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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

The association between use of cardiovascular drugs and antidepressants: a nationwide register-based study

Kristina Johnell · Johan Fastbom

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Abstract
Purpose To investigate whether cardiovascular drug classes and specific beta-blockers are associated with antidepressant drug use in a large study population of older people.
Methods We analyzed data from the Swedish Prescribed Drug Register from October-December 2005 for people aged 75 years and older (n=732,230). Logistic regression analysis was used to study the association between the cardiovascular drugs and antidepressants, after adjustment for age, sex, and number of other dispensed drugs.
Results All the cardiovascular drug classes were negatively or not associated with use of any antidepressant, non-selective monoamine reuptake inhibitors, and SSRIs, after adjustment for age, sex, and number of other dispensed drugs. However, propranolol was associated with an increased use of any antidepressant, non-selective monoamine reuptake inhibitors, and SSRIs, after adjustment for age, sex, and number of other dispensed drugs. Atenolol was positively associated with non-selective monoamine reuptake inhibitors, although to a lesser extent than propranolol.
Conclusions None of the cardiovascular drug classes were associated with increased antidepressant drug use, after adjustment for age, sex, and use of other drugs. However, when focusing specifically on beta-blockers, our results indicate that propranolol may be the beta-blocker most closely associated with use of antidepressants in the elderly.

Keywords Antidepressants · Cardiovascular drugs · Elderly · Pharmacoepidemiology · Register-based research

K. Johnell (✉) · J. Fastbom
Aging Research Center, Karolinska Institutet,
Gävlegatan 16,
113 30 Stockholm, Sweden
e-mail: Kristina.Johnell@ki.se

Introduction

Many cardiovascular drugs have been postulated to have depressive symptoms as side effects. However, with the exception of beta-blockers, few of these drugs have been epidemiologically studied in relation to depression outside the controlled environment of the clinical trial [1, 2]. Nevertheless, digitalis, diuretics, calcium-channel blockers, angiotensin converting enzyme (ACE) inhibitors, and lipid-lowering agents have been associated with depression [2–7], although this has been disputed by others [3, 4, 7–9]. Regarding studies on beta-blockers and depression, the results are inconsistent [3, 4, 10–13], and this matter is still open for debate. In particular, the lipophilic beta-blocker propanolol has been suggested to be linked to depression [4, 11, 12, 14]. However, many of the studies on cardiovascular drugs and depressive symptoms were conducted quite a few years ago, used small study samples, did not adjust for any measure of comorbidity, and focused on beta-blockers. Therefore, we wanted to provide an updated analysis on the association between different cardiovascular drugs and antidepressants in a nationwide study population.

Depression and depressive symptoms are common disorders among older people and decrease their quality of life, impair functional abilities, and increase use of health care. Drug-induced depression might be a potentially preventable cause of depressive symptoms in the elderly [3], and cardiovascular drugs are among the most frequently used drugs among older people [15, 16]. Thus, if cardiovascular drugs cause depression in the elderly, a great deal of suffering and costs related to depression could be saved by alternative solutions. On the other hand, older people should not be denied valuable cardiovascular drug therapy due to unjustified reluctance to prescribe these drugs due to fear of depressive side effects.

The aims of this study were to investigate whether (1) cardiovascular drug classes (i.e., digitalis, thiazide diuretics, loop diuretics, potassium-sparing diuretics, beta-blockers, calcium-channel blockers, ACE inhibitors, angiotensin II antagonists, and lipid-lowering agents) and (2) specific beta-blockers (according to lipophilicity) are associated with antidepressant drug use [i.e., any antidepressant, non-selective monoamine reuptake inhibitors, and selective serotonin reuptake inhibitors (SSRIs)] in a large study population of older people.

Methods

Study population

The Swedish Prescribed Drug Register (SPDR) contains data with unique personal identification numbers of all dispensed prescriptions to the whole population of Sweden (about 9 million inhabitants). The data collection is administered by the state-owned National Corporation of Swedish Pharmacies and then transferred to the Centre for Epidemiology at the National Board of Health and Welfare, responsible for keeping the register [17]. The SPDR is intended for epidemiological studies, research, and statistics within the health-care area.

We analyzed nonidentifiable data from individuals aged 75 years and older who were registered in the SPDR during October-December 2005, with information about every individual's age, sex, and dispensed drugs [Anatomical Therapeutic Chemical (ATC)-code [18], amount of prescribed drug, when the prescription was filled, and prescribed dosage (i.e., from the prescriptions written by the prescribers)]. The study population consisted of 732,230 older people.

