

Evidence of Depression Provoked by Cardiovascular Medication: A Prescription Sequence Symmetry Analysis

Jesper Hallas

Many cardiovascular drugs have been implicated as causes of depression. With the exception of beta-blockers, few have been studied in formal epidemiologic designs. I present a new approach to such analyses that effectively controls for confounders that are stable over time. I analyzed the exposure histories of 11,244 incident antidepressant users, using the Odense University PharmacoEpidemiologic Database. All persons starting both beta-blockers and antidepressants during a predefined period were identified. If beta-blockers do not cause depression, this particular population should show equal numbers of persons starting either drug first. A depression-provoking effect of beta-blockers would generate an excess of persons

starting beta-blockers first, that is, a nonsymmetrical distribution of prescription orders. Confounders causing the two drugs to be co-prescribed would rarely be expected to affect the symmetry. The initial screening showed nonsymmetrical prescription orders for a wide range of cardiovascular drugs. After adjustment for an increasing incidence of antidepressant prescribing, I found a depression-provoking effect only for angiotensin-converting enzyme (ACE) inhibitors (rate ratio = 1.29; 95% confidence interval = 1.08–1.56) and calcium channel blockers (rate ratio = 1.31; 95% confidence interval = 1.14–1.51). This prescription sequence symmetry analysis may be useful as a screening tool. (*Epidemiology* 1996;7:478–484)

Keywords: depression, antidepressants, ACE inhibitors, calcium channel blockers, diltiazem, beta-blockers, propranolol, adverse drug reaction, salicylates, study design.

The beta-adrenergic receptor antagonists (beta-blockers) are the mainstay of therapy for a variety of cardiovascular disorders.¹ In 1967, Waal² reported a remarkably high prevalence of depression among users of propranolol, up to 50% among those using 120 mg or more per day. Although propranolol and other beta-blockers undoubtedly have important effects on cerebral functions,³ the suspicion concerning a depressogenic effect has received little support from a number of small-scale controlled studies published since then.^{4–14} Only three major epidemiologic studies have addressed the issue, with highly conflicting results.^{15–17} At present, the controversy is still unresolved.¹⁸

Nearly all other cardiovascular drugs have been implicated as causing depression, mainly substantiated by case reports and spontaneous reports (for example, those collected in the World Health Organization database in Sweden). With the exception of studies on beta-block-

ers, controlled epidemiologic studies on depression provoked by cardiovascular medication are virtually nonexistent.

The present study is an attempt to find evidence of drug-related depression by use of individualized prescription data using a formal epidemiologic design. A recurrent problem in such studies is the inherent tendency of drug therapies to aggregate in certain individuals: the elderly, nursing home residents, patients with overzealous prescribers, hypochondriacs, etc. These confounders may cause a myriad of noncausal associations. This paper presents an approach that effectively adjusts such confounding caused by simple clustering of drug therapies. Owing to its simplicity in processing and robustness toward confounding, it may be useful as a screening tool for unknown adverse drug reactions.

Subjects and Methods

SETTING

The Odense University PharmacoEpidemiologic Database (OPED) has previously been described in detail.¹⁹ In brief, the database has captured all computerized prescription refund claims from the County of Funen in Denmark since 1990. The prescription coverage has been at least 90% since October 1990 and became complete by November 1992; it now totals a population of some 470,000 persons. Each record has data on the identity of the prescription holder, the date of redemp-

From the Department of Clinical Pharmacology, Institute of Medical Biology, Odense University, Odense, Denmark.

Address correspondence to: Jesper Hallas, Department S, Odense University Hospital, 5000 Odense C, Denmark.

This work was supported by Sygesikringens Helsefond, Grant 11/211-93.

Submitted October 10, 1995; final version accepted May 24, 1996.

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tion, a full account of the dispensed product, the pharmacy, and the prescriber. Confidentiality is protected by a scrambling of personal identifiers.

DESIGN

The data comprise all 896,811 recorded prescriptions presented by all 17,636 antidepressant users recorded in OPED during the period October 1990 through December 1993. Of these 17,636 antidepressant users, 11,244 redeemed their first prescription after March 1991 and were considered incident users in the following analyses.

