CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Analgesic Use and the Risk of Hearing Loss in Men

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ABSTRACT

BACKGROUND: Hearing loss is a common sensory disorder, yet prospective data on potentially modifiable risk factors are limited. Regularly used analgesics, the most commonly used drugs in the US, may be ototoxic and contribute to hearing loss.

METHODS: We examined the independent association between self-reported professionally diagnosed hearing loss and regular use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen in 26,917 men aged 40-74 years at baseline in 1986. Study participants completed detailed questionnaires at baseline and every 2 years thereafter. Incident cases of new-onset hearing loss were defined as those diagnosed after 1986. Cox proportional hazards multivariate regression was used to adjust for potential confounding factors.

RESULTS: During 369,079 person-years of follow-up, 3488 incident cases of hearing loss were reported. Regular use of each analgesic was independently associated with an increased risk of hearing loss. Multivariate-adjusted hazard ratios of hearing loss in regular users (2+ times/week) compared with men who used the specified analgesic <2 times/week were 1.12 (95% confidence interval [CI], 1.04-1.20) for aspirin, 1.21 (95% CI, 1.11-1.33) for NSAIDs, and 1.22 (95% CI, 1.07-1.39) for acetaminophen. For NSAIDs and acetaminophen, the risk increased with longer duration of regular use. The magnitude of the association was substantially higher in younger men. For men younger than age 50 years, the hazard ratio for hearing loss was 1.33 for regular aspirin use, 1.61 for NSAIDs, and 1.99 for acetaminophen.

CONCLUSIONS: Regular use of aspirin, NSAIDs, or acetaminophen increases the risk of hearing loss in men, and the impact is larger on younger individuals.

 • *The American Journal of Medicine (2010) 123, 231-237*

KEYWORDS: Analgesics; Hearing loss; Prospective study

Hearing loss is the most common sensory disorder in the US and afflicts over 36 million people.[1] Data from the National Health and Nutrition Examination Survey (NHANES) demonstrate that not only is hearing loss highly prevalent among the elderly, but approximately one third of those aged 40-49 years already suffer from hearing loss.[2] The 5-year incidence of developing hearing loss in adults aged 48 years and older is 21%.[3] Even mild hearing loss can compromise the ability to understand speech in the presence of background noise or multiple speakers, leading to social isolation, depression, and poorer quality of life.[4-7]

Aspirin, acetaminophen, and ibuprofen are the 3 most commonly used drugs in the US.[8] Although 17% of the total population uses aspirin at least weekly, over 28% of men aged 45 years and above are aspirin users. Similarly, acetaminophen is used at least weekly by 23% of the population and ibuprofen is used by 17%.[8] The ototoxic effects of high doses (several grams per day) of salicylates, reversible hearing loss and tinnitus, are well documented.[9] In contrast, low-dose salicylate has been reported to protect against aminoglycoside[10] and noise-[11] induced hearing loss, possi-

Funding: This work was supported by National Institutes of Health grant P01 CA055075 and the Massachusetts Eye and Ear Infirmary Foundation, Boston, Mass.

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of Interest: The authors have no conflicts of interest to report.

Authorship: All authors had access to the data and a role in writing the manuscript.

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0002-9343/$ -see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.amjmed.2009.08.006

bly through an effect on the outer hair cell motor protein or inhibition of cyclooxygenage.[12] High doses of nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to be ototoxic in animals and in human case reports,[13] potentially through a reduction in cochlear blood flow.[9] Pre-exposure to salicylates and NSAIDs might potentiate noise-induced hearing loss.[14,15] Acetaminophen might deplete glutathione,[16] which has been shown to protect the cochlea from noise-induced damage.[17,18] The relation between acetaminophen and hearing loss has not been studied.

Given that analgesic use might result in pathophysiologic changes in the cochlea and that regular use of these analgesics is so common, the relation of these medications and hearing loss might be an important public health issue. Therefore, we prospectively examined the association between regular analgesic use and risk of hearing loss in over 26,000 men.