First, information from the 3-month period about when the prescription was filled, amount of drug, and prescribed dosage was processed to calculate the duration of drug exposure [19]. When prescribed dosage was incomplete or missing, we used defined daily doses (DDDs) [18] for calculation of the duration of drug exposure. We assumed 0.9 DDDs for regularly used drugs (based on calculations for regularly used drugs among the elderly in the database) and 0.45 DDDs (50% of 0.9) for drugs prescribed as needed, as indicated on the prescription. We assumed 1 DDD for drugs for external use and for the eye. Second, a list of current prescriptions was constructed based on the calculations of the duration of drug exposures for every individual on the arbitrarily chosen date of December 31, 2005. If a person was dispensed the same drug in different doses during the study period, it was counted as one dispensed drug [20].

This study was approved by the ethical board in Stockholm (Dnr 2006/948–31).

Definitions

Use of any antidepressant was defined by the ATC-code N06A and subdivided into non-selective monoamine reuptake inhibitors (N06AA) and SSRIs (N06AB) because these two types of antidepressants may be used differently [21–24].

The cardiovascular drugs classes were digitalis (C01AA), thiazide diuretics (C03A), loop diuretics (C03C), potassium-sparing diuretics (C03D), beta-blockers (C07A), calcium-channel blockers (C08), ACE inhibitors (C09A), angiotensin II antagonists (C09C), and lipid-lowering agents (C10A). The beta-blockers were classified according to their lipophilicity [25] into high [propranolol (C07AA05) and carvedilol (C07AG02)], moderate [pindolol (C07AA03), metoprolol (C07AB02), and labetalol (C07AG01)], and low lipophilicity [sotalol (C07AA07), atenolol (C07AB03), and bisoprolol (C07AB07)].

Age was used as a continuous variable.

Number of other dispensed drugs (a proxy for comorbidity [26–28]) was also a continuous variable and consisted of the number of dispensed drugs used by the person other than the specific cardiovascular drug and antidepressant under study.

Statistical analysis

Multivariate logistic regression analysis was used to study the association between the cardiovascular drugs and antidepressants. In model i, we adjusted for age and sex, and in model ii, we also included number of other dispensed drugs.

The results are shown as odds ratios (ORs) with 95% confidence intervals (CIs). SPSS 14.0 for Windows (SPSS, 1989–2005) was used for the analyses.

Results

Mean age among the 732,230 elderly was 82.1 years. They received on average 5.4 dispensed drugs per person, and 61.6% were women (Table 1).

At least one antidepressant was used by 15.2% of the study population, including non-selective monoamine reuptake inhibitors by 1.6% and SSRIs by 11.3%. Cardiovascular drugs were used by 66.4%. Among the cardiovascular-drug users, 15.6, 1.6, and 11.7% used any antidepressant, non-selective monoamine reuptake inhibitors, and SSRIs, respectively. The most frequently used cardiovascular drug

Table 1 Descriptive data of the 732,230 older people from the Swedish Prescribed Drug Register, 2005

Parameter	Number (%)
Mean age (years ± SD)	82.1±5.3
Sex	
Men	281,239 (38.4)
Women	450,991 (61.6)
Mean ± SD number of dispensed drugs	5.4±3.9
≥1 antidepressant	111,299 (15.2)
Non-selective monoamine reuptake inhibitors	11,590 (1.6)
Selective serotonin reuptake inhibitors (SSRIs)	82,957 (11.3)
≥1 of the cardiovascular drugs	485,902 (66.4)
Digitalis	51,717 (7.1)
Thiazide diuretics	52,422 (7.2)
Loop diuretics	182,550 (24.9)
Potassium-sparing diuretics	53,614 (7.3)
Beta-blockers	256,679 (35.1)
Lipophilicity	
High	
Propranolol	7,731 (1.1)
Carvedilol	4,492 (0.6)
Moderate	
Pindolol	3,363 (0.5)
Metoprolol	127,733 (17.4)
Labetalol	260 (0)
Low	
Sotalol	13,250 (1.8)
Atenolol	82,021 (11.2)
Bisoprolol	20,312 (2.8)
Calcium-channel blockers	123,393 (16.9)
ACE inhibitors	105,407 (14.4)
Angiotensin II antagonists	50,098 (6.8)
Lipid-lowering agents	122,229 (16.7)

class was beta-blockers (35.1%), followed by loop diuretics (24.9%), calcium-channel blockers (16.9%), lipid-lowering agents (16.7%), and ACE inhibitors (14.4%) (Table 1).

Digitalis, loop diuretics, and potassium-sparing diuretics were positively associated with any antidepressant, non-selective monoamine reuptake inhibitors, or SSRIs, after adjustment for age and sex (Table 2). However, after additional adjustment for number of other drugs (i.e., a proxy for comorbidity), all the cardiovascular drug classes were negatively or not associated with antidepressants. Regarding the different beta-blockers, propranolol was associated with any antidepressant, non-selective monoamine reuptake inhibitors, and SSRIs, including after additional adjustment for number of other drugs. Sotalol, atenolol, and bisoprolol were weakly associated with antidepressants, non-selective monoamine reuptake inhibitors, or SSRIs, after adjustment for age and sex. However, after additional adjustment for number of other drugs, the only remaining association was between atenolol and non-selective monoamine reuptake inhibitors.