For the analysis of the beta-blocker-antidepressant association, I identified all persons who redeemed their first antidepressant and beta-blocker prescriptions after March 1991. In other words, they were required to have at least a 6-month run-in period in which neither of the drugs was prescribed. The purpose of this restriction was to include only persons who were incident users of both drugs. I determined the order of therapies for each user. With a noncausal relation between antidepressant and beta-blocker therapy, we would expect that the number of persons who started beta-blocker therapy first in this group would equal the number starting antidepressant therapy first. Factors such as high age, female gender, nursing home residency, frequent physician contact, hypochondriacy, or overzealous prescribers would all entail a noncausal clustering of drug therapies and would be important confounders in a conventional epidemiologic study. These factors, however, do not predict the prescription order, given that the patient became a user of both drugs. On the other hand, if beta-blockers do cause depression, we should expect an excess of persons starting antidepressants second, that is, an asymmetrical distribution of prescription orders. I designated the degree of asymmetry by the crude sequence ratio, r_c , which was the ratio of the number of persons with antidepressants prescribed second and the number with antidepressants prescribed first.

I applied the same principle to the other main groups of cardiovascular drugs. The grouping of the drugs was as follows: digoxin and analogues, class 1 and 3 antiarrhythmic drugs, short- and long-acting nitrates, methyl-dopa, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, thiazides, loop diuretics, potassium-sparing diuretics, propranolol, and beta-blockers in general. If any of the groups suggested a signal, I extended the analysis to include the most used drugs within the group.

For the main positive findings, I fitted a logistic regression model for factors that were predictive of one sequence (for example, beta-blockers → antidepressants), rather than the contrary. The analysis included factors that could elucidate the plausibility of a causal relation, for example, dose-response effects, confounders, mutual indications, etc. Dosages were expressed by the defined daily dose (DDD) unit, developed by the World Health Organization Drug Utilization Research Group.²⁰

INCIDENCE ADJUSTMENT

In a further attempt to validate the findings, I categorized all users of cardiovascular drugs or antidepressants recorded in the entire OPED database by their first prescription on the drug. I termed this analysis a "waiting-time" distribution. It implicitly poses the question of how long you would have to wait before a patient fills his first prescription for a given drug. As expected, the resulting curves showed a steeply descending limb, reaching a more or less stable plateau after a few months (Fig 1). I assumed that patients presenting their first prescriptions during the stable, terminal phase of the curves were incident users. The curves thus allowed an evaluation of the stability of drug use incidences and whether the drug-free run-in period was long enough.

If a drug is prescribed with increasing incidence, we should expect a nonspecific excess of persons with that drug prescribed second. Unfortunately, the waiting-time curves showed a clearly increasing incidence of antidepressant prescribing (Fig. 1). This trend had been noted in a pilot study, and a model was developed to adjust for it. A detailed description of the model is given in the Appendix. The null-effect sequence ratio, r_n , produced by the proposed model may be interpreted as a reference value for the crude sequence ratio. Thus, r_n is the expected sequence ratio in the absence of any causal association, taking the incidence trends into account. An r_n value above unity reflects an increasing incidence of antidepressant prescribing relative to the incidence of cardiovascular drug prescribing. The estimated r_n values are shown in Table 1.

On a theoretical basis, the ratio r_c/r_n can be shown to be identical to the incidence rate ratio of antidepressant prescribing in cardiovascular drug-exposed vs nonexposed person-time. The variance of the r_n is negligible compared with the variance of the r_c , as it was invariably based on a more than 20-fold larger data material. Consequently, the confidence interval of the r_c/r_n ratio is determined almost entirely by the confidence interval of the r_c . The latter can be calculated by using the binomial distribution and the crude number of sequences.²¹

Results

SEQUENCES INVOLVING BETA-BLOCKERS AND ANTIDEPRESSANTS

In all, 806 persons redeemed their first prescriptions on beta-blockers and antidepressants during the period April 1991 through December 1993, that is, after a 6-month run-in period in which neither of the drugs was prescribed. Of these, I excluded 44 who filled their first prescriptions for antidepressants and beta-blockers on the same date. Of the remaining 762 persons, 420 started beta-blockers first, and 342 started antidepressants first ($r_c = 1.23$).