CLINICAL SIGNIFICANCE

- Hearing loss is the most common sensory disorder in the US and factors other than age and noise might influence the risk of hearing loss.
- Regular use of aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs, the most commonly used drugs in the US, might increase risk of hearing loss.
- The increased risk of hearing loss associated with regular analgesic use might be greater among younger men, particularly those below age 60 years.

METHODS

Participants

The Health Professionals Follow-up Study originally enrolled 51,529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians who were 40-75 years of age at baseline in 1986. Study participants filled out detailed questionnaires about diet, medical history, and medication use. These questionnaires have been administered every other year, and the 20-year follow-up exceeds 90%. The 2004 long-form questionnaire included a question about whether the participant had been professionally diagnosed with hearing loss, and if so, the date of diagnosis. Of the 31,496 men who returned the long-form questionnaire, 8291 (26.3%) reported a diagnosis of hearing loss. Those who reported hearing loss diagnosed before 1986 (n = 2845) or cancer other than nonmelanoma skin cancer (due to possible exposure to ototoxic chemotherapeutic agents) were excluded from the analysis. Recent data from NHANES demonstrate that 43% of white men aged 60-69 years exhibit low- to mid-frequency hearing loss and 93% exhibit high-frequency hearing loss.[2] Thus, because age is such a strong risk factor and the prevalence of hearing loss is so high among the elderly, we also excluded men as they reached age 75 years during follow-up. The number of men included in the analysis was 26,917.

Ascertainment of Analgesic Use

On the 1986 questionnaire and every 2 years thereafter, men were asked about regular use, defined as 2 or more times per week, of aspirin, NSAIDs, and acetaminophen. Our primary analyses examined regular analgesic use. If information on analgesic intake was missing for a time period, person-time for that participant was not included for that time period. Analgesic use assessed in this manner has been shown to be associated with a number of important outcomes in this cohort, such as colorectal cancer[19] and hypertension.[20]

Ascertainment of Outcome

The primary outcome, self-reported professionally diagnosed hearing loss, was determined based on the response to a hearing loss question on the 2004 long-form questionnaire. The question asked whether the participant had ever had professionally diagnosed hearing loss and the year of first diagnosis.

We defined incident cases as hearing loss diagnosed after 1986. Although standard pure-tone audiometry is generally considered the gold standard of hearing loss evaluation, due to the cost and logistic limitations of audiometric screening, several survey instruments have been developed to evaluate large populations. Studies that have compared the reliability of self-report to the gold standard of audiometry[21-24] demonstrate that self-reported hearing loss is a reasonably reliable measure of hearing loss.[21] For example, based on NHANES data using the definition of hearing loss to be a pure-tone average (at 500, 1000, 2000, and 4000 kHz) ≥25 dB in both ears, the sensitivity was 65% and the specificity was 83% in a comparison of self-report to audiometry.[2]

Ascertainment of Covariates

We selected covariates that have been purported to be risk factors for hearing loss. Covariates considered in the multivariate analysis included: age,[2] race,[2] body mass index (BMI),[25] alcohol intake,[26] folate intake,[27] physical activity,[28] smoking,[26] hypertension, diabetes,[29] cardiovascular disease,[30] elevated cholesterol,[30] and use of furosemide.[31]

Age and race were obtained from biennial questionnaires. Height and weight were obtained from the baseline questionnaire, with self-reported weight updated every 2 years. BMI was calculated as weight in kilograms divided by the square of height in meters. Information on smoking status and physical activity was updated every 2 years. Intakes of alcohol and folate were calculated from semi-quantitative food frequency questionnaires that were mailed to participants every 4 years. Information on other covariates was available from the biennial questionnaires, including diagnoses of hypertension, diabetes mellitus, cardiovascular disease, elevated cholesterol, and use of furosemide.

