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Demographic, medical, and behavioral characteristics associated with over the counter non-steroidal anti-inflammatory drug use in a population based cohort: results from the Multi-Ethnic Study of Atherosclerosis

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Abstract

Background—Three types of non-steroidal anti-inflammatory drugs (NSAIDs) can be obtained both over the counter (OTC) and by prescription in the United States. OTC NSAID use is not recorded in prescription claims databases; this might lead to differential misclassification of NSAID exposure status in studies that use computerized pharmacy databases to study NSAID use.

Objective—To evaluate characteristics of OTC versus prescription NSAID users

Methods—This analysis is set within the Multi-Ethnic Study of Atherosclerosis (MESA) study; a prospective cohort study of 6,814 adults from 4 ethnic groups (European descent, Asian, African-American and Hispanic) with a mean age of 62 years. The cohort was restricted to those who initiated NSAID use (aspirin, ibuprofen or naproxen) during follow-up. We compared information about age, sex, ethnicity, body mass index, smoking, diabetes, medication use, education, income, health insurance status and exercisebetween groups.

Results—OTC NSAID use was prevalent at baseline (25% Aspirin, 9% Ibuprofen, 2% Naproxen). Compared to prescribed NSAID use, OTC NSAID use was lower for users of non-European descent for all classes: aspirin ($p<0.0001$), ibuprofen ($p<0.0001$) and naproxen ($p=0.0094$). For aspirin, differences were seen for male gender (Relative Risk (RR):0.92; 95% (Confidence interval) CI:0.86–0.98), use of lipid lowering drugs (RR:0.88; 95% CI: 0.80–0.96), low income (RR:0.89; 95%CI:0.81–0.97), and participants one standard deviation above average in intentional exercise (RR:1.03; 95%CI:1.01–1.05).

Conclusions—OTC NSAID use is prevalent in an older multi-ethnic population and OTC users differ from prescription NSAID users. Caution should be exercised when using prescribed NSAIDs as a proxy for NSAID use.

Keywords

Aspirin; over the counter drug use; ethnicity; Multi-Ethnic Study of Atherosclerosis

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDS) are commonly used to treat a variety of chronic medical conditions. For example, the NSAID aspirin is prescribed for both primary [1] and secondary prevention [2] of serious cardiovascular events such as myocardial infarction. However, the other major indication for aspirin use (as well as for many other members of the NSAID drug class) is for pain management [3]. NSAIDs may be used both for acute and chronic pain conditions (including arthritis), where it is often self-administered [4].

While NSAIDS can be prescribed, some NSAIDS (aspirin, ibuprofen, and naproxen) are also available over the counter (OTC) in the United States. For example, aspirin is the most common over the counter analgesic taken by Americans [4]. There is evidence in the literature that OTC aspirin may be utilized differently in some sub-populations or among different ethnic groups [5–6] so one cannot necessarily study patterns of NSAID utilization based on prescriptions alone.

Different ethnic preferences for OTC aspirin use could also impact the validity of important approaches to adverse event surveillance. Many studies of adverse events (where aspirin was the primary exposure, a population restriction, or a critical confounder) have been based in either a clinical [7,8] or a prescription claims database [9,10] where OTC NSAID use will not be captured. This exposure misclassification can lead to misleading estimates [11] especially if the use of OTC NSAIDs is differential. If this differential exposure misclassification is by characteristics that are not commonly measured in prescription claims databases (such as ethnicity or socioeconomic status) but are also related to the outcome then it may make this misclassification bias impossible to account for analytically (e.g. via stratification).

The Multi-Ethnic Study of Atherosclerosis (MESA) study was developed to determine the predictors of cardiovascular disease in an asymptomatic population [12]. In the MESA study, there is comprehensive ascertainment of both prescription and OTC drug use in all participants [12] due to the design of the medication recording system [13].

The objective of this study is to describe the characteristics associated with OTC use for aspirin, ibuprofen and naproxen NSAIDs and contrast these with those characteristics associated with prescription NSAID use.