The waiting-time curves showed a clearly increasing incidence of antidepressant prescribing (Figure 1). As explained previously, this trend should result in a nonspecific tendency for antidepressants to be prescribed

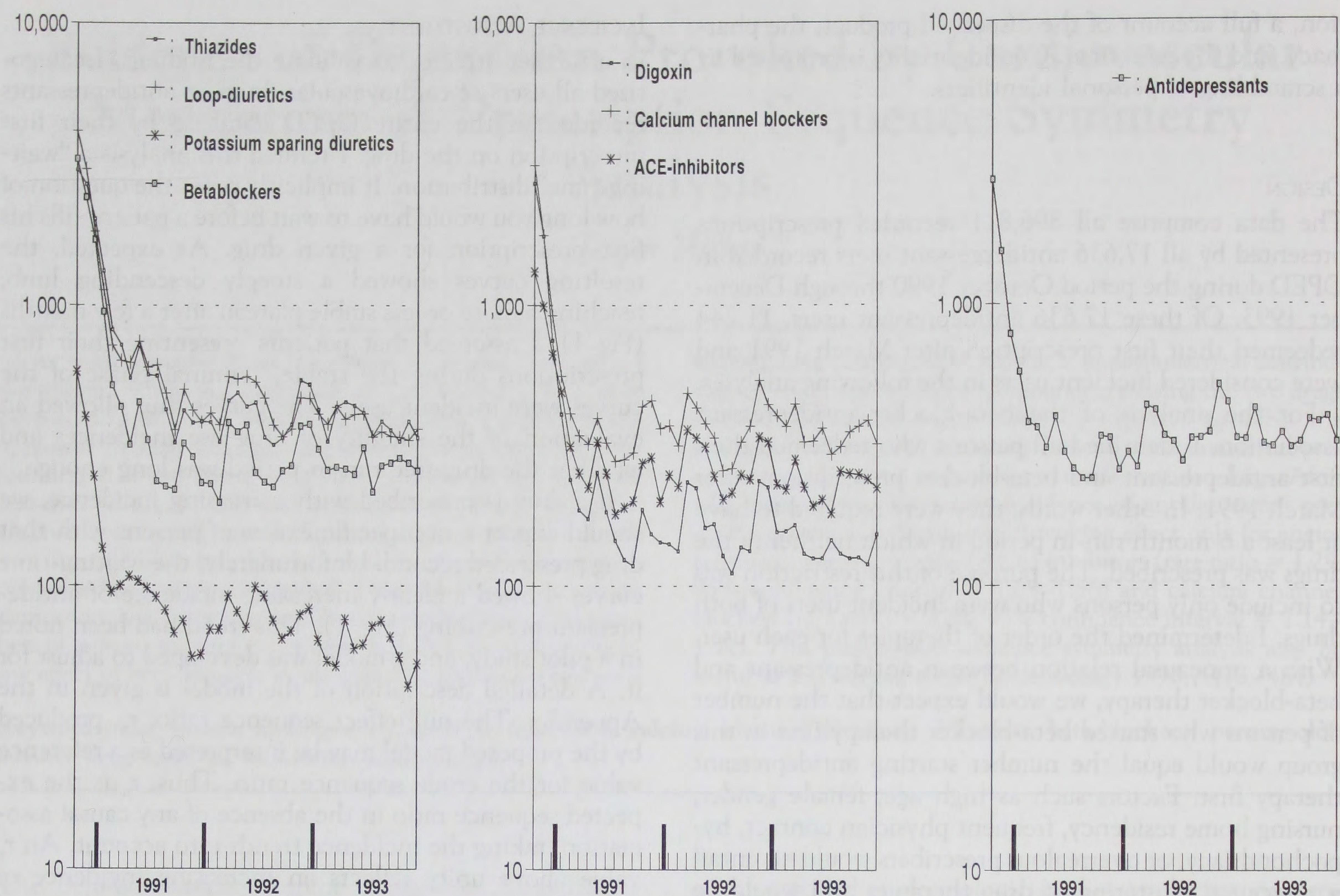


FIGURE 1. Waiting-time distributions for users of antidepressants and various cardiovascular drugs. For each consecutive month during the period October 1990 through December 1993, the graph depicts the number of persons who presented their first recorded prescription during that month. The data indicate a clearly increasing incidence of antidepressant prescribing. Note the logarithmic y-axis.

second. Accordingly, the crude sequence ratios, r_c , were above unity for nearly all cardiovascular drugs (Table 1).

By use of r_n as reference, a null estimate of the propranolol-antidepressant association emerged (rate ratio = 1.01; 95% confidence interval = 0.84–1.24). There was no suggestion that the beta-blockers as a whole would have any major depressogenic effect (rate ratio = 1.09; 95% confidence interval = 0.95–1.26).