Questionnaire-derived information has been validated for many of the covariates by comparison with directly

measured values or detailed diaries, with correlations of 0.97 for weight,[32] 0.79 for physical activity,[33] and 0.9 for alcohol intake.[34]

Statistical Analysis

All analyses were prospective, using information on analgesic use that was collected before the diagnosis of hearing loss. For the primary analyses, the frequency of use of a particular analgesic was categorized as regular users (2 or more times per week) or nonregular users (less than twice per week). For each participant, person-time was allocated based on the response to the analgesic questions at the beginning of each follow-up period. Participants were censored at the date of diagnosis of hearing loss or cancer, age 75 years, or the date of death, whichever came first. Age- and multivariable-adjusted hazard ratios (HRs) were calculated using Cox proportional hazards regression models. Multivariable models were adjusted for potential confounders listed above as well as simultaneously for use of the other analgesic types.

To examine whether the relation between regular analgesic use and hearing loss varied by age, we performed analyses stratified by age <50 years, 50-59 years, and 60 years and older.

Secondary analyses examined the association between duration of regular analgesic use and hearing loss. Duration of regular aspirin use was categorized according to years of regular use (0, 1-4, 5-8, >8). For NSAIDs and acetaminophen, duration of regular use was categorized similarly; however, the highest categories were collapsed into a category of >4 years of regular use, as too few cases were in the categories of longer duration. We also examined whether the relation between hearing loss and regular analgesic use varied with concomitant regular use of more than one class of analgesic. Analgesic use was categorized as regular use of all 3 classes of analgesics, regular use of aspirin and NSAIDs only, NSAIDs and acetaminophen only, aspirin and acetaminophen only, aspirin only, NSAIDs only, acetaminophen only, or no regular analgesic use.

For all HRs, we calculated 95% confidence intervals (CIs). All *P* values are 2-tailed. Statistical tests were performed using SAS statistical software, version 9 (SAS Institute Inc, Cary, NC).

RESULTS

Characteristics of participants at baseline according to analgesic use are shown in Table 1. Although updated information was used for the analysis, characteristics are presented from baseline to provide representative values. Regular aspirin and NSAID users were older and acetaminophen users were younger than nonregular users. Hypertension was more common among regular analgesic users. It was common for an individual to use more than one type of analgesic regularly.

During 369,079 person-years of follow-up, 3488 cases of hearing loss were reported. Regular analgesic use was independently associated with an increased risk of hearing loss for all 3 types of analgesics (Table 2). After adjusting for age, race, profession, BMI, alcohol intake, folate intake, physical activity, smoking, hypertension, diabetes, and the use of the other classes of analgesics, the multivariate HRs of hearing loss in participants who were regular users com-

Table 1 Characteristics of Men According to Analgesic Use in 1986

	Aspirin Regular Use		NSAID Regular Use		Acetaminophen Regular Use	
Variable	Yes n = 7217	No n = 19,700	Yes n = 1311	No n = 25,606	Yes n = 1439	No n = 25,478
Age, years	52.5	50.6	52.0	51.1	49.6	51.2
Race, %						
African American	0.5	0.9	0.7	0.8	0.5	0.8
Asian	0.7	1.8	0.7	1.6	1.0	1.6
Body mass index, kg/m^2	25.5	25.3	26.0	25.3	25.4	25.3
Alcohol, g/d	13	11	12	11	11	11
Folate, μg/d	493	469	484	476	497	475
Physical activity, mets/wk	21	22	23	22	18	22
Hypertension, %	21	16	21	17	20	17
Diabetes, %	2	2	2	2	1	2
Smoking never, %	45	50	40	49	43	49
Smoking past, %	46	37	52	39	39	47
Smoking current, %	8	8	8	8	9	8
Aspirin use, %	—	—	39.6	26.2	47.3	25.7
NSAID use, %	7.2	4.0	—	—	14.0	4.4
Acetaminophen use, %	9.4	3.9	15.3	4.8	—	—

mets/wk = metabolic equivalent tasks per week; NSAID = nonsteroidal anti-inflammatory drug.
Regular use is defined as at least 2 times per week.
Values are means unless otherwise specified.

