SHORT REPORT

Treatment with antidepressants and lithium is associated with increased risk of treatment with antiparkinson drugs: a pharmacoepidemiological study

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Objective: To estimate the risk for persons treated with antidepressants or lithium of subsequent treatment with antiparkinson drugs (APD).

Methods: The Danish national prescription database supplied data on all persons who received antidepressants, lithium, or antidiabetics (first control group). A second control group was included comprising persons from the general population. Outcome was purchase of APD and the study period was 1995 to 1999.

Results: In total, 1 293 789 persons were included. The rate ratio of treatment with APD after treatment with antidepressants was 2.27 (95% CI 2.14 to 2.42) for men and 1.50 (95% CI 1.43 to 1.58) for women. Figures for lithium were almost identical.

Conclusion: Persons treated with antidepressants or lithium are at increased risk of subsequently treatment with APD, showing an association between anxiety/affective disorder and Parkinson's disease.

Patients with Parkinson's disease (PD) have high prevalence of depressive symptoms and depressive disorder.^{1–2} More recently, a few studies have reported on the opposite association and found affective and anxiety disorders to be possible risk factors for PD.^{3–7}

In this study we compared the risk of getting treated with antiparkinson drugs (APD) for three different patient groups: patients treated with antidepressants, lithium, and antidiabetic drugs and for a large random sample of persons from the general population.

METHODS

The registers

We used a register linkage cohort study design and data from a national prescription database. Indications for treatment were not coded during the study period. Data were persons identifiable by means of the Danish Civil Registration System. The study period was from 1 January 1995 to 31 December 1999. The study was approved by the Danish Data Protection Agency.

The medicinal products were classified in accordance with the anatomical therapeutic chemical (ATC) classification system.⁸ All formulations of antidepressants, lithium, antidiabetics, and specified APDs available on the Danish market during the study period were included. Prescription from a medical doctor is necessary for purchase of all the included drugs.

APD are categorised in two ATC codes: N04A- and N04B-. ATC code N04A- contains the group of anticholinergic drugs, which have several indications beside PD. Because this may

represent a possible confounding factor, the N04A-group was excluded. Restrictions were also made for bromocriptine and cabergoline, as women 40 years or younger who purchased these drugs were excluded.

Amantadine was used for both PD and influenza A⁹ during the first years of the study but the indications could not be distinguished because the ATC code was identical. Since 1998 the use of amantadine has almost ceased.

No restrictions were made for inclusion of antidepressants (ATC-code N06A-), lithium (ATC-code N05AN01) or antidiabetic drugs (ATC-code A10A- (insulin), and A10B- (oral antidiabetics)).

A complete list of all included drugs by generic names is available from the authors.

The cohorts

The study population comprised four cohorts, three exposed and one unexposed. Event of interest (outcome) was purchase of APD. Because PD is extremely rare among young people, only persons 30 years or older were included. The three exposed groups included all Danish inhabitants who during the five year study period purchased antidepressants, lithium, or antidiabetics (index drugs). The unexposed group comprised a large random sample from the general population. Persons from the unexposed group would change to one of the exposed groups if they purchased any index drugs during the study period.

Statistical analyses

Poisson regression models were used to estimate risk ratios (RR). The unexposed group was followed up from study start until purchase of APD or censoring (that is, excluded from further participation in the study from this point of time). The exposed groups were followed up from inclusion date until purchase of APD (event) or censoring. Censoring occurred because of the following: date of change of treatment group, date of migration, date of death, or end of study. Censoring because of change of treatment group was done if a person from the antidepressant or lithium groups purchased antidiabetics or vice versa. Persons were allowed to change from the group of antidepressants to the group of lithium, thus consecutively contributing with time under risk (person years) in both groups.

Sex and age group (divided in 10 year intervals) were included in the model as covariates.

RESULTS

Table 1 presents characteristics of the included persons. A total of 1 293 789 persons were included, and among these 11 498 persons purchased APD. Average follow up time was

Abbreviations: APD, antiparkinson drugs; PD, Parkinson's disease; ATC, anatomical therapeutic classification; RR, rate ratio

Table 1 Number of exposed and unexposed persons, events, and of censorings

	Unexposed	Lithium	Antidepressants	Antidiabetics	Total
Number at end of study	790817	12071	376780	114121	1293789
Antiparkinson drugs (outcome)	6676	154	3954	714	11498
Censoring:					
Death	59178	1246	56553	19378	136355
Emigration	9505	51	1875	539	11970
End of study	715105	10295	306780	78402	1110582
Change of treatment	353	325	7618	15088	23384

4.5 years. Persons who purchased antidepressants had a RR of 1.79 (95% CI: 1.72 to 1.86) for subsequent purchase of APD compared with the unexposed group. For lithium, the corresponding RR was 1.88 (95% CI: 1.60 to 2.20) and for antidiabetics 0.80 (95% CI: 0.74 to 0.86).

Table 2 shows that both men and women had significantly increased risk of getting APD after antidepressants or lithium but the RRs were lower for women. The RRs were highest during the first six months after prescription of antidepressants or lithium but still was significantly increased after one year.

DISCUSSION

Overall, we found an increased risk of subsequently getting APD for persons who received antidepressants or lithium. The risk was increased for all age groups and for both sexes, most pronounced for men and highest during the first six months after purchase of antidepressants or lithium. No significant differences were found between antidepressants and lithium.