METHODS

The MESA study includes 6,814 participants between the ages of 45 and 84 years from four different race/ethnic groups (28% African-American, 12% Asian, 38% European descent, and 22% Hispanic). MESA participants were recruited from six different field centers across the United States: Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York, NY and St. Paul, MN. The design of the MESA study and the recruitment of participants have been described in detail elsewhere [12]. To date, there have been four exams in the MESA study: a baseline exam and 3 follow-up exams. The baseline exam occurred from July 2000 to April 2002. The first follow up exam (visit 2) occurred from September 2002 to January 2004. The second follow-up exam (visit 3) occurred from March 2004 and July 2005. The third follow-up exam (visit 4) occurred from September 2005 and June 2007.

Participants with a self reported history of either prevalent cardiovascular disease or previous surgery for cardiovascular disease were excluded from the MESA study. In

addition, we also excluded the 845 participants who did not return for at least one follow-up exam as we could not assess new aspirin use among these participants.

Data Collected

The MESA study collected a broad range of data on study participants. MESA participants were asked to come to a morning clinic examination after an overnight fast for each exam. Participants were given standard questionnaires to assess a variety of risk factors which included demographic information, smoking, and any medical history of either hypertension or diabetes at the time of the exam. Participants were asked to bring their medications to the clinic and medication use was assessed using a medication inventory approach [13,14]. Anthropometric measures were also taken on all study participants at each exam. The amount of physical activity was assessed via questionnaire for both intentional exercise and sedentary activities (defined as time spent reading or television watching) [15].

Primary Endpoint

For the purposes of this study we are using an operational definition of NSAID use as a prescription that is identified during the medication inventory [13]. This definition is a form of the “any use” definition of medication use as it defines a subject exposed to medication if they took any medication during the study window (two weeks prior to the exam) regardless of the amount of medication taken. In particular, we assessed aspirin, ibuprofen and naproxen use as these were the medications that were available OTC during the period of the study. We then restricted the population to only participants who started that particular NSAID during the course of the MESA study (a new user cohort). There was a separate new user cohort formed for each type of medication under study. This new user approach limited the the potential for misclassification by levels of adherence to medication use if some participants were more likely to adhere to prescribed therapy than others. Although there will still be some adherence effects due to the length of the assessment windows, this approach acts to reduce the magnitude of the potential impact of this source of misclassification. The primary outcome was taking an OTC NSAID (with participants taking prescription NSAIDs acting as the reference category). Participants who reported both OTC and prescription NSAID use were considered to be taking prescribed NSAIDs.

Data Validity

Trained interviewers were instructed to list medications separately depending on whether a medication had been directly prescribed by a medical doctor. Only aspirin prescriptions that were directly prescribed were recorded as prescriptions; aspirin taken on advice of physician was recorded as over the counter. Prescribed medications were cross-checked to ensure that valid prescription information was present (in terms of dose per day prescribed). Valid prescription instructions consistent with standard aspirin prescriptions were present in 95.3% of records recorded as being prescribed aspirin. All doses of aspirin were available over the counter so we could not use pill dose to check data validity for OTC aspirin. However, we also considered Naproxen, -- another class of NSAIDs that is available both OTC and by prescription in the United States. In the case of Naproxen, only lower doses are available in OTC form and higher doses are prescription only. In the MESA study, 92.8% of Naproxen prescriptions listed as OTC had the correct (lower) dose listed in the database while 3.8% of prescriptions had no dose recorded and 3.4% had an higher pill dose listed than would be available OTC (and were thus likely to be either misclassified prescription naproxen or errors in dose entry or possibly MD prescriptions of low-dose drugs (in order to obtain insurance coverage for the medication use).

Statistical Analysis

We used relative risk regression [16] to estimate the association of baseline characteristics with OTC aspirin use. We used prescription NSAID use as the reference group for each sub-cohort. The use of relative risk regression instead of logistic regression was needed as neither OTC nor prescription NSAID use met the criteria for being considered a rare event. We used robust confidence intervals. All analysis was conducted in SAS 9.1.3.

