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Is aspirin useful in patients on lithium? A pharmacoepidemiological study related to bipolar disorder

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Abstract

Objectives—Administration to rats of mood stabilizers approved for bipolar disorder (BD) downregulates markers of the brain arachidonic acid (AA, 20:4n-6) metabolic cascade, including phospholipase A₂ (PLA₂) and cyclooxygenase (COX) expression. We hypothesized that other agents that target the brain AA cascade, nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, also would ameliorate BD symptoms.

Methods—Medication histories on subjects who had been prescribed lithium were collected from the Netherlands PHARMO Record Linkage System. Data were stratified according to drug classes that inhibit PLA₂ and/or COX enzymes, and duration of use. Incidence density (ID) of medication events (dose increase or substance change) was used as a proxy for clinical worsening. ID ratios in patients with the inhibitors plus lithium were compared to ratios in patients using lithium alone.

Results—Low-dose acetylsalicylic acid (aspirin) significantly reduced the ID ratio of medication events, independent of use duration. The ID ratios of NSAIDs and glucocorticoids did not differ significantly from 1.0 if prescribed for ≥ 180 or ≥ 90 days, but exceeded 1.0 with shorter use. Selective COX-2 inhibitors had no significant effect and multiagent administration increased the ID ratio above 1.0.

Conclusions—Low-dose aspirin produced a statistically significant duration-independent reduction in the relative risk of clinical deterioration in subjects on lithium, whereas other NSAIDs and glucocorticoids did not. These tentative findings could be tested on larger databases containing detailed information about diagnosis and disease course, as well as by controlled clinical trials. (238 words)

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Keywords

bipolar disorder; aspirin; NSAIDs; glucocorticoids; lithium; arachidonic acid; pharmacoepidemiology

1. Introduction

Bipolar disorder (BD) is characterized by episodes of mania alternating with periods of depression or euthymia. Its 12-month prevalence is about 1%, and its cumulative lifetime prevalence is between 1.5% and 2.0% [1]. Its pathological mechanisms are poorly understood, but markers of neuroinflammation and excitotoxicity, as well as of the arachidonic acid (AA, 20:4n-6) metabolic cascade [2], have been reported to be upregulated in the postmortem BD brain [3,4].

Lithium has been one of the first-line treatments of BD for over 50 years; the anticonvulsants carbamazepine, divalproex (valproate), lamotrigine and several atypical antipsychotics (e.g., olanzapine and quetiapine) are more recent therapeutic options [5,6]. Multiple hypotheses for the action of these agents have been suggested, including the inositol depletion hypothesis and inhibition of glycogen synthase kinase-3 for lithium; inhibition of histone deacetylation for valproic acid; modulation of sodium channels, adenosine receptors and adenylate cyclase for carbamazepine [7]; and inhibition of calcium currents and glutamate release for lamotrigine [8,9]. However, none of these mechanisms has been validated as the mode of action of these “mood stabilizers” in BD.

One mechanism recently suggested by Rapoport and colleagues [10–15], based on studies in unanesthetized rats, is that the mood stabilizers downregulate parts of the brain arachidonic acid (AA, 20:4n-6) cascade, which can include AA turnover in phospholipids, expression of phospholipase A₂ (PLA₂) and/or cyclooxygenase (COX) enzymes. PLA₂ and COX enzymes catalyze, respectively, release of AA from membrane phospholipid and AA conversion to eicosanoids such as prostaglandin E₂ and thromboxane B₂. The AA cascade is involved in neuroreceptor-initiated signaling and can be pathologically upregulated by neuroinflammation and excitotoxicity [16–18].

In this study, we tested the hypothesis [10] that nonsteroidal anti-inflammatory agents (NSAIDs) or glucocorticoids, because of their ability to interfere with PLA₂ and/or COX activity [19–21], also would be beneficial in BD patients. We used a database of individuals that had been treated with lithium (which we took as a surrogate marker of BD), and quantitatively assessed the association between exposure to inhibitors of PLA₂ and/or COX enzymes and symptom worsening (taken as increased dispensing of concomitant medication).

