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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Influence of initial use of serotonergic antidepressants on antiparkinsonian drug use in levodopa-using patients

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Abstract
Objective To assess whether there is an association between initial use of serotonergic antidepressants and changes in antiparkinsonian drug treatment.
Methods A retrospective cohort study was performed with the PHARMO record linkage system. All patients from 1994 until 2004 of 40 years or older who were first time users of an antidepressant and who had used a levodopa-containing drug at least 180 days before initiation of the antidepressant were included. The maximum follow-up time was 180 days. The first change in antiparkinsonian drug treatment, defined as an increase in the daily dosage of any antiparkinsonian drug, the start of a new antiparkinsonian drug or a change in the dosage form during the follow-up period, was taken as an endpoint. Antidepressants were classified in two ways: according to their class [selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA) or other antidepressants] or by the extent of their inhibition of serotonin reuptake (high, intermediate or low).
Results A total of 221 patients was included in our study. The adjusted hazard ratio for a change in antiparkinsonian drug treatment was 0.7 (95% CI 0.3–1.5) comparing SSRI with TCA users, and it was 0.9 (95% CI 0.4–2.1) comparing users of other antidepressants with TCA users. The adjusted hazard ratio for a change in antiparkinsonian drug treatment was 0.6 (95% CI 0.3–1.4) comparing users of antidepressants with high versus low extent of inhibition of serotonin reuptake, and it was 0.7 (95% CI 0.3–1.4) comparing users of antidepressants with intermediate versus low extent of inhibition of serotonin reuptake.
Conclusion Based on these observations, we found no evidence to be more cautious using SSRIs or serotonergic antidepressants compared to other antidepressants in patients with Parkinson's disease.

Keywords Antiparkinsonian drugs · Depression · Antidepressants

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Introduction

Depression occurs in approximately 20–40% of patients with Parkinson's disease (PD), sometimes as a symptom prodromal to PD [1]. Selective serotonin reuptake inhibitors (SSRIs) are often considered as the first choice treatment for depression in the general population. However, it is unclear whether SSRIs are the best choice for patients with PD, since case reports have suggested an association

between the use of SSRIs and worsening of PD [2]. The hypothesis is that worsening of PD by SSRIs is mediated by the inhibitory effects of serotonin on dopamine release.

Unfortunately, data from controlled studies on the association between use of SSRIs and worsening of PD or new extrapyramidal adverse effects are scarce and characterised by small sample size [3, 4]. To our knowledge no randomised trials have been performed with either SSRIs or tricyclic antidepressants (TCA) in patients with PD. In a cohort study, Van de Vijver et al. used a change in antiparkinsonian drug treatment as a marker for worsening of symptoms of PD and found a four times higher risk for worsening of PD in patients starting a course of treatment with an SSRI versus starting a TCA treatment [5]. This finding is in contrast with the work of Gony and coworkers, who could not demonstrate any statistical difference in the risk for serious extrapyramidal symptoms between SSRIs and other antidepressant drugs in patients with PD [6]. Moreover, Chung et al. examined the motor effects of the SSRI paroxetine versus a placebo on responses to 2-h levodopa infusions in 14 subjects with PD. Paroxetine did not affect tapping scores or dyskinesia but had a positive effect on baseline walking speed [7]. Thus, from the literature it remains unclear whether there is an association between SSRI use and worsening of PD.

The primary objective of our study was to assess whether there is an association between initial use of SSRIs and changes in antiparkinsonian drug treatment compared to initial use of other antidepressants.

It is hypothesised that antidepressants with a high extent of inhibition of serotonin reuptake will cause a higher rate of change in antiparkinsonian drug treatment as compared to those with a low extent of inhibition of serotonin reuptake. The secondary objective of our study was therefore to assess whether there is an association between initial use of antidepressants with a high versus low extent of inhibition of serotonin reuptake and a change in antiparkinsonian drug treatment.

Methods

Setting

This study was performed with the use of the PHARMO record linkage system. PHARMO includes pharmacy dispensing records from community pharmacies linked to hospital discharge records of all 950,000 community-dwelling residents of 25 population-defined areas in the Netherlands from 1985 onwards [8]. Since almost all patients in the Netherlands are registered with a single community pharmacy, independent of prescribing physician, pharmacy records are virtually complete with regard to prescription drugs.

The computerised drug dispensing histories contain information concerning the dispensed drug, dispensing date, the prescribing physician, amount dispensed, prescribed dosage regimen, and the estimated duration of use. The duration of use of each dispensed drug is estimated by dividing the number of dispensed units by the prescribed number of units to be used per day.