RESULTS

Across the course of the period under study, aspirin use was initiated by 1562 MESA participants who did not report aspirin use at baseline. Of these new users, 435 participants were prescribed aspirin and 1127 participants used OTC aspirin (Table 1). There were also more participants (n=452) who began taking OTC ibuprofen than prescribed ibuprofen (n=169). However, in the naproxen new user population, new prescription naproxen use was more common (n=246) than OTC naproxen use (n=128). Some behavioral factors, such as higher levels of intentional exercise and rates of health insurance coverage, were higher among OTC NSAID users as compared to prescription NSAID users.

OTC aspirin use was always more common than prescription aspirin use through-out study follow-up (Table 2). Among participants who did not report aspirin use at baseline, 10.9% of participants reporting taking prescribed aspirin during follow-up. In contrast, 28.2% of participants not taking aspirin at baseline reported taking OTC aspirin over the course of the study. Most of the aspirin that was reported in the medication inventory was low dose aspirin; 78.3% of the prescribed aspirin and 76.0% of the OTC aspirin users reported using pills that were under 100 mg per tablet.

Prevalent users of ibuprofen (Table 3) and naproxen (Table 4) are also much more likely to be of European descent. Both ibuprofen and naproxen have lower levels of utilization in the MESA cohort than aspirin. The absolute level of naproxen use is less than that of ibuprofen and naproxen appears much more likely to be prescribed than taken as an OTC medication in this population. Naproxen also differs in that participants of African American and European descent have similar levels of utilization in the MESA population (as opposed to aspirin and ibuprofen – for these drugs we observe that utilization by African American participants is lower than by participants of European descent).

The characteristics associated with less OTC aspirin use (Table 5) among new users included Asian (Relative Risk (RR): 0.80; 95% Confidence Interval (CI): 0.70–0.91), African-American (RR: 0.83;95% CI:0.77, 0.90) or Hispanic (RR: 0.72;95% CI:0.6– 0.80) ethnicity, male gender (RR: 0.92;95% CI:0.86–0.98), use of lipid lowering drugs (RR: 0.88; 95% CI: 0.80–0.96) and low income (RR: 0.89; 95% CI: 0.81–0.97). Increased OTC aspirin use was associated with participants being one standard deviation above average in intentional exercise (RR:1.03; 95% CI: 1.01– 1.05). There was also an association between decreased OTC aspirin use and each decade of increased age (RR:0.96; 95% CI: 0.93–1.00) and with having diabetes (RR:0.89; 95% CI: 0.80–0.99), but the statistical significance of these findings was borderline.

Table 5 also presents the characteristics of new use of OTC ibuprofen and OTC naproxen in those sub-cohorts as well. Ethnicity remains an important characteristic that is associated with OTC NSAID use. OTC ibuprofen use (as compared to prescription ibuprofen use) was associated with graduate level education (RR: 1.14, 95% CI: 1.02–1.27) and antihypertensive medication use (RR: 0.88, 95% CI: 0.78–0.99). OTC naproxen use was statistically significantly associated with very high levels of income of > $100,000 per year

(RR: 1.21, 95% CI: 1.01–1.43) and a higher systolic blood pressure (RR: 1.05, 95% CI: 1.00–1.10 for a 10 mmHG increase).

DISCUSSION

In the MESA cohort, OTC NSAID use was more common than prescribed NSAID use for both aspirin and ibuprofen. Furthermore, there are differences in socio-economic status, behavioral factors (such as intentional exercise) and ethnicity between OTC NSAID users and prescribed NSAID users.

These differences between prescription and OTC drug use may have consequences for the interpretation of studies set in computerized databases. Furthermore, the use of OTC NSAIDS was associated with other major CVD risk factors including other medication use, income, systolic blood pressure, and diabetes. These may impede the interpretation of NSAID studies in computerized databases with a cardiovascular endpoint. There were also demographic differences (such as higher income levels and higher levels of intentional exercise) between OTC and prescription NSAID users that are potentially important for studies of cardiovascular disease as they may also be related to the outcome under study. These differences make using prescription NSAID medications as a proxy for all NSAID medications vulnerable to differential misclassification in studies of cardiovascular endpoints.