2. Materials and methods

2.1. Study setting

The setting was the PHARMO Record Linkage System (RLS) in the Netherlands[22,23]. This system contains pharmacy dispensing records from community pharmacies, linked to hospital discharge records of more than two million community-dwelling residents in more than 25 population-defined areas in the Netherlands from 1985 onwards. Since nearly all people in the Netherlands are registered with a single community pharmacy, independent of prescriber, their pharmacy records are virtually complete with regard to prescription drugs.

The computerized drug dispensing histories in the PHARMO RLS contain information on the dispensed drug, dispensing date, prescriber, amount dispensed and the prescribed dosage

regimen. Each patient is registered with an anonymous unique patient identification code that allows for the observation of patient medication over time. All medicines are coded according to the WHO Anatomical Therapeutic Chemical (ATC) classification system [22,24]. However, a major limitation of the database is that it does not provide information concerning indications (e.g., disease or diagnosis) for the use of medicines. Our study covered the 10-year period from 1 January 1996 to 31 December 2005. It was approved under the terms of the PHARMO RLS and, for one author (S. I. Rapoport), by the Institutional Review Board of the National Institute on Aging, National Institutes of Health, Bethesda, MD, USA.

2.2. Cohort selection

We selected all patients of at least 18 years of age who had been dispensed at least five prescriptions for lithium and who had at least one year of drug dispensing history prior to inclusion. Follow-up started on the day of the first dispensing of a lithium prescription and ended on the theoretical end date of the last prescription. A maximum gap between the theoretical end date of a prescription and the dispensing date of the next prescription of 90 days was accepted. More than one period of follow-up per patient was possible.

Exposure—Exposure episodes for additional drugs that are reported to interfere with AA metabolism were constructed for each subject based on the theoretical end date of a prescription (based on the prescribed dose and the amount dispensed). The following six classes of reported inhibitors of COX and/or PLA₂ were evaluated:

1. Acetylsalicylic acid (aspirin) at a low dose of 30 mg or 80 mg (a preferred inhibitor of COX-1, an acetylator of COX-2) [21,25,26]
2. Acetylsalicylic acid at high dose (> 80 mg)
3. NSAIDs (inhibitors of both COX-1 and COX-2), excluding acetylsalicylic acid and selective inhibitors of COX-2 [19]
4. COX-2 selective inhibitors [19]
5. Glucocorticoids for systemic use (inhibitors of PLA₂ and COX enzymes) [27]
6. More than one inhibitor type (among 1–5)

Data were evaluated using different minimum durations for an episode: ≥ 1 day, ≥ 45 days, ≥ 90 days, and ≥ 180 days.

2.3. Outcomes of interest

For each subject being dispensed lithium, medication “events” in the dispensing history were considered to be a proxy for deterioration of BD. Medication events were evaluated with regard to prescribing the following five classes of drugs, based on ATC codes [24] 1- Anxiolytics (N05B), 2- Hypnotics and sedatives (N05C), 3- Antipsychotics (N05A), except lithium (N05AN), 4- Antidepressants (N06A), 5- Other drugs (mood stabilizer anticonvulsants [28]) used in treating BD (valproate (N03AG01), carbamazepine (N03AF01), and lamotrigine (N03AX09)).

Within these five drug classes, the following medication events were evaluated as an indication of disease deterioration:

Substance change—Introduction of a new active substance used by the patient. ‘New’ is defined as a substance that was not dispensed in the prior 180 days. In practice, this indicates medication switching, or the start of combination therapy.

Dose change—An increase in the calculated daily dose of a substance of > 30%, compared to the prior prescription. This increased dose, or a higher dose, must not have been used in the previous 180 days.