In addition, we studied interactions in the different analyses. However, due to the large study sample and, hence, great statistical power in the analyses, many interactions were statistically significant, although not necessarily clinically significant. Noteworthy, there was an interaction between loop diuretics and number of other drugs [any antidepressant: $OR_{\text{loop diuretics}\times\text{number of other dispensed drugs}} = 0.95$ (95% CI 0.95–0.96)], with the interpretation that those who used fewer other drugs had a positive association between loop diuretics and antidepressants and those who used several other drugs had a negative association between loop diuretics and antidepressants.

Discussion

Main findings

In our large study population of older people, none of the cardiovascular drug classes were associated with an increased use of antidepressants, after adjustment for age, sex, and use of other drugs (i.e., a proxy for comorbidity). Thereby, our results support the previous reports claiming that there is no evidence that digitalis, diuretics, calcium-channel blockers, ACE inhibitors, and lipid-lowering agents cause depressive symptoms [1, 3, 4, 7–9]. However, there is also research supporting depressive effects of these cardiovascular drugs [2–7]. In general, the studies in this field are quite old, have used small study samples, have not controlled for any measure of comorbidity, or have relied on case reports.

The relationship between beta-blockers, in particular propranolol, and depression has been more extensively studied [3, 4, 10–12]. There is both evidence for [4, 12, 14] and against [2, 13] an association between propranolol and depressive symptoms. In other words, the issue of propranolol has not yet been resolved, and more large-scale studies comparing different beta-blockers are needed [11]. We observed that propranolol, but not beta-blockers in general [2, 4, 6, 10, 11, 28], was associated with use of any antidepressant, non-selective monoamine reuptake inhibitors, and SSRIs, after adjustment for age, sex, and use of other drugs. Moreover, atenolol was associated, although more weakly than propranolol, with non-selective monoamine reuptake inhibitors, after adjustment for age, sex, and use of other drugs. One suggested explanation for the relationship between beta-blockers and depression has been that these drugs alter noradrenergic activity in the brain. In that case, propranolol would be the beta-blocker most likely to cause depression because propranolol is the most lipophilic beta-blocker and, therefore, most likely to cross

Table 2 Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for dispensed antidepressants in the elderly study population (n=732,230)

	Any antidepressant		Non-selective monoamine reuptake inhibitors		Selective serotonin reuptake inhibitors	
	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]
Digitalis	1.17 (1.15–1.20)	0.90 (0.88–0.92)	1.01 (0.94–1.09)	0.82 (0.76–0.88)	1.20 (1.17–1.24)	0.95 (0.92–0.97)
Thiazide diuretics	0.77 (0.75–0.79)	0.84 (0.82–0.87)	0.90 (0.83–0.96)	0.98 (0.91–1.05)	0.78 (0.75–0.80)	0.85 (0.83–0.88)
Loop diuretics	1.54 (1.52–1.56)	0.95 (0.94–0.97)	1.42 (1.37–1.48)	0.96 (0.92–1.00)	1.56 (1.53–1.58)	1.01 (0.99–1.02)
Potassium-sparing diuretics	1.25 (1.22–1.28)	0.88 (0.86–0.90)	1.24 (1.17–1.32)	0.94 (0.88–1.00)	1.26 (1.23–1.30)	0.92 (0.89–0.94)
Beta-blockers	0.87 (0.86–0.88)	0.69 (0.68–0.70)	1.00 (0.96–1.04)	0.86 (0.83–0.90)	0.87 (0.86–0.89)	0.72 (0.71–0.73)
Lipophilicity						
High						
Propranolol	1.13 (1.06–1.20)	1.21 (1.14–1.29)	1.61 (1.40–1.85)	1.68 (1.46–1.94)	1.04 (0.97–1.11)	1.09 (1.02–1.18)
Carvedilol	0.97 (0.89–1.06)	0.75 (0.68–0.82)	1.11 (0.88–1.41)	0.92 (0.73–1.17)	0.98 (0.89–1.08)	0.77 (0.70–0.86)
Moderate						
Pindolol	0.60 (0.53–0.67)	0.67 (0.59–0.75)	0.76 (0.56–1.04)	0.85 (0.62–1.16)	0.58 (0.51–0.67)	0.65 (0.57–0.75)
Metoprolol	0.86 (0.84–0.87)	0.73 (0.71–0.74)	0.88 (0.83–0.92)	0.79 (0.75–0.83)	0.88 (0.86–0.89)	0.76 (0.74–0.77)
Labetalol	1.09 (0.78–1.54)	0.96 (0.68–1.37)	0.99 (0.37–2.67)	0.90 (0.33–2.43)	1.14 (0.78–1.67)	1.02 (0.69–1.51)
Low						
Sotalol	1.05 (1.00–1.11)	0.99 (0.94–1.04)	1.03 (0.90–1.19)	0.99 (0.86–1.13)	1.08 (1.02–1.14)	1.02 (0.97–1.08)
Atenolol	0.89 (0.87–0.91)	0.90 (0.88–0.92)	1.09 (1.03–1.15)	1.11 (1.05–1.18)	0.88 (0.86–0.91)	0.90 (0.88–0.92)
Bisoprolol	1.05 (1.01–1.09)	0.73 (0.70–0.76)	1.07 (0.96–1.20)	0.81 (0.72–0.90)	1.04 (0.99–1.09)	0.74 (0.71–0.78)
Calcium-channel blockers	0.87 (0.86–0.89)	0.75 (0.74–0.76)	0.95 (0.90–1.00)	0.86 (0.81–0.90)	0.89 (0.87–0.91)	0.78 (0.76–0.80)
ACE inhibitors	0.97 (0.95–0.99)	0.75 (0.73–0.76)	0.99 (0.94–1.04)	0.82 (0.77–0.86)	1.01 (0.99–1.03)	0.80 (0.78–0.82)
Angiotensin II antagonists	0.95 (0.93–0.98)	0.78 (0.76–0.80)	0.91 (0.85–0.98)	0.79 (0.73–0.85)	0.98 (0.95–1.01)	0.82 (0.80–0.85)
Lipid-lowering agents	0.90 (0.89–0.92)	0.67 (0.66–0.68)	0.96 (0.91–1.01)	0.78 (0.74–0.82)	0.94 (0.93–0.97)	0.73 (0.71–0.75)