Furthermore, classifying NSAID exposure status by prescriptions alone would also result in differential misclassification by ethnicity (Table 2). Let us consider aspirin as an illustrative example. At baseline, a prescription claims approach to indentifying aspirin users would indicate that 4.8% of participants of European descent were aspirin users. However, the actual proportion of this population that is exposed to aspirin would be 39.9% (eight times higher than the estimate of prevalence that is obtained using the claims approach). This difference between using a prescriptions claims approach and medication inventory approach demonstrates that a prescription claims approach would misclassify 88% of “actual” aspirin users as being unexposed to the agent. In contrast, among Asian participants, a prescription claims approach would identify 6.5% of participants as aspirin users when the actual proportion exposed to aspirin would be 17.0%. This difference between approaches to assessing aspirin exposure gives a 62% misclassification of aspirin users among the Asian participants. The degree of difference between the two approaches (medication inventory versus prescriptions claims) represents an important level of exposure misclassification; examination of Table 2 would suggest that a prescription claims approach would indicate that more Asian participants are exposed to aspirin at baseline than those of participants of European descent. In actuality, the true level of aspirin exposure among participants of European decent is more than double that of the Asian participants. The use of prescriptions claims to identify aspirin users is clearly giving highly misleading estimates of the population rate of aspirin exposure.

This phenomenon has been seen in other contexts. When a drug becomes available OTC, this availability generally leads to a decline in the number of prescriptions that are reported in administrative databases [17]. This decline is generally interpreted as people switching from the prescribed version of the medication to the OTC version of the medication [17] and not an overall drop in utilization. In some classes of medication (such as statin class lipid lowering medications), this effect can be small with prescription volumes remaining relatively stable [17]. However, to return to our illustrative example, the total amount of OTC aspirin use seen in the MESA participants is much larger than the prescribed aspirin use. The overall rate of OTC aspirin use seen in the MESA study is consistent with the rates reported in previous cohort studies of OTC aspirin use [18,19] so it is unlikely that the high

rates of OTC medication use is highly unrepresentative of the general population. This suggests that any estimate of aspirin use based on prescriptions given or claimed may greatly underestimate the degree of aspirin use in the population under study.

As a consequence, prescription claims databases may not be the ideal setting to evaluate adverse drug effects when aspirin, ibuprofen or naproxen are acting as either the primary exposure, used to restrict the population, or modeled as a key confounding factor. Information on ethnicity, income and exercise are likely to be absent from most administrative and clinical databases [20]. This means that these NSAID users will be differentially misclassified across certain factors, such as ethnicity, that are thought to be independently associated with important clinical outcomes, such as cardiovascular disease [21]. Therefore, using prescribed NSAIDs as a proxy variable for overall NSAID use could result in misleading estimates of associations and is best avoided.

There are several limitations to this study. One, there may be potential under-reporting of medication use due to a failure by the participant to include a medication in the supply brought to a study visit. Two, drug exposure was sampled at visits that were approximately 18 months apart and information about treatments between visits is not available so this may misclassify some short term NSAID users as unexposed. Three, we have assumed that the time to new use is not confounding the decision to use prescription versus over the counter medications. Finally, we were unable to interpret baseline associations with NSAID use as there was no information on duration of use at baseline. This limitation made it impossible to separate characteristics that are associated with NSAID use and those that were associated with adherence to therapy for baseline NSAID users. It also made the causation of factors like blood pressure more difficult to assess as NSAID use, itself, may increase cardiovascular risk factors such as blood pressure [22]. To avoid the concerns raised by this limitation, this study focused on a new user design [23] which decreased our power to detect associations by reducing our sample size (due to the exclusion of prevalent users).