OTHER CARDIOVASCULAR DRUGS

Only ACE inhibitors (rate ratio = 1.29; 95% confidence interval = 1.08–1.56) and calcium channel blockers (rate ratio = 1.31; 95% confidence interval = 1.14–1.51) showed a pattern compatible with a depression-provoking effect (Table 1). The signal was stronger for diltiazem than for other calcium channel blockers (rate ratio = 1.49; 95% confidence interval = 1.14–2.00). For the diuretics, there were more sequences with antidepressants prescribed first than expected ($r_c < r_n$), resulting in rate ratio estimates below unity.

The excess of ACE inhibitor → antidepressant sequences ($N = 82$) and calcium channel blocker → antidepressant sequences ($N = 138$) can be construed as an estimate of the number of antidepressant therapies that was attributable to such cardiovascular therapy.

Adjusting for the incidence trends by use of the r_n resulted in lower estimates, 61 and 114 cases, respectively. The total number of incident ACE inhibitor and calcium channel blocker therapies in the study base was 8,165 and 11,926, respectively. It can thus be estimated that the risk of becoming an antidepressant user stemming from use of these cardiovascular drugs is of the order of 0.5–1%, provided that the association is causal.

PREDICTORS OF THE PRESCRIPTION ORDER

I subjected the sequences involving ACE inhibitors and calcium channel blockers to a multivariate analysis of factors that were predictive of one prescription order (for example, calcium channel blocker → antidepressants) over the opposite order (Tables 2 and 3). The models included all individuals on whom the r_c estimate was based. Both models included age and gender. In addition, the models included recorded lithium use and a high antidepressant dose, both used as an indicator that the antidepressant was prescribed for depression and not for sleeping difficulties, pain, or other alternative indications. Finally, both models included available markers of ischemic or congestive heart disease.

None of the models showed any consistent or important relation between prescription order and gender, age,

TABLE 1. Distribution of Sequences Involving Antidepressants and Various Cardiovascular Drugs in Persons Who Started Both Drugs during a Predefined Period. An Excess of Persons Starting Antidepressant Therapy Last Indicates a Possible Depression-Provoking Effect

Drug	Number*	Antidepressant Prescribed First/Second (n)	Crude Sequence Ratio (r_c)	Null-Effect Sequence Ratio (r_n)	Rate Ratio (95% Confidence Interval)
Digoxin and analogues	5,138	144/183	1.27	1.18	1.07 (0.87–1.34)
Class 1 + 3 antiarrhythmics	560	8/22	2.75	1.53	1.80 (0.9–4.7)
Nitrates and analogues	7,863	245/293	1.20	1.19	1.01 (0.85–1.20)
Methyldopa	480	4/4	1.00	1.40	0.70 (0.2–3.8)
Calcium channel blockers	11,926	338/476	1.41	1.07	1.31 (1.14–1.51)
Verapamil	2,482	84/106	1.26	1.19	1.06 (0.81–1.43)
Nifedipine	1,525	49/62	1.27	1.20	1.06 (0.74–1.57)
Diltiazem	3,289	75/140	1.87	1.26	1.49 (1.14–2.00)
ACE inhibitors	8,165	192/274	1.43	1.11	1.29 (1.08–1.56)
Captopril	1,641	51/55	1.08	1.10	0.98 (0.68–1.46)
Enalapril	3,745	86/115	1.34	0.99	1.35 (1.03–1.80)
Thiazides	13,933	455/493	1.08	1.21	0.90 (0.79–1.02)
Loop diuretics	14,690	499/574	1.15	1.29	0.89 (0.79–1.00)
Potassium-sparing diuretics	2,419	86/90	1.05	1.26	0.83 (0.62–1.13)
Beta-blockers	9,375	342/420	1.23	1.12	1.09 (0.95–1.26)
Propranolol	3,764	186/211	1.13	1.12	1.01 (0.84–1.24)

* Number of incident users of the drug, during the period April 1991 through December 1993.

or any of the markers of cardiac disease. For the ACE inhibitors, there was a negative association between use of loop diuretics and the occurrence of an ACE inhibitor → antidepressant order (odds ratio = 0.67; 95% confidence interval = 0.4–1.0). The calcium channel blocker → antidepressant sequence was negatively associated with a short span between initiation of the two therapies (odds ratio = 0.7; 95% confidence interval = 0.5–0.9).