Study population

A retrospective cohort study was performed. All patients from 1994 until 2004, of 40 years or older who were first time users of an antidepressant and had used a levodopa-containing drug at least 180 days before initiation of the antidepressant were included. Patients with a single prescription of an antidepressant were excluded. In addition, patients initially using antipsychotics (ATC code N05A, except lithium), metoclopramide, cinnarizine or flunarizine in the period from 180 days before until 180 days after start of follow-up were excluded, because these drugs may induce or cause worsening of PD [9], which could lead to a change in antiparkinsonian drug treatment.

Start of follow-up was the first dispensing date of the antidepressant. The time of follow-up was either 180 days, or until an endpoint was reached, or until the final dispensing date of the antidepressant, or until the final dispensing date of any antiparkinsonian drug, whichever came first (Fig. 1). Literature reports state that the majority of SSRI-associated extrapyramidal reactions occur within

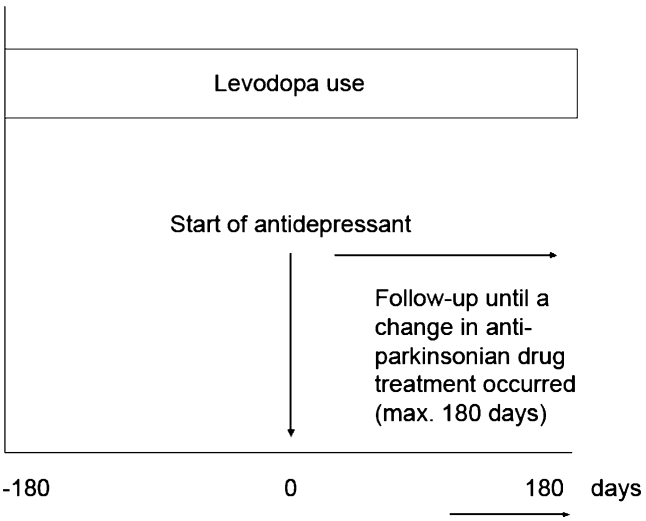

Fig. 1 Follow-up began on the first dispensing date of the antidepressant, and time of follow-up was either 180 days, or until occurence of an endpoint, or the final dispensing date of the antidepressant, or the final dispensing date of any antiparkinsonian drug

28 days after start of SSRI treatment [10]. Therefore a maximum follow-up period of 180 days seemed sufficient.

Endpoint

The first change in antiparkinsonian drug treatment during the follow-up period was taken as an endpoint. A change was defined as an increase in the daily dosage of any antiparkinsonian drug, the start of a new antiparkinsonian drug or a change in the dosage form (e.g. change to controlled-release formulation).

Exposure

Antidepressants were classified in two ways: according to their class (SSRI, TCA or other antidepressants) and according to the extent of inhibition of serotonin reuptake (high, intermediate or low). This classification was described by Walraven et al. [11] and is based on the antidepressant's dissociation constant (K_d) for the serotonin transporter categorised as 0–1 nM, 1–10 nM or >10 nM [12]. Lower dissociation constants reflect a higher affinity for the serotonin transporter and therefore a higher inhibition of serotonin reuptake. Moclobemide was not classified according to the extent of inhibition of serotonin reuptake, because moclobemide alters serotonin concentrations by inhibiting mono-amine oxidase. Table 1 lists the classification of the antidepressants used in this study.

Potential confounding factors

In order to adjust for factors that may confound the association between initial antidepressant drug use and the occurrence of change in antiparkinsonian drug treatment, the following covariates at baseline were studied as potential confounders: age, gender, time on levodopa, daily levodopa dosage used, concomitant use of dopamine agonists, selegeline, amantadine, anticholinergics and catechol-O-methyltransferase (COMT) inhibitors, and antidepressants dose (in DDD/day) during follow-up [5].

Data analysis

Univariate analysis with a Bonferroni correction was used to evaluate potential differences of baseline patient characteristics. Time on levodopa in file and daily levodopa dosage were analysed with a Kruskal-Wallis non-parametric test.

Incidence densities (ID) were calculated by dividing the number of patients with a change in antiparkinsonian drug treatment by the total exposure period, and were expressed as the number of patients reaching an endpoint per 1,000 exposed days. Cox proportional hazard analysis was used to estimate the hazard ratios for a change in antiparkinsonian drug treatment associated with antidepressant use, in which TCA and antidepressants with a low extent of inhibition of serotonin reuptake, respectively, were taken as reference for each classification. The final Cox proportional hazard analysis included all univariately associated (at $P \leq 0.1$) risk factors for a change in antiparkinsonian drug treatment.

All analyses were performed using SPSS 12.0 (SPSS, Chicago, IL).