The use of OTC aspirin, ibuprofen and naproxen is common in this United States based cohort and is dependent on key demographic factors; some of the factors that predict OTC NSAID use are also associated with increased cardiovascular risk. The likely direction of this bias due to differential misclassification would be to reduce the magnitude of protective associations and to increase the magnitude of adverse associations of OTC NSAIDS with cardiovascular outcomes. Therefore, caution should be used in interpreting results of studies estimating the association between aspirin, ibuprofen or naproxen and a cardiovascular outcome when the assessment of aspirin exposure is based solely on prescription records or claims.

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Table 1

Description of new users of aspirin, ibuprofen and naproxen; comparing characteristics of participants reporting over the counter (OTC) medication use with those who report prescription (Rx) medication use. Data from the Multi-Ethnic Study of Atherosclerosis.

	OTC Aspirin User (n=1127)	Prescription Aspirin User (n=435)	OTC Ibuprofen User (n=452)	Rx Ibuprofen User (n=169)	OTC Naproxen User (n=128)	Rx Naproxen User (n=246)
African American Ethnicity	26.4%	31.0%	1.6%	32.5%	33.3%	26.6%
Asian Ethnicity	7.5%	12.0%	19.2%	7.7%	1.6%	2.3%
European Descent Ethnicity (reference)	47.5%	20.7%	60.0%	26.7%	54.9%	30.5%
Hispanic Ethnicity	18.7%	36.3%	19.2%	33.1%	10.2%	40.6%
Smoker	13.2%	13.3%	15.0%	18.9%	13.8%	11.7%
Ex Smoker	39.3%	37.2%	40.0%	26.0%	39.8%	35.9%
Non-Smoker (reference)	47.5%	49.5%	35.0%			
Male	45.6%	51.7%	39.8%	41.4%	39.4%	37.5%
Age (years) [Standard Deviation]	61.6 [9.7]	64.0 [9.7]	59.2 [9.7]	60.6 [9.7]	60.4 [9.9]	62.4 [10.1]
BMI (kg/m^2) [Standard Deviation]	28.8 [5.6]	29.1 [16.8]	28.7 [5.5]	29.4 [5.6]	30.3 [6.3]	30.2 [5.3]
Baseline antihypertensive Medication use	32.8%	42.8%	24.8%	37.2%	34.1%	39.8%
Baseline lipid lowering Medication use	14.0%	21.8%	13.5%	15.4%	17.1%	20.3%
Less than High School Education	13.8%	26.2%	10.6%	23.7%	8.5%	26.6%
High School Education	47.3%	53.8%	45.8%	55.0%	54.5%	47.6
College Education	19.4%	15.2%	20.1%	13.0%	19.1%	11.7%
Graduate School	19.5%	12.4%	23.5%	8.3%	17.9%	14.1%
Income < $25,000	28.3%	49.0%	24.3%	44.4%	23.2%	46.9%
Income ≥$ 25,000 and ≤ $50,000	28.1%	24.8%	55.1%	30.8%	31.7%	27.3%
Income >$ 50,000 and ≤ $100,000	29.6%	17.0%	30.1%	18.3%	26.8%	21.1%
Income > $100,000	14.0%	9.2%	17.5%	6.5%	18.3%	4.7%
No Health Insurance	5.4%	10.6%	6.4%	14.2%	3.7%	14.1%
Diabetes	13.3%	24.4%	8.4%	12.4%	9.3%	18.8%
Sedentary activities (MET-min/wk) [Standard Deviation]	1720 [1138]	1739 [1169]	1773 [1257]	1672 [1138]	1912 [1187]	1745 [1237]
Intentional exercise (MET-min/wk) [Standard Deviation]	2738 [3274]	2127 [2584]	2314 [2496]	2247 [2656]	2446 [2464]	2026 [2541]

	OTC Aspirin User (n=1127)	Prescription Aspirin User (n=435)	OTC Ibuprofen User (n=452)	Rx Ibuprofen User (n=169)	OTC Naproxen User (n=128)	Rx Naproxen User (n=246)
Systolic Blood Pressure (mmHG)	127 [21]	132 [21]	123 [21]	127 [20]	127 [21]	127 [22]
Diastolic Blood Pressure (mmHG)	73 [11]	73 [10]	71 [10]	72 [9]	72 [10]	72 [10]

Table 2

Pattern of use of prescription (Rx) and over the counter (OTC) NSAIDuse as reported by medication inventory among the 5655 participants who were present for all follow-up visits. Data from the Multi-Ethnic Study of Atherosclerosis.