Discussion

The present study provides clear evidence against a causal association between propranolol and antidepressant use. The number of persons who started antidepressant therapy after beta-blockers was very similar to the number of persons following the opposite order. The slight asymmetry could be explained entirely by an increasing incidence of antidepressant prescribing. There was nothing to suggest that propranolol differed from

TABLE 2. Logistic Regression Model Describing 814 Persons Who Started Antidepressant (AD) and Calcium Channel Blocker (CCB) Therapy during a Predefined Period. The Model Analyzes Predictors of the CCB → AD Sequence (Calcium Channel Blockers Prescribed First) over the Opposite Order

Variable	Number of Persons with Variable	Odds Ratio	95% Confidence Interval
Age >64 years	438	1.17	0.9–1.6
Male gender	192	1.17	0.9–1.6
AD dose >0.5 DDD*/day	290	0.76	0.6–1.0
CCB dose >0.5 DDD/day	497	1.34	0.9–1.8
AD and CCB therapy initiated within a 100-day span	203	0.69	0.5–0.9
Recorded use of loop diuretics	236	1.05	0.8–1.5
Recorded use of beta-blockers	233	0.94	0.7–1.3
Recorded use of lithium	18	0.91	0.3–2.4
Recorded use of nitrates	233	0.98	0.7–1.4
Recorded use of ACE inhibitors	179	0.99	0.7–1.4
Recorded use of low-dose salicylate	140	1.16	0.8–1.7
Intercept		1.41	1.00–1.99

* DDD = defined daily dose.

TABLE 3. Logistic Regression Model of 466 Persons Starting Both Antidepressant (AD) and Angiotensin-Converting Enzyme Inhibitor (ACEI) Therapy during a Predefined Period. The Model Analyzes Predictors of the ACEI → AD Sequence over the Opposite Order

Variable	Number of Sequences with Variable	Odds Ratio	95% Confidence Interval
Age above 64 years	240	0.96	0.6–1.4
Male gender	207	1.15	0.8–1.7
AD dose >0.5 DDD*/day	182	0.90	0.6–1.3
ACEI dose >0.5 DDD/day	187	1.21	0.8–1.8
AD and ACEI therapy initiated within a 100-day span	106	1.52	0.9–2.4
Recorded use of loop diuretics	212	0.67	0.4–1.0
Recorded use of beta-blockers	138	1.08	0.7–1.7
Recorded use of lithium	7	1.78	0.3–9.7
Recorded use of nitrates	97	0.94	0.6–1.5
Recorded use of calcium channel blockers	178	1.33	0.9–2.0
Recorded use of low-dose salicylate	75	1.49	0.9–2.6
Intercept		1.30	0.83–2.05

* DDD = defined daily dose.

other beta-blockers in this respect. Admittedly, using antidepressants is not synonymous with having depression. On the other hand, if beta-blockers did cause depression, we would expect a signal.

Three other major controlled epidemiologic studies on beta-blockers and depression have been carried out. In a cross-sectional study using Medicaid data, Avorn *et al*¹⁵ reported a moderately higher level of antidepressant prescribing among users of propranolol, compared with users of other antihypertensives, insulin, or oral antidiabetics. Thiessen *et al*¹⁶ confirmed the association in a retrospective cohort study from the Saskatchewan Prescription Drug Plan. In a large case-control study by Bright and Everitt,¹⁷ a weak association was observed initially; however, the association was consistently weaker in subgroups with more strict criteria for depression, and the odds ratio was 0.98 if allowance was made for frequent physician contact, multiple prescriptions, and use of benzodiazepines. The authors concluded that the association between use of propranolol and antidepressants was noncausal, at least for prevalent, ongoing propranolol therapies. Apart from confirming this notion, the present study adds that the absence of association also applies to new, incident propranolol therapies.

Diltiazem,²² verapamil,²³ and nifedipine²⁴ have also been claimed to cause depression. The report on diltiazem included eight cases of severe depression, extracted from the World Health Organization database of spontaneous reports in Sweden.²² Two of the cases showed a positive rechallenge test, and one apparently represented a dose-related effect. There are also a few detailed case reports on depression in users of ACE inhibitors,^{25,26} but judging from a thorough literature search, no controlled epidemiologic data have been published on depression related to either ACE inhibitors or calcium channel blockers.