Results

The PHARMO database for 1994–2004 contained records of 4,568 patients who had used a levodopa-containing drug, of which 1,439 patients had used an antidepressant at some point. We included 319 patients aged 40 years or more who had used levodopa at least 180 days before starting with an antidepressant; 53 patients who had started with an exclusion drug in the period from 180 days before until 180 days after the start of follow-up were excluded.

Table 1 Classification of antidepressants. *TCA* Tricyclic antidepressant, *SSRI* selective serotonin reuptake inhibitor

		Extent of serotonin reuptake inhibition			
		High	Intermediate	Low	Not classified
Class	TCA	Clomipramine	Imipramine Amitriptyline	Desipramine Doxepine Maprotiline Nortriptyline	
	SSRI	Paroxetine Fluoxetine Sertraline	Citalopram Fluvoxamine		
	Other		Venlafaxine	Bupropion Mirtazepine Nefazodon Trazodon	Moclobemide

Furthermore, 45 patients were excluded because they had only one antidepressant prescription. Finally, data from 221 patients were included for analysis. Eight patients using moclobemide were not included in data analysis where the classification was according to extent of serotonin reuptake inhibition.

Table 2 summarises the baseline characteristics of all study participants at the start of follow-up. The mean age was 74 years and female patients constituted 57% of the study population. Age did not differ between the sexes. The mean follow-up time was 120 days. Paroxetine and amitriptyline were the most frequently prescribed antidepressants (22% and 37%, respectively).

In the classification according to antidepressant class there were more selegeline users in the TCA group compared to the SSRI group (P=0.02). Selegeline was used significantly more in the period 1994 –1999 compared to the period 1999–2004 (P<0.0001). There was no significant difference in use of class of antidepressant in the period 1994–1999 compared to the period 1999–2004. The mean of the prescribed Defined Daily Dosage antidepressant was 0.39 (SD ± 0.21) in the TCA group, 0.87 (SD ± 0.25) in the SSRI group and 0.66 (SD ± 0.33) in the other antidepressants group (P<0.0001 between SSRI and TCA and between TCA and other antidepressants, and P=0.02 between SSRI and other antidepressants).

In the classification according to extent of inhibition of serotonin reuptake there were more dopamine agonist users among users of antidepressants with low versus high extent of inhibition of serotonin reuptake (P=0.04).

Fifty-eight patients (26%) had a change in antiparkinsonian drug treatment during follow-up. In eight patients (14%) this appeared to be a change in the levodopa formulation, in 17 (29%) the start of a different antiparkinsonian drug, in 30 patients (52%) an increase of dose of any antiparkinsonian drug, and in 3 patients (5%) a multiple change.

There was no difference in change in antiparkinsonian drug treatment among users of SSRIs compared to users of TCA, neither was there a significant difference in antiparkinsonian drug treatment among users of other antidepressants compared to users of TCA. The adjusted hazard ratio for a change in antiparkinsonian drug treatment was 0.7 (95% CI 0.3–1.5) comparing SSRI with TCA users, and it was 0.9 (95% CI 0.4–2.1) comparing users of other antidepressants with TCA users (Table 3). Stratification for age (≤ 70 versus > 70 years) did not alter the results significantly.

There was no difference in change in antiparkinsonian drug treatment among users of antidepressants with a high versus low extent of inhibition of serotonin reuptake. The adjusted hazard ratio for a change in antiparkinsonian drug treatment was 0.6 (95% CI 0.3–1.4) comparing users of antidepressants with a high versus low extent of inhibition of serotonin reuptake, and it was 0.7 (95% CI 0.3–1.4) comparing users of antidepressants with intermediate versus low extent of inhibition of serotonin reuptake.

Discussion

In this study, we evaluated the risk for a change in antiparkinsonian drug treatment attributed to SSRIs or serotonergic antidepressants in general. The results indicate that initiation of an SSRI was not associated with a change in antiparkinsonian drug treatment as compared to TCA or other antidepressants. Furthermore, initiation of antidepres-

Table 2 Patient characteristics at start of follow-up categorised according to drug class and according to the extent of serotonin reuptake inhibition