Table 2 Age- and Multivariate-adjusted Hazard Ratios (95% CI) for Analgesic Use and Incident Hearing Loss

Analgesic Medication	Cases	Person-years	Age-adjusted Hazard Ratio	Multivariate Hazard Ratio*
Aspirin				
<2 per week	1769	213,831	1.0	1.0
2+ per week	1711	154,412	1.13 (1.06-1.21)	1.12 (1.04-1.20)
NSAIDs				
<2 per week	2852	320,467	1.0	1.0
2+ per week	636	48,612	1.38 (1.27-1.50)	1.21 (1.11-1.33)
Acetaminophen				
<2 per week	3214	347,362	1.0	1.0
2+ per week	274	21,717	1.32 (1.17-1.50)	1.22 (1.07-1.39)

NSAID = nonsteroidal anti-inflammatory drug.
*Adjusted for age, body mass index, alcohol, physical activity, folate, smoking, hypertension, diabetes, profession, and race, as well as the other analgesics.

pared with participants who used the specified analgesic less than twice per week were 1.12 (95% CI, 1.04-1.20) for aspirin, 1.21 (95% CI, 1.11-1.33) for NSAIDs, and 1.22 (95% CI, 1.07-1.39) for acetaminophen. When further adjusted for history of elevated cholesterol, cardiovascular disease or use of furosemide, or after exclusion of individuals with rheumatoid arthritis or osteoarthritis, the results were materially unchanged.

For NSAIDs and acetaminophen, the risk of hearing loss increased with longer duration of regular use (Table 3). Those who used aspirin regularly for 1-4 years were 28% (95% CI, 17-40) more likely to develop hearing loss than those who did not use aspirin regularly; the risk did not increase further with longer duration of use. Those who used NSAIDs regularly for 4 or more years were 33% (95% CI, 18-49) more likely to develop hearing loss than those who did not use NSAIDs regularly. The risk of 4 or more years of regular acetaminophen use also was 33% (95% CI, 14-56) higher.

The association between hearing loss and regular use of aspirin (P, interaction = .005), NSAIDs (P, interaction = .10), and acetaminophen (P, interaction = .09) varied by age (Table 4). For each class of analgesic, the magnitude of the association tended to decrease with advancing age. For aspirin, regular users aged <50 years and those aged 50-59 years were 33% more likely to have hearing loss than were nonregular users, but there was no association among men aged 60 years and older. For NSAIDs, regular users aged <50 years were 61% more likely, those aged 50-59 years were 32% more likely, and those aged 60 years and older were 16% more likely to develop hearing loss than nonregular users of NSAIDs. For acetaminophen, regular users aged <50 years were 99% more likely, regular users aged 50-59 years were 38% more likely, and those aged 60 years and older were 16% more likely to have hearing loss than nonregular users of acetaminophen.

The association between hearing loss and concomitant use of more than one class of analgesic appeared to be

Table 3 Age and Multivariate Adjusted Hazard Ratios (95% CI) for Hearing Loss According to Duration of Analgesic Intake

Duration of Use (Years)	Cases	Person-years	Age-adjusted Hazard Ratio	Multivariate Hazard Ratio*
Aspirin				
0	1042	156,188	1.0	1.0
1-4	1122	108,177	1.35 (1.24-1.46)	1.28 (1.17-1.40)
5-8	687	56,431	1.34 (1.22-1.48)	1.30 (1.17-1.44)
>8	637	48,282	1.26 (1.14-1.40)	1.17 (1.04-1.31)
NSAIDs				
0	2409	284,706	1.0	1.0
1-4	721	59,774	1.30 (1.20-1.42)	1.23 (1.12-1.34)
>4	358	24,600	1.41 (1.26-1.57)	1.33 (1.18-1.49)
Acetaminophen				
0	2897	320,893	1.0	1.0
1-4	420	36,348	1.23 (1.11-1.36)	1.19 (1.07-1.32)
>4	171	11,838	1.39 (1.19-1.62)	1.33 (1.14-1.56)

NSAID = nonsteroidal anti-inflammatory drug.
*Adjusted for age, body mass index, alcohol, physical activity, folate, smoking, hypertension, diabetes, profession, and race, as well as the other analgesics.