[a] Model i: adjusted for age and sex
[b] Model ii: adjusted for age, sex, and number of other dispensed drugs

the blood-brain barrier [12]. However, this lipophilic hypothesis was not entirely supported by our data, as the hydrophilic beta-blocker atenolol was associated with non-selective monoamine reuptake inhibitors, although to a lesser extent than propranolol. An alternative explanation for our finding may be that propranolol is used among the elderly to a higher extent for other indications possibly related to depression, e.g., tremor and migraine, than the other beta-blockers.

Limitations

The cross-sectional design of our study does not allow us to draw conclusions regarding causality. Also, confounding by indication is difficult or even impossible to avoid in pharmacoepidemiological studies [2]. Unmeasured confounding may provide an alternative explanation for our findings. However, we did control for a proxy for comorbidity (i.e., number of other dispensed drugs) [26–28], regarded as one of the most important confounders, particularly in studies of older people with multiple medical conditions [11]. Further, older people may be prescribed antidepressants, especially non-selective monoamine reuptake inhibitors, for other reasons than depression, e.g., sleep disturbances and chronic pain [21], which may result in misclassification. Therefore, we subdivided the antidepressants into non-selective monoamine reuptake inhibitors and SSRIs.

We have used data on elderly registered in the SPDR during October-December 2005, corresponding to 92% of the population 75 years and older in Sweden [29]. The SPDR does not include data on over-the-counter drugs, herbal drugs, and drugs used in hospitals. Also, the register is incomplete with regard to drugs used in nursing homes, which may lead to an underestimation of the drug use. Moreover, our method is built on an assumption that all current drugs were dispensed during the observed 3-month period, which is based on the fact that drugs are prescribed for use for at most 90 days in Sweden. In this way, we might miss drugs that were dispensed before the 3-month period and used at a slower rate than intended. At the same time, we might include drugs that were dispensed during the 3-month period but discontinued prematurely. In addition, our method is built on interpretations of the entries describing the dispensed drugs' dosages, as well as assumptions about DDDs when the information about dosage was incomplete or missing [19, 30]. Finally, a

general limitation of studies on drug registers is that dispensed drugs may not reflect what is actually used by the patients [31], as the adherence rate may be low [32].

Implications

Until a relationship between different beta-blockers and depression has been established, caution might be exercised when prescribing propranolol to elderly patients with susceptibility to depression.

Previous studies have been severely limited by insufficient number of participants, and larger study samples are necessary to study specific drugs [3]. Large observational studies, such as this one, may complement clinical trials with data from real-world patients who would be excluded from clinical trials due to advanced ages, comorbidities, and multiple drug use [1, 33, 34].

Conclusion

None of the cardiovascular drug classes were associated with increased antidepressant drug use, after adjustment for age, sex, and use of other drugs. However, when focusing specifically on beta-blockers, our results indicate that propranolol may be the beta-blocker most closely associated with use of antidepressants in the elderly, although high lipophilicity may not be the explanation. Future research at large scales is warranted for elucidating the relationship between different beta-blockers and depression.

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