	Class				Extent of serotonin reuptake inhibition			
	TCA	SSRI	Other	P [a]	Low	Intermediate	High	P [a]
Number in study	99	90	32		31	118	64	
Male patients, *n* (%)	45 (45.5%)	37 (41.1%)	13 (40.6%)	NS	11 (35.5%)	52 (44.1%)	29 (45.3%)	NS
Mean age (years) ± SD	73 ± 10	75 ± 9	75 ± 8	NS	77 ± 7	72 ± 10	76 ± 9	NS
Time on levodopa in file (range in days)	190–2,964	182–2,671	187–2,012	NS	187–2,405	190–2,964	182–2,522	NS
Daily levodopa dosage (range in mg)	50–1,303	100–1,352	50–799	NS	50–799	50–1,303	100–1,352	NS
Concomitant use of, *n* (%)								
Dopamine agonist	28 (28.3%)	16 (17.8%)	10 (31.3%)	NS	11 (35.5%)	32 (27.1%)	8 (12.5%)	0.04 [c]
Selegeline	22 (22.2%)	7 (7.8%)	7 (21.9%)	0.02 [b]	7 (22.6%)	20 (16.9%)	6 (9.4%)	NS
Amantadine	7 (7.1%)	7 (7.8%)	3 (9.4%)	NS	2 (6.5%)	10 (8.5%)	4 (6.3%)	NS
Anticholinergic	7 (7.1%)	10 (11.1%)	2 (6.3%)	NS	1 (3.2%)	13 (11.0%)	4 (6.3%)	NS
COMT inhibitor	4 (4.0%)	2 (2.2%)	1 (3.1%)	NS	0 (0%)	5 (4.2%)	1 (1.6%)	NS

[a] ANOVA with bonferroni correction, time on levodopa in file and daily levodopa dosage: Kruskal-Wallis non–parametric test, *NS* not significant
[b] SSRI vs TCA
[c] High vs low

Table 3 Hazard ratios for a change in antiparkinsonian drug treatment associated with serotonergic antidepressant use. *ID* Incidence density (=number of patients with endpoint ×1,000/cumulative follow-up period), *IDR* incidence density ratio (=ID / ID reference group), *HR* hazard ratio, *CI* confidence interval

	Endpoint (*n*, %)	Cumulative follow-up period (days)	ID / 1,000 days	IDR	HR (95% CI)	HR [a] (95% CI)
Class (*n*=221)						
TCA (99)	25 (25.3%)	10,670	2.3	1.0[b]	1.0[b]	1.0[b]
SSRI (90)	24 (26.7%)	11,945	2.0	0.9	0.9 (0.5–1.5)	0.7 (0.3–1.5)
Other (32)	9 (28.1%)	3,949	2.3	1.0	1.0 (0.5–2.1)	0.9 (0.4–2.1)
Extent of serotonin reuptake inhibition (*n*=213)						
Low (31)	10 (32.3%)	3,331	3.0	1.0[b]	1.0[b]	1.0[b]
Intermediate (118)	30 (25.4%)	13,756	2.2	0.7	0.7 (0.4–1.5)	0.7 (0.3–1.4)
High (64)	17 (26.6%)	8,331	2.0	0.7	0.7 (0.3–1.5)	0.6 (0.3–1.4)

[a] Adjusted for concomitant selegeline use, levodopa dosage (in mg/day) and antidepressants dose (in DDD/day)
[b] Reference group

sants with a high inhibition of serotonin reuptake was not associated with a change in antiparkinsonian drug treatment in comparison with antidepressants with a low inhibition of serotonin reuptake.

Prior evidence for the association between SSRI use and the risk of worsening of PD stems mainly from small studies and case reports. In 1998, Gerber and Lynd found 127 published reports of SSRI-induced movement disorders [3]. Schillevoort and colleagues reported that spontaneous reporting of extrapyramidal symptoms (EPS) was twice as high with SSRI use as compared to other antidepressants [4].

Using the same database, Van de Vijver et al. found an almost five times higher risk for increase of antiparkinsonian drug treatment for patients beginning SSRI treatment versus those starting with a TCA [5]. However, our study overcomes some of the methodological difficulties of the latter study. A limitation of the study of Van de Vijver et al. is the sample size; the number of SSRI users in their study was small, although they could show a statistically significant difference in the increase of antiparkinsonian drug treatment for those starting SSRI treatment versus those beginning a TCA course. However, this study was likely to be underpowered to investigate potential confounding factors. The current study included 90 SSRI users, which enabled us to study, and correct for, potential confounding factors. We cannot rule out that the difference in findings between the two studies is due to chance. However, we feel that the reported point estimate is rendered more valid by a sixfold expansion of the study population. Furthermore, Van de Vijver et al. covered the study period 1985–1998 compared to the 1994–2004 period of the current study. Another explanation for the discrepant results could be that the characteristics of the PD patients were different. In our study 41% of the SSRI users was male whereas in the study of Van de Vijver men accounted for 20% of the study population. Moreover, the percentage of patients using anticholinergics was different (Van de Vijver 20%, our study 7%). In our opinion, there is no other clear explanation for the different findings of the two studies.