An important aspect of the symmetry principle presented here is that confounders that cause a simple, time-independent clustering of drugs will not affect the symmetry. The case-crossover design suggested by Macclure²⁷ has similar properties in controlling for confounders that are constant over time. The case-crossover design could not have been applied in this study, however, since it cannot analyze for chronic exposure. The case-crossover design can be viewed as a matched design where exposure attributes are compared for the case date and some date(s) before that in the same individual. With chronic exposure, however, you would find few, if any, discordant pairs where the patient is nonexposed on the case date and exposed on a previous date. The symmetry principle, on the other hand, is amenable to analyzing effects of chronic drug exposure.

Like other observational designs used in pharmaco-epidemiology, the symmetry analysis is sensitive to confounding by indication, which may be difficult or even impossible to adjust for. Cardiovascular drugs are prescribed for cardiovascular conditions, some of which may be serious. It should not be a surprise if such patients subsequently developed depression, which would then be attributed to the cardiovascular drug. Some studies

have reported very high prevalences of depression in patients with ischemic heart disease,^{5,28} and hypertensive labeling has been found to induce depressive symptoms.^{29,30} In two of the major epidemiologic studies on depression and propranolol, the authors addressed the problem by having reference groups that were assumed to be under a comparable psychological stress, for example, users of antidiabetics, insulin, or other antihypertensives.^{15,16} In the present study, confounding by indication would clearly explain a false presence of a signal, but not a false absence. It is hardly relevant when interpreting the negative findings, such as those for digoxin, nitrates, all diuretics, propranolol, and other beta-blockers. What remains are the weak signals seen for calcium channel blockers and ACE inhibitors.

I have attempted to address the confounding by indication problem by multivariate analyses of sequence predictors. In analytical terms, these are analyses of effect modification; the analyses bring to light the patient categories in which the skewness was most pronounced. Neither of the two multivariate models of sequence predictors showed any striking association between the order of therapies and age, gender, or use of nitrates and low-dose salicylates (Tables 2 and 3). If the sequence asymmetry could be attributed to ischemic heart disease, we would have expected at least one of these variables to be associated with the cardiovascular drug → antidepressant sequence. Furthermore, use of loop diuretics was negatively associated with the ACE inhibitor → antidepressant order (odds ratio = 0.7). In other words, users of loop diuretics tended to use antidepressants before ACE inhibitors. This finding implies that the excess of ACE inhibitor → antidepressant sequences is definitely not explained by patients with congestive heart failure, who develop depression because of their underlying cardiac disease. The argument can be viewed as one of a severity gradient; if the asymmetry is explained by the underlying cardiovascular disease, we would expect that the asymmetry was most pronounced in persons with severe disease. If anything, the contrary was found in the multivariate models.

A number of other caveats have to be considered for the positive signals. A list of some possible causes of asymmetry is shown in Table 4. Nearly all are well known biases that would affect any observational design. A few are specific for the symmetry analysis, namely the sensitivity to trends in both exposure and outcome rates, the possibility of confusing a harmful effect going in one direction with a protective effect going the opposite way (reverse causation), and the sensitivity to selective loss of follow-up. Most of the possibilities are either unlikely to be relevant in the present context (B, D, E, F, G, I) or have been addressed in the analysis (C, H).

The main analysis did not account for the possibility of selective loss of follow-up. If use of antidepressants were associated with a particularly high mortality, there would be less person-time following antidepressants as compared with the cardiovascular drugs, which would result in a spurious signal. To address that, I performed a supplementary analysis, restricted to persons who had

TABLE 4. Some Possible Causes of Nonsymmetrical Prescription Orders

A	A biological effect
B	Mutual indications First-line drugs would systematically precede second-line drugs, given for the same indication, eg, propranolol might systematically be tried before antidepressants in patients with migraine
C	Confounding by indication Ex. A cardiovascular drug is prescribed for a cardiovascular disease, which may by itself trigger a depression
D	Confounding by contraindication Ex. Nonsteroidal antiinflammatory drugs precede ulcer drugs more often than the reverse, since an ulcer history (use of ulcer drugs) is a contraindication for prescribing nonsteroidal antiinflammatory drugs
E	Altered threshold for prescribing Ex. Diabetes mellitus (use of insulin) may lower the physician's threshold for treating hypertension
F	Natural progression of disease Ex. Insulin would precede drugs used to treat painful diabetic neuropathy
G	Reverse causation Ex. A relative excess of ACE inhibitor → AD therapies could imply that ACE inhibitors provoke depression, but also that ADs protect against use of ACE inhibitors
H	Time trends in prescribing for either exposure or outcome drug
I	Age dependency in use of exposure or outcome drug Ex. If a very wide time-window is allowed, several years or decades, asymmetry would emerge if one drug was used mainly by the young and the other by the old
J	Selective loss of follow-up Ex. An experimental antineoplastic drug would systematically precede few other drugs, as it is used in persons with a short life expectancy