Exam	Aspirin (OTC)	Aspirin (Rx)
Baseline Exam	23.9%	5.3%
First Follow-up	24.0%	9.2%
Second Follow-up	29.8%	5.9%
Third Follow-up	30.8%	7.2%

Exam	Ibuprofen (OTC)	Ibuprofen (Rx)
Baseline Exam	9.4%	2.2%
First Follow-up	6.6%	1.8%
Second Follow-up	6.2%	1.6%
Third Follow-up	6.1%	1.8%

Exam	Naproxen (OTC)	Naproxen (Rx)
Baseline Exam	1.6%	3.1%
First Follow-up	1.1%	2.2%
Second Follow-up	1.1%	2.6%
Third Follow-up	1.4%	2.7%

Table 3

Baseline characterstics of over the counter (OTC) medication use versus prescription medication use among the new users of aspirin, ibuprofen and naproxen in the Multi-Ethnic Study of Atherosclerosis: estimates of the Relative Risk (95% Confidence Interval) of starting an OTC versus a prescribed medication during follow-up

Parameter	Aspirin	Ibuprofen	Naproxen
African American Ethnicity	0.83 (0.77–0.90)	0.79 (0.69–0.91)	0.94 (0.80–1.10)
Asian Ethnicity	0.80 (0.70–0.91)	0.48 (0.27–0.87)	0.84 (0.47–1.51)
Hispanic Ethnicity	0.72 (0.66–0.82)	0.83 (0.71–0.98)	0.50 (0.35–0.70)
Smoker	1.02 (0.92–1.12)	1.00 (0.86–1.16)	1.09 (0.87–1.37)
Ex Smoker	1.01 (0.94–1.07)	1.13(1.03–1.25)	1.04 (0.89–1.20)
Male	0.92 (0.87–0.98)	0.96 (0.87–1.05)	0.98 (0.85–1.13)
Age (per 10 years)	0.96 (0.93–1.00)	0.97 (0.92–1.02)	1.00 (0.92–1.09)
BMI (per 5 kg/m^2)	1.01 (0.98–1.04)	0.98 (0.94–1.04)	1.05 (0.99–1.11)
Baseline anti-hypertensive Medication use	0.95 (0.89–1.02)	0.88 (0.78–0.99)	0.92 (0.79–1.08)
Baseline lipid lowering Medication use	0.88 (0.80–0.96)	0.99 (0.86–1.14)	0.87 (0.71–1.07)
Less than High School Education	0.96 (0.85–1.07)	0.93 (0.74–1.15)	0.96 (0.80–1.13)
College Education	0.98 (0.91–1.06)	1.11 (0.98–1.25)	0.95 (0.80–1.13)
Graduate School	1.01 (0.93–1.09)	1.14 (1.02–1.27)	0.89 (0.74–1.08)
Income < $25,000	0.89 (0.81–0.97)	0.95 (0.81–1.10)	0.87 (0.70–1.08)
Income >$ 50,000 and ≤ $100,000	1.03 (0.96–1.11)	1.06 (0.94–1.19)	0.96 (0.80–1.16)
Income > $100,000	0.95 (0.86–1.05)	1.12 (0.98–1.28)	1.21 (1.01–1.43)
No Health Insurance	0.86 (0.74–1.00)	0.92 (0.73–1.18)	0.71 (0.42–1.19)
Diabetes	0.89 (0.80–0.99)	1.02 (0.84–1.25)	0.92 (0.69–1.22)
Sedentary activities (1 standard deviation)	0.99 (0.94–1.03)	1.05 (0.98–1.12)	1.04 (0.93–1.16)
Intentional exercise (1 standard deviation)	1.03 (1.01–1.05)	0.98 (0.94–1.04)	1.04 (0.96–1.13)