To determine whether the number of medication events taken as a proxy for disease deterioration varied among the different exposure groups, incidence density (ID) of medication events was calculated for each exposure episode. ID was defined as the number of medication events divided by the total duration of the follow-up episode, expressed in person years.

2.4. Potential Risk Factors

Several cofactors were assessed that may have influenced the outcome of interest. Age at the start of the episode and sex were included as baseline patient characteristics. The total number of prescriptions for all drugs dispensed to a patient during an episode was taken as a proxy for total health care utilization. Subjects were assigned to one of three categories (low, medium, or high) of health care utilization, based on tertiles. As a measure of chronic disease burden we determined the Chronic Disease Score. This score has been used previously as a gauge of chronic disease status based on dispensing records [29–31]. We calculated this score based on the drugs dispensed during the year prior to an exposure episode. Patients were classified according to their Chronic Disease Score in three categories (0 points, 1–3 points, >3 points).

To determine the possible influence of selectivity for COX-1 or COX-2, we also compared crude ID ratios of NSAIDs at the substance level. We divided the NSAIDs into groups, based on their COX selectivity according to a comparative analysis by Warner et al [19]. A sub-analysis also was performed for the COX-2 inhibitor group, focusing on whether the ability to penetrate the blood-brain-barrier was of influence [32]. Rofecoxib and valdecoxib are reported to achieve a therapeutic concentration in the human central nervous system, leading to COX-2 inhibition, whereas the concentration reached by celecoxib is considered too low for a therapeutic effect [32].

2.5. Data Analysis

Incidence densities (IDs) for the different exposure groups were compared by calculating ID ratios, with patients using lithium alone as the reference group, with 95 % confidence intervals. Poisson logistic regression was used to adjust for the influence of covariates.

3. Results

As illustrated in Table 1, a total of 5145 subjects (38.5% male and 61.5% female) who were prescribed a lithium-containing drug fulfilled our initial criteria for inclusion in the study. Their average age of entry into the database was 48.6 ± 15.1 (SD) years, and the average length of an episode of lithium use was 847.1 days. Within the 10 year period of observation, follow-up started in 30% of the patients when < 40 years of age, 22.7% when > 60 years, the remainder between 41 and 60 years.

Table 2 summarizes the number of medication “events” (interpreted as disease worsening), person years, incidence density (ID) and crude and adjusted ID ratios (with 95% confidence intervals) for lithium and each of the 6 drug exposure classes under investigation.

The adjusted ID ratios are corrected for age category, sex, Chronic Disease Score and health care utilization by including them as categorical variables in the Poisson regression model. The data are stratified according to minimum duration of exposure to AA cascade inhibitors. Statistically significant ID ratios at $p < 0.05$ are indicated in bold. ID ratios were significantly less than 1.0 for low dose acetylsalicylic acid prescribed for an unspecified time or for $\geq 1, 45, 90$ or 180 days. ID ratios were significantly greater than 1.0 for NSAIDs excluding COX-2

inhibitors prescribed for ≥ 1 , 45 or 90 days, but not for ≥ 180 days. They were significantly greater than 1.0 for glucocorticoids prescribed for ≥ 1 or 45 days, but did not differ from 1.0 when glucocorticoids were dispensed for ≥ 90 or 180 days. The ID ratios were significantly greater than 1.0 for administration of more than one AA cascade inhibitor at all treatment times, but did not differ from 1.0 for acetylsalicylic acid (excluding low dose acetylsalicylic acid) or for COX-2 inhibitors prescribed for ≥ 1 , 45, 90 or 180 days.

We also determined crude ID ratios of NSAIDs, divided according to COX selectivity based on a comparative analysis by Warner et al. [19] (data not shown). We found no statistically significant effect of COX selectivity on the ID ratio, when the drugs were prescribed for an unspecified time.