Table 4 Analgesic Use and the Age-adjusted and Multivariate* Hazard Ratios (95% CI) for Incident Hearing Loss Stratified by Age

Analgesic	Age <50 Years	Age 50-59 Years	Age 60+ Years
Aspirin			
Age-adjusted	1.32 (1.02-1.69)	1.36 (1.20-1.54)	1.03 (0.94-1.12)
Multivariate	1.33 (1.03-1.72)	1.33 (1.17-1.50)	1.02 (0.93-1.11)
NSAIDs			
Age-adjusted	1.59 (1.14-2.23)	1.35 (1.15-1.58)	1.17 (1.04-1.31)
Multivariate	1.61 (1.15-2.26)	1.32 (1.13-1.55)	1.16 (1.03-1.30)
Acetaminophen			
Age-adjusted	1.91 (1.29-2.82)	1.37 (1.09-1.73)	1.17 (0.99-1.37)
Multivariate	1.99 (1.34-2.95)	1.38 (1.09-1.74)	1.16 (0.99-1.37)

NSAID = nonsteroidal anti-inflammatory drug.
*Adjusted for age, body mass index, alcohol, physical activity, folate, smoking, hypertension, diabetes, profession, and race, as well as the other analgesics.

approximately additive (Table 5). For the combined use of 2 analgesics, the risk was highest for use of NSAIDs and acetaminophen (HR 1.58 [95% CI, 1.16-2.16]), as compared with those who did not use any of the analgesics regularly. This risk was similar to the impact of regular use of all 3 analgesics (HR 1.60 [95% CI, 1.23-2.09]).

DISCUSSION

Regular analgesic use was independently associated with an increased risk of hearing loss. The increased risk of hearing loss seen with regular analgesic use was greatest among younger men, particularly those below age 60 years. In men aged 60 years and above, there was no relation observed between the risk of hearing loss and regular aspirin use, and the relation between regular use of NSAIDs and acetaminophen was attenuated. The risk of hearing loss increased with longer duration of analgesic use for both NSAIDs and acetaminophen.

The ototoxic effects of high-dose salicylates, reversible hearing loss and tinnitus, are well documented.[9] In animal models, salicylate administration results in abnormal outer hair cell function and decreased cochlear blood flow.[9] Salicylates induce biochemical and electrophysiological changes that alter membrane conductance of outer hair cells[35] and vasoconstriction in auditory microvasculature, possibly mediated by antiprostaglandin activity.[36]

High doses of NSAIDs also have been reported to be ototoxic in animal studies and in human case reports.[15] Similar to salicylates, NSAIDs inhibit cyclooxygenase and decrease prostaglandin activity, potentially reducing cochlear blood flow.[9]

Histopathologic studies of human temporal bones[37] and in animals show degeneration of strial microvasculature.[38] These studies suggest that vascular compromise, such as that which may result from salicylate or NSAID use, contributes to strial degeneration. Degeneration of the stria vascularis, a highly vascularized and metabolically active region of the cochlea, is a notable pathophysiologic change characteristic of age-related hearing loss[39] that may reduce the endolymphatic potential and the function of the cochlear amplifier.

The relation between acetaminophen and hearing loss has not been studied previously. Frequent use of acetaminophen has been associated with hypertension[20,40,41] and chronic renal dysfunction.[42,43] Acetaminophen use increases risk of renal function decline, potentially due to depletion of glutathione.[16] Acetaminophen also might deplete endogenous cochlear glutathione, which is present in the cochlea in substantial amounts and protects the cochlea from noise-induced damage.[17,18]

The prevalence of hearing loss increases with age.[44] After age 60 years, hearing thresholds worsen on average by

Table 5 Age- and Multivariate-adjusted Hazard Ratios (95% CI) for Concomitant Regular Use of More Than 1 Type of Analgesic and Incident Hearing Loss