The study population comprised more than one million persons, contributing with almost four million person years of follow up. The size of the sample is reflected in the narrow confidence intervals for risk estimates. The study took advantage of the comprehensive population based registries in Denmark, which contain uniform, person identifiable, continuously updated information on purchase of all prescription drugs, emigration, and vital status of the residents.

Methodological aspects

The Danish prescription database does not hold individual information on the indication for prescription. Our data therefore have to be interpreted as indirect evidence. The included drug classes all have well defined indications, for which they primarily, but not exclusively, are prescribed. An important question is to which degree drug consumption corresponds to specific disorders. Antidepressants are mainly prescribed for depressive and anxiety disorders,¹⁰ but also for obsessive-compulsive disorder, social phobia, eating disorders, neuropathic pain conditions, etc. Lithium is only used in affective disorders and antidiabetic drugs only for diabetes mellitus. Most APDs are prescribed for treatment of PD but a minor part may be prescribed for a few other conditions, like Lewy body dementia, multiple system atrophy, and restless

legs syndrome.¹¹ The whole group of anticholinergics (N04A-) were excluded because their primary use presumably is other conditions than PD. We have no indications that these factors can explain our results, as there is no evidence showing that patients with anxiety/affective disorders more often develop Lewy body dementia, multiple system atrophy, or restless legs syndrome than do patients with diabetes or persons from the general population.

Choice of control groups

Two control groups were included. One comprising persons from the general population who had not purchased any index drugs and a second of persons who had purchased antidiabetics, which allowed for an estimate of the possible effect of Berkson's bias¹² (an increased risk for persons diagnosed with one disorder of receiving additional diagnoses). However, we did not find indications of Berkson's bias, as persons who were diagnosed with diabetes did not have increased risk of getting diagnosed with a second disorder (such as, PD) compared with the unexposed control group. Diabetes has been shown to cause both diffuse and focal changes in the brain, especially if inadequately regulated,¹³ but to the best of our knowledge, diabetes has not been associated with the development of PD.

Possible biases

A number of potential biases have been avoided because of the study design and access to the comprehensive Danish registries, but it should be noticed that only patients who received prescriptions were included.

The risk of selection bias and information bias, particularly recall bias, is minimised. Data are routinely collected by electronic registration of all prescriptions and sales of medicinal products. The registries are nationwide and inclusive of the entire Danish population. The rate of emigration from Denmark is low (table 1). None of the included drugs can be obtained without a prescription from a medical doctor. The treatment setting therefore is of no significance in data collecting. Medical treatment is tax financed with easy access and with a 75% reimbursement from the state on all prescriptions. Thus, the risk of bias attributable to socioeconomic factors can be regarded low.

Table 2 Sex specific rate ratios of purchasing antiparkinson drugs and temporal associations

	Unexposed	Antidepressants RR (95% CI)	Lithium RR (95% CI)	Antidiabetics RR (95% CI)
Women	1.00	1.50 (1.43 to 1.58)	1.64 (1.34 to 2.02)	0.67 (0.60 to 0.76)
Men	1.00	2.27 (2.14 to 2.42)	2.22 (1.73 to 2.86)	0.93 (0.84 to 1.03)
Women v men	0.91 (0.87 to 0.96)	0.60 (0.57 to 0.64)	0.68 (0.49 to 0.93)	0.66 (0.57 to 0.77)
Temporal associations:				
0-0.5 years		3.23 (3.03 to 3.43)	3.76 (2.33 to 6.04)	
0.5-1.0 years		2.42 (2.25 to 2.60)	1.94 (0.97 to 3.88)	
1+ years		1.29 (1.23 to 1.36)	1.82 (1.30 to 2.54)	

Possible effects of antidepressants or lithium on the risk of developing PD

The basic pathophysiological feature of PD is reduced availability of dopamine in substantia nigra but the aetiology of PD remains elusive. Neuroprotective as well as neurotoxic drug effects should be considered. Available data show that both antidepressants and lithium have neuroprotective effects^{14–17} with the strongest evidence for lithium while no evidence points to neurotoxic effects.

Common pathogenesis of affective disorders and PD?

According to the "serotonin hypothesis",^{7, 18} mood disorders can be seen as prodromal symptoms in PD, because of a decreased serotonin activity that may express a cerebral adaptation to the decrease of striatal dopaminergic activity before onset of the core parkinsonian symptoms. Speculatively, treatment with antidepressants or lithium might precipitate PD by interfering with a delicate cerebral neurotransmitter homeostasis. Alternatively, the presence of anxiety or affective disorders may be a risk factor for later development of PD.

We found the strongest association between antidepressants or lithium and APD during the first six months after purchase of antidepressants or lithium. This might partly be explained as detection bias and partly as affective/anxiety symptoms as prodromals to PD. However, a significant association persisted also in the long run, which may reflect that anxiety/affective disorders and PD are separate disease entities with a common, but presently unclear biological pathogenesis or a mutual genetic susceptibility.

In conclusion, patients treated with antidepressants or lithium are at increased risk of subsequent treatment with APD, suggesting that patients with anxiety or affective disorders are at increased risk of developing PD.

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