanzien van EPS: vergeleken met cinnarizine treedt het verhoogde risico op EPS met flunarizine eerder op, is het effect aanzienlijk sterker (OR 17.1; 95% BI 9.5-30.8 versus OR 3.0; 95% BI 2.1-4.2) en houdt het langer aan na staken van medicatie. Deze verschillen zijn te verklaren door het verschil in chemische structuur en klinisch-chemische eigenschappen die hiervan het gevolg zijn.

In *hoofdstuk 5* wordt een Engelse samenvatting van het proefschrift gegeven, worden de belangrijkste beperkingen besproken en worden de implicaties van de bevindingen in dit proefschrift voor de praktijk en voor toekomstig onderzoek uiteengezet.

DANKWOORD

Iedereen bedanken die –direct of indirect- bijgedragen heeft aan de totstandkoming van dit proefschrift is een bijna onmogelijke opgave. Desalniettemin wil ik toch een poging wagen.

Ton, jouw kennis van de epidemiologie, heldere blik en ontspannen houding hebben mij vele malen weer op het rechte pad gezet. Zonder jouw begeleiding zou dit promotie-onderzoek een stuk moeilijker zijn geweest. Mocht je in de toekomst nóg een AIO krijgen die moeite heeft met tijdsplanningen dan moet je maar zo denken: “The sooner you are behind schedule, the more time you have to catch up”.

Beste Bert. Mijn interesse voor de epidemiologie is ontstaan tijdens jouw colleges. Ondanks de zes voor mijn tentamen (en dan heb je me waarschijnlijk nog gematst) heb je mij indertijd toch geattendeerd op de AIO-positie bij de afdeling Farmacoepidemiologie & Farmacotherapie. Goed personeel is de basis voor succes... Zonder gekheid. Ik vind het een groot voorrecht dat ik aan “jouw” afdeling promotie-onderzoek heb mogen doen. De aanwezige kennis, open sfeer en collegialiteit hebben gemaakt dat ik met bijzonder veel plezier aan mijn onderzoek heb gewerkt. Daarnaast waardeer ik het zeer dat je in een moeilijke periode tijd hebt vrij kunnen maken voor mijn begeleiding.

Raymund Roos, Paul Jansen en David van de Vijver bedank ik voor hun waardevolle inbreng in ons gezamenlijke overleg en snelle commentaar op manuscripten. Jullie kritische blik heeft me altijd geholpen dieper over mijn onderzoek na te denken en zaken in een ander licht te zien.

Beste Ron. Ondanks onze korte samenwerking heb ik een groot deel van mijn inzicht in de epidemiologie te danken aan jouw begeleiding en zeer brede onderzoekservaring. Ik hoop nog veel publicaties van jouw hand te mogen lezen.

Zonder data geen epidemiologie. Ik ben dan ook dank verschuldigd aan al diegenen die mij hebben geholpen de gegevens voor de verschillende onderzoeken te verzamelen. Miriam Sturkenboom en Jeanne Dieleman voor de IPCI-gegevens, Gerard Hugenholtz voor de gegevens uit Altrecht, Martien Panneman en Nancy Breekveldt voor de PHARMO gegevens, Jan van der Weide, Linda Steijns, Marga van Weelden, Annemiek Bosman, Kim Notenboom, Dirk van der Glind en Hendrik-Jan Luiting voor de gegevens van Meerkanten en Eugene van Puijenbroek voor de Lareb-gegevens.

Alle mede-AIO’s en collega’s op de afdeling bedank ik voor hun hulp, borrels, tips, kletspraatjes, roddels en advies. Ik krijg het idee dat ik jullie van voldoende materiaal heb voorzien voor een geïnspireerd lied. Lucy Kutikova, Bas Evers, Robert Kapel, Bas van Dongen, Vincent Hong, Carolien Meyer, Chantal Foeken, Layen Chen en Liesbet van den Heuvel dank ik voor hun bijdrage aan dit onderzoek in de vorm van hun scriptie of bijvak.

Ik ben ook dank verschuldigd aan Ed Moret. Beste Ed, hoewel je met dit proefschrift niets te maken hebt gehad, ben jij degene geweest die mijn interesse in onderzoek heeft gewekt. Door je kennis en interesse in zowel onderwijs als onderzoek ben je van grote waarde voor de faculteit.

En dan waren er natuurlijk de nodige “buitenschoolse activiteiten”. Alle “gèrse gasten” uit Rotterdam, ik hoop dat er na circa 15 jaar vriendschap nog vele zullen volgen. Iedereen uit Caboose, de repetities, optredens, diners en weekenden met jullie zijn altijd om naar uit te zien. Datzelfde geldt voor Be Sharp!. Jullie gouden keeltjes zijn elke woensdag-avond een oase van ontspanning. Jetse, als jij vraagt hoe het met mijn scriptie gaat, zie ik alles weer een beetje in perspectief. Arjen en Frans, bedankt dat jullie zonder enige aarzeling mijn paranimfen wilden zijn. Ik heb het getroffen met jullie als vrienden.

Ben, Buddhi, Kenji, Raj, Rejoy, Rob, Soraya, Taka and Tanya, being at the School of Public Health wouldn’t have been as much fun without you. Now that this “thesis thing” is over, I hope I’ll have a bit more time to hang out with you.

Lieve Mirjam, als je van te voren geweten had wat je te wachten stond had je het waarschijnlijk niet gedaan, en of die 30 herdrukken er komen weet ik ook nog niet zo zeker, maar ik wil je desondanks bedanken dat je dit proefschrift voor me hebt willen drukken.

Vincent en Ingrid, bedankt voor jullie vertrouwen in mij als oppas. Ik hoop binnenkort meer tijd te hebben voor jullie en het kleine grut. Lieve pa en ma, hoewel dingen soms misschien anders gaan dan je hoopt had ik me geen betere ouders kunnen wensen.

Lieve Marieke, ik mis je. Ik hoop snel weer bij je te zijn en nog lang van je humor en liefde te mogen genieten.

Boston, januari 2002

LIST OF PUBLICATIONS

Schillevoort, I., de Boer, A., Herings, R.M.C, Roos, R.A.C., Jansen, P.A.F, Leufkens, H.G.M, *Antipsychotic-induced extrapyramidal syndromes. Risperidone compared with low- and high-potency conventional antipsychotic drugs.* European Journal of Clinical Pharmacology, 2001. **57**(4): p. 327-31.

Schillevoort, I., de Boer, A., Herings, R.M.C., Roos, R.A.C., Jansen, P.A.F., Leufkens, H.G.M., *Risk of extrapyramidal syndromes with haloperidol, risperidone, or olanzapine.* Annals of Pharmacotherapy, 2001. **35**(12): p. 1517-22.

Schillevoort, I., de Boer, A., van der Weide, J., Steijns, L.S.W., Roos, R.A.C, Jansen, P.A.F., Leufkens, H.G.M., *Antipsychotic-induced extrapyramidal syndromes and Cytochrome P450-2D6 genotype.* Pharmacogenetics. (in press).

Schillevoort, I., Van Puijenbroek, E.P., de Boer, A., Roos, R.A.C., Jansen, P.A.F., Leufkens, H.G.M., *Extrapyramidal syndromes associated with selective serotonin reuptake inhibitors; a case-control study using spontaneous reports.* International Clinical Psychopharmacology (in press).

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