Additionally, we looked at differences between COX-2 inhibitors based on their reported ability to penetrate the blood-brain barrier [32]. In a sub-analysis at the substance level for the COX-2 inhibitors, the unadjusted relative risk was 2.69 (CI 95%: 0.87–8.36) for rofecoxib (which does cross the barrier) and 1.24 (CI 95%: 0.75–2.06) for celecoxib (which crosses the barrier very slowly), not taking into account duration of use. There were too few prescriptions for valdecoxib in the dataset to calculate a relative risk.

4. Discussion

This initial pharmacoepidemiological study on patients treated with lithium does not establish a statistically significant association between the use of the whole class of drugs that inhibit PLA₂ and/or COX enzymes and amelioration of BD symptoms. However, the adjusted ID ratio was significantly less than 1.0 for subjects who had been dispensed low-dose aspirin in addition to lithium. In contrast, use of NSAIDs (excluding COX-2 inhibitors), as well as of glucocorticoids, resulted in ID ratios significantly above 1.0 when prescribed for ≥ 180 days and ≥ 90 days, but ID ratios did not differ from 1.0 when episodes of a shorter duration were included in the analysis. There was no significant effect of COX selectivity on the ID ratio.

That low-dose aspirin decreased the number of medication events, i.e., reduced the ID ratio when compared to the ratio with lithium treatment alone, irrespective of prescription duration, is consistent with the hypothesis that inhibitors of brain PLA₂ and/or COX enzymes would be beneficial in BD [10,12]. This finding also is in line with results of a study indicating that acetylsalicylic acid produced positive mood-modulating effects in men undergoing coronary angiography [33]. Thus, the decreased ID ratio associated with use of low-dose aspirin may have reflected a direct effect on the disease state in BD. On the other hand, taking low-dose acetylsalicylic acid may characterize conscientious, organized individuals concerned about the prophylaxis of coronary disease, the major reason for prescribing low-dose aspirin. Such personality characteristics are unlikely in patients with more severe BD, who are poorly compliant. This so called ‘healthy user’ bias may have influenced our results [34]. Our data are insufficient to resolve this issue.

Our finding that short-term NSAIDs and glucocorticoids increased the ID ratio in subjects on lithium is inconsistent with the AA cascade hypothesis for their action. One explanation for the discrepancy, illustrated by the duration of use analysis, is that an AA cascade inhibitor must be given for a longer period of time to produce a positive effect in BD. Another explanation is that aspirin, NSAIDs and glucocorticoids have different mechanisms of action and ancillary effects.

Aspirin is considered to inhibit COX-1 activity much more than COX-2 activity [25,35], to downregulate transcription of the *COX-2* gene [36], to elevate lipoxygenase-derived eicosanoids such as the anti-inflammatory lipoxin A₄ [37], and to acetylate COX-2 protein to a modified enzyme that can convert unesterified AA to anti-inflammatory mediators such as

15-epi-lipoxin A4 [26]. The acylated enzyme also can convert docosahexaenoic acid (DHA, 22:6n-3) to 17-(**R**)-OH-DHA, which, like its metabolites di(**R**)-OH-DHA (neuroprotectin (**R**) D1) and tri(**R**)-OH-DHA (resolvin (**R**) D1), is highly anti-inflammatory [38]. Lithium given chronically to rats with lipopolysaccharide-induced neuroinflammation also increases the brain concentration of 17-OH-DHA (M. Basselin, M. Chen, S. I. Rapoport, R. C. Murphy and S. E. Farias, unpublished observations). Thus, there may be a synergy between aspirin and lithium in forming anti-inflammatory brain DHA metabolites. In this regard, neuroinflammation is reported in BD [3], and dietary DHA supplementation was found in some but not all clinical trials to be helpful in BD patients [39–41].

Glucocorticoids may inhibit PLA₂ and prostaglandin formation by inducing the formation of lipocortin-1, but glucocorticoids have a number of effects that could aggravate BD and enhance psychiatric symptoms [20,42,43]. Another explanation for a lack a significant positive NSAID (excluding aspirin) or glucocorticoid effect is that the increased ID ratios for these agents at the shorter prescription times represented ‘confounding by indication’ [44,45]. The clinical indication for prescribing the drugs also may be associated with a more severe disease state for BD, as well as alternative comorbidities. For example, NSAIDs are prescribed for rheumatoid arthritis, and both the disease and the drugs themselves are reported to increase psychiatric symptoms [46,47]. We could not fully correct for this by including the Chronic Disease Score in our model.