Analgesic	Cases	Person-years	Age-adjusted Hazard Ratio	Multivariate Hazard Ratio*
None	1378	182,380	1.0	1.0
All 3 analgesics	60	3809	1.75 (1.35-2.26)	1.60 (1.23-2.09)
NSAIDs + acetaminophen	43	3015	1.72 (1.27-2.32)	1.58 (1.16-2.16)
Aspirin + acetaminophen	97	7769	1.44 (1.17-1.76)	1.40 (1.13-1.73)
Aspirin + NSAIDs	250	19,832	1.37 (1.20-1.57)	1.25 (1.09-1.44)

NSAID = nonsteroidal anti-inflammatory drug.
*Adjusted for age, body mass index, alcohol, physical activity, folate, smoking, hypertension, diabetes, profession, race, and all categories of analgesic use.

1 dB per year,[45] and the rate of decline might be even greater in men aged 48-59 years.[46] The magnitude of the relation between regular analgesic use and hearing loss was greatest in men younger than age 60 years. Possibly, the relative contribution of regular analgesic use to hearing loss may be greater in younger individuals before the cumulative effects of age and other factors have accrued. A similar impact of age on the relative contribution of diabetes to hearing loss was seen by Bainbridge et al.[29]

The risk of hearing loss increased with longer duration of regular use of NSAIDs and acetaminophen, but not of aspirin. However, years of use were counted from the 1986 baseline questionnaire when the mean age of participants was 51 years. Thus, those who reported 11 or more years of aspirin use were older. As the relation between analgesic use and hearing loss diminished with increasing age, this likely explains the lack of association between longer duration of aspirin use and hearing loss.

The impact of regular use of multiple analgesics appeared to be additive. This raises the possibility that the different classes of analgesics may impair auditory function through different mechanisms.

Our study has limitations. Assessment of hearing loss was based on self-report of professionally diagnosed hearing loss, and individuals who did not report hearing loss were considered not to be hearing impaired. Although standard pure-tone audiometry is generally considered the gold standard of hearing loss evaluation, self-reported hearing loss has been demonstrated to be a reliable assessment. Moreover, participants were specifically queried as to whether they had been "professionally diagnosed" with hearing loss, a more objective measure than the frequently used single question, "Do you feel you have a hearing loss?" Nevertheless, given the high prevalence of hearing loss in men of this age group,[2] there may have been misclassification of outcome.

We also did not have information on lifetime noise exposure or reasons for analgesic use. Noise is a common cause of hearing loss, and its targets overlap with those that may be compromised by analgesics. Moreover, noise exposure might increase the vulnerability to hearing loss related to age[47-49] or other causes.[50] A study of patterns of medication use in the US found that 58% of older men reported that cardiovascular prophylaxis was the most common reason for aspirin use. Other reasons for use of over-the-counter medications, of which acetaminophen, ibuprofen, and aspirin were the most common, included headache and pain.[8] We did not find any published reports relating common headache with hearing loss. Although migraine headaches might be associated with temporary hearing loss,[51] the prevalence of migraine headaches in men in the US is low (6%),[52] thus unlikely to explain our findings. Autoimmune diseases, such as rheumatoid arthritis, might cause hearing loss,[53] but these conditions are extremely rare in men and unlikely to have influenced our results. Hypertension might increase the risk of hearing loss due to changes in the cochlear microvasculature,[54] as might cardiovascular disease, such as stroke, coronary heart disease, and intermittent claudication;[30] however, we adjusted for these in our analyses and our results were not materially changed.

The present study was carried out in a population of predominantly white men, thus the results might not be generalizable to other racial groups. Although the participants in this cohort might not be representative of the adult population in the US, follow-up rates are high and information provided is reliable. The observed associations are likely to apply to other groups inasmuch as the underlying biologic and pharmacologic mechanisms are likely to be similar. However, additional studies are needed to examine these associations in women, younger men, and other racial groups.

Regular use of analgesics, specifically aspirin, NSAIDs, and acetaminophen, might increase the risk of adult hearing loss, particularly in younger individuals. Given the high prevalence of regular analgesic use and health and social implications of hearing impairment, this represents an important public health issue.

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