filled at least one prescription during the last 3 months of the study period (74.9% of the incident antidepressant users). They were intended to represent persons with complete follow-up. The ACE inhibitors and calcium channel blockers showed rate ratios of 1.21 (95% confidence interval = 0.99–1.49) and 1.25 (95% confidence interval = 1.08–1.47), respectively. None of the other drugs or drug classes shown in Table 1 showed important deviations from symmetry or from previous results.

One way to limit some of the biases is to constrain the interim time allowed, for example by including only persons with less than 1 year between start of the two index therapies. That would reduce the effect of time trends in prescribing, selective loss of follow-up, natural course of disease, and age dependency of prescribing (Table 4). The 33-month interval allowed in this study is probably about the upper limit of what should comfortably be used. I chose to use it because I did not want to overlook a late-onset depressogenic effect. Instead, the interim time was included as an effect modifier in the multivariate models.

In the case of propranolol and antidepressants, we should also consider the biases that would lead to a false absence of a signal. Ordinarily, if the drug effect was well known, physicians who encountered a propranolol user with depression might respond by discontinuing propranolol rather than prescribe an antidepressant. I have tested the symmetry analysis on several known drug effects, for example, cough induced by ACE inhibitors. Contrary to propranolol-induced depression, this effect

is well known, well documented, and very common. Nevertheless, I could show a clear excess of ACE inhibitor → antitussive prescription orders. A pilot project on drug-induced dyspepsia has confirmed the sensitivity of the method with well known drug effects (unpublished data).

In conclusion, the large and very symmetrical numbers of sequences found for most drugs indicate that the presumption of sequence symmetry is sound. The method does not respond to nonspecific clustering of drug therapies, which may be difficult to control by other designs. Possibly, it may be extended to other exposures and outcomes than drugs, forming an "event symmetry" principle. In spite of certain biases not encountered in other designs, it appears to have a reasonable specificity, as evidenced by the mainly negative findings. Used judiciously, it may thus be a useful screening instrument for detecting unknown adverse drug reactions.

Acknowledgments

I am indebted to David Gaist and Alexander Walker for fruitful and inspiring discussions. I also thank the County of Funen for their cooperation. Ralph Edwards from the World Health Organization database in Uppsala kindly assisted in providing data on spontaneous reports.

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Appendix

Model for Estimating the Null-Effect Sequence Ratio, r_n

The model assumes *a priori* that all co-prescribing of the two index drugs occurs by coincidence.

For persons who are prescribed both a cardiovascular drug (CV) and an antidepressant (AD) during the survey period, the probability that the AD was prescribed last depends on when the CV was prescribed. If the CV was prescribed on the first date of the survey period, we can be certain that the

sequence would be CV → AD. Conversely, if the CV was prescribed on the last date, the sequence would be AD → CV.

For persons starting CV therapy on a specific index day, m , the probability of a CV → AD sequence is:

$$p = \frac{\sum_{n=m+1}^u AD_n}{\sum_{n=1}^u AD_n}, \quad (1)$$

where

m or n = consecutive days of the survey period, excluding the run-in period

u = the last day of the survey period

AD_{index} = number of persons presenting their first antidepressant prescription on index day

CV_{index} = number of persons presenting their first prescription on a specific cardiovascular drug on index day.

The numerator is the total number of incident AD therapies prescribed after the index day, and the denominator is the total number of incident AD therapies throughout the survey period.

The overall probability of a CV → AD sequence, a , can be calculated as the average p for all days, weighted by the number of incident CV therapies on each day:

$$a = \frac{\sum_{m=1}^u [CV_m \cdot (\sum_{n=m+1}^u AD_n)]}{\sum_{m=1}^u CV_m \cdot \sum_{n=1}^u AD_n}, \quad (2)$$

yielding a null-effect sequence ratio, r_n , of:

$$r_n = \frac{a}{1-a}. \quad (3)$$