NSAIDs can increase lithium serum levels to the toxic range through their effect on the kidney [48], but this did not likely cause the increased relative risk found in this study. Toxic effects of lithium (e.g. tremor, diarrhea, nausea, vomiting and renal effects) are not easily confused with acute episodes in BD, and therefore are unlikely to result in changes in the prescribing of the drug classes that were used as a proxy for deterioration of BD in this study.

When interpreting our results, important limitations of this study should be recognized. Firstly, we assumed that all the subjects taking lithium had BD. Because of the nature of the database, we were unable to validate the diagnosis of BD, and lithium may have been prescribed for other indications, mainly unipolar depression [49–51]. However, when we performed an analysis excluding individuals who had been prescribed an antidepressant in the year before their first lithium prescription in the database, we did not find changes in the direction of effect for the calculated relative risks. Furthermore, no beneficial psychiatric effect has been established for the drug classes of interest in this study regarding unipolar depression, and thus this misclassification would rather lead to a bias towards the null hypothesis.

Secondly, the outcome that was taken as a proxy for disease deterioration was a change in medication use. We employed this measure elsewhere to quantify disease deterioration [52], but it is limited since data on actual clinical symptoms and disease course were unavailable. Future studies should include clinical outcomes, such as suicide, altered scores on the bipolar rating scale (YMRS), psychiatric hospitalization and total health care utilization (including number of doctor visits and type of medical intervention).

Thirdly, in the Netherlands some NSAIDs (e.g. ibuprofen and diclofenac) are available as non-prescription ‘over-the-counter’ medicines. This use was not captured in our database, which only contains information for prescription drugs. Nevertheless, misclassification resulting from nonprescription drug use likely is random with regard to the outcome and would therefore lead to a bias towards the null.

In conclusion, while our results do not support the hypothesis that drugs that inhibit or otherwise alter expression of PLA₂ and/or COX enzymes in the AA cascade generally will ameliorate symptoms of BD [10–13], they do indicate significant duration-independent reduction by aspirin in the relative risk of disease deterioration (ID) ratio in subjects on lithium, compared

with subjects on lithium alone. To test these initial findings, follow-up epidemiological studies are needed, using a database with larger cohorts, longer durations of drug use, and detailed information about diagnosis, hospitalization, and clinical course of BD, in subjects off and on lithium or other mood stabilizers. Controlled clinical trials with aspirin plus lithium also would be of interest.

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Abbreviations

AA	arachidonic acid
BD	bipolar disorder
COX	cyclooxygenase
DHA	docosahexaenoic acid
ID	incidence density
NSAID	nonsteroidal anti-inflammatory drug
PLA ₂	phospholipase A ₂
RLS	record linkage system

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Table 1

Baseline characteristics of lithium users and number of medication events during lithium use, categorized according to drug classes.

Sex	1983 Males (38.5%) 3162 Females (61.5 %)
Average age (years) on first lithium Rx during follow-up	48.6 ± 15.1 (S.D.)
Age at start of first episode	
< 40 years	1546 (30.0%)
41–60 years	2430 (47.3%)
> 60 years	1169 (22.7%)
Average duration of exposure episode	847.1 days
Medication events (Substance change/dose change)	
All groups	6904/9530
1- Anxiolytics	1469/2339
2- Hypnotics and sedatives	1630/1236
3- Antipsychotics	1782/2467
4- Antidepressants	1885/2746
5-Other drugs used to treat bipolar disorder	138/742

Table 2

Medication events, person years, incidence density, and incidence density relative to lithium (Incidence ratio), with 95% confidence limits, at different minimum exposure durations to inhibitors of phospholipase A₂ and/or cyclooxygenase enzymes. Incidence densities are defined as number of events/person year.