Gony et al., studying patients with PD using data from the French Pharmacovigilance database, did not find an increase in the risk for EPS between SSRIs and other antidepressants [6]. Nine cases with EPS were found among 199 patients using antiparkinsonian medication as well as antidepressants.

A few prospective studies have been published that study the motor effects of certain SSRIs. Chung et al. examined the motor effects of the SSRI paroxetine and placebo on responses to 2-h levodopa infusions in 14 subjects with PD. Paroxetine did not affect tapping scores or dyskinesia but did increase baseline walking speed [7]. Ceravolo et al. evaluated the effect of paroxetine on motor performance in 29 non-demented depressed patients with PD [13]. Add-on therapy with paroxetine did not significantly modify the Unified Parkinson's Disease Rating Scale (UPDRS) motor part score. Dell'Agnello et al. assessed the effects of citalopram, fluoxetine, fluvoxamine and sertraline on motor performance in 52 non-demented depressed patients with PD [14]. UPDRS scores were not significantly modified by the add-on therapy of each of the SSRIs studied. Hegerl and coworkers found that reboxetine, a noradrenaline reuptake inhibitor, had more favourable effects on fine motor function than citalopram [15].

Literature reports have hypothesised that serotonin has an inhibitory function on dopamine release, probably mediated through stimulation of the 5-HT_4-receptor [16]. Therefore, it was expected that antidepressants with a high extent of inhibition of serotonin reuptake would cause a more severe onset of worsening of PD as compared to those with a low extent of inhibition of serotonin reuptake. However, our results show no relation between initial use of antidepres-

sants with a high versus low extent of inhibition of serotonin reuptake and worsening of PD. Therefore, the extent of inhibition of serotonin reuptake does not seem to be a contributor to the motor side effects of antidepressants. Furthermore, it can be hypothesised that antidepressants could have a compensating effect on symptoms of PD by inhibition of dopamine reuptake or antagonistic effects on the muscarine receptors in the brain. However, adjustment for the antidepressants' extent of inhibition of dopaminergic reuptake and the antidepressants' muscarinergic receptor affinity as a covariate did not alter the hazard ratios (data not shown, K_d values from Richelson [17] and Tatsumi [12]).

A low affinity for the serotonin transporter does not necessarily reflect a low occupation of the serotonin transporter in the brain, because of differences in dosing between antidepressants. However, adjustment for the antidepressant's dose is difficult because there is a non-linear relation between dose used and occupation of serotonin transporter in the brain [18, 19].

There are several possible limitations to our study. First, the chosen outcome may be criticised. The endpoint was defined as the first change in antiparkinsonian drug treatment during the follow-up period, which was 180 days maximum. We feel that in this study a difference of change in antiparkinsonian drug treatment between the treatment groups can be used as a crude marker for worsening of symptoms of PD. However, worsening of symptoms of PD not leading to a change in antiparkinsonian drug treatment would not be identified by our method. Nevertheless, it is unlikely that the degree of misclassification is different between the groups. Furthermore, we have investigated whether concentrating on dose increase alone provides a different picture, but the results give no indication to allow for a different conclusion (data not shown).

Secondly, the use of antidepressants does not necessarily imply that these patients were depressed. Although depression is the main indication of antidepressants, these drugs are also prescribed, probably in lower doses, for other indications such as panic disorders, anxiety, pain and sleeping problems. Furthermore, TCAs may be prescribed for treating hypersialorrhea in patients with PD [20]. Indeed, TCAs were used in lower doses than SSRIs. Based on the hypothesis that initiation of SSRIs would lead to a higher change in antiparkinsonian drug treatment, this would lead to an overestimation of the effect of SSRIs.

Finally, our study included only patients with levodopa. We were not able to verify the diagnosis of those patients. However, Van de Vijver et al. have assessed levodopa as a reliable marker for PD [21]. Levodopa could also be used in the treatment of restless legs syndrome; however, in The Netherlands the first choice treatment for this indication is a dopamine agonist like ropinirole.

Patients with a single prescription of an antidepressant were excluded because the follow-up period was too short to measure a change in antiparkinsonian drug treatment. However, the proportion of patients with a single prescription of an antidepressant could be an indication for deterioration of symptoms of PD, but further analysis shows no significant differences between the groups (data not shown).

In conclusion, in this retrospective cohort study no relationship was found between initial use of SSRIs or serotonergic antidepressants and a change in antiparkinsonian drug treatment compared to the use of other antidepressants. Based on this observation, we found no evidence to be more cautious using SSRIs or serotonergic antidepressants compared to other antidepressants in patients with PD.

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