Exposure history	Events	Person years	Incidence density	Incidence Density Ratio to Lithium Only	
				CRUDE	ADJUSTED*
Unexposed (lithium only)					
≥45 days	15365	19241	0.799	Reference	Reference
≥90 days	15271	19220	0.795	Reference	Reference
≥180 days	15096	19156	0.788	Reference	Reference
	14330	18781	0.763	Reference	Reference
Exposure to:					
Low dose (30 or 80 mg per day) acetylsalicylic acid	360	544.0	0.662	0.83 (0.75 – 0.92)	0.86 (0.77 – 0.96)
≥ 45 days	355	541.1	0.656	0.83 (0.74 – 0.92)	0.86 (0.77 – 0.95)
≥ 90 days	344	537.6	0.640	0.81 (0.73 – 0.90)	0.84 (0.75 – 0.93)
≥ 180 days	329	525.4	0.626	0.82 (0.74 – 0.92)	0.84 (0.75 – 0.94)
High dose (> 80 mg per day) acetylsalicylic acid	33	32.32	1.021	1.28 (0.91 – 1.80)	1.33 (0.94 – 1.87)
≥ 45 days	24	23.64	1.015	1.28 (0.86 – 1.91)	1.24 (0.83 – 1.85)
≥ 90 days	23	20.54	1.120	1.42 (0.94 – 2.14)	1.33 (0.88 – 2.00)
≥180 days	13	15.01	0.866	1.14 (0.66 – 1.96)	1.03 (0.60 – 1.77)
Non-selective NSAIDs	525	471.7	1.113	1.39 (1.28 – 1.52)	1.52 (1.39 – 1.66)
≥ 45 days	415	402.3	1.032	1.30 (1.18 – 1.43)	1.37 (1.24 – 1.51)
≥ 90 days	338	361.9	0.934	1.19 (1.06 – 1.32)	1.21 (1.09 – 1.35)
≥180 days	255	305.4	0.835	1.09 (0.97 – 1.24)	1.09 (0.97 – 1.24)
COX-2 selective inhibitors	19	19.61	0.967	1.21 (0.77 – 1.90)	1.40 (0.89 – 2.20)

Exposure history	Events	Person years	Incidence density	Incidence Density Ratio to Lithium Only	
				CRUDE	ADJUSTED*
≥ 45 days	14	15.35	0.912	1.15 (0.68 – 1.94)	1.29 (0.76 – 2.18)
≥ 90 days	14	13.20	1.061	1.35 (0.80 – 2.27)	1.43 (0.85 – 2.41)
≥ 180 days	10	9.98	1.002	1.31 (0.71 – 2.44)	1.44 (0.77 – 2.68)
Glucocorticoids	83	64.80	1.281	1.60 (1.29 – 1.99)	1.62 (1.30 – 2.01)
≥ 45 days	69	58.52	1.179	1.48 (1.17 – 1.88)	1.48 (1.17 – 1.87)
≥ 90 days	52	52.08	0.998	1.27 (0.96 – 1.66)	1.23 (0.94 – 1.62)
≥ 180 days	39	43.75	0.891	1.17 (0.85 – 1.60)	1.12 (0.82 – 1.54)
More than one inhibitor type	45	31.12	1.446	1.81 (1.35 – 2.43)	1.90 (1.42 – 2.55)
≥ 45 days	42	26.92	1.560	1.96 (1.45 – 2.66)	2.01 (1.48 – 2.73)
≥ 90 days	33	23.05	1.432	1.82 (1.29 – 2.56)	1.79 (1.27 – 2.53)
≥ 180 days	29	17.39	1.668	2.19 (1.52 – 3.15)	2.08 (1.44 – 3.00)

* Adjusted for age category, sex, Chronic Disease Score and health care utilization.