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Impact of Nonaspirin Nonsteroidal Anti-inflammatory Agents and Acetaminophen on Sensorineural Hearing Loss: A Systematic Review

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Abstract

Objective—To perform a systematic review evaluating the association between sensorineural hearing loss and (1) nonsteroidal anti-inflammatory drugs (NSAIDs) as a class, (2) NSAIDs available over the counter, (3) NSAIDs in short intravenous courses, (4) prescription NSAIDs utilized by patients without systemic inflammatory conditions, (5) prescription NSAIDs in patients with arthritides, and (6) acetaminophen with and without concomitant narcotic usage.

Data Sources—Computerized searches of PubMed, EMBASE, and the Cochrane Library were updated through May 2014, along with manual searches and inquiries to topic experts.

Review Methods—The systematic review was performed according to an a priori protocol. Data extraction was performed by 2 independent investigators, and it focused on relevant audiologic measurements, methodological elements related to risk of bias, and potential confounders.

Results—The 23 criterion-meeting studies included a total of 92,532 participants, with mixed results. Sulindac was the only specific agent to have been studied with formal audiometry in a randomized double-blind placebo-controlled trial in which hearing was the reported primary outcome: Although an effect was seen in the unadjusted analysis (pure tone threshold > 15 dB, 9.3% vs 2.9%; relative risk [RR], 3.2; confidence interval [CI], 1.09-9.55; $P = .02$), the effect dissipated in the adjusted analysis ($P = .09$). There was a significant effect on self-reported hearing loss from NSAIDs as a class (RR, 1.21; CI, 1.11-1.33), ibuprofen (RR, 1.13; CI, 1.06-1.19), and acetaminophen (RR, 1.21; CI, 1.11-1.33), but no formal audiometric data confirm or refute this

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Author Contributions

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suggested effect. Audiometry has demonstrated profound loss in some instances of acetaminophen-narcotic combination ingestions.

Conclusions—Data are varied regarding the impact of NSAIDs and acetaminophen on population hearing health.

Keywords

nonsteroidal anti-inflammatory drugs; indomethacin; ibuprofen; sulindac; pirofen; naproxen; piroxicam; ketorolac; fenoprofen; diflunisal; sulindac; acetaminophen; hearing loss

Introduction

Nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are the 2 most commonly utilized medications,¹ widely recognized for their analgesic, antipyretic, and anti-inflammatory properties.^{2,3} Among adults, 7% to 24% of survey responders report taking ibuprofen in the previous week, while 16% to 28% describe taking acetaminophen in that time frame.¹ Among adolescent girls and young women (age, 14-21 years), 66% experiencing menstrual discomfort use a combination of NSAIDs or acetaminophen, with 42% using ibuprofen and 95% taking acetaminophen.⁴ Among children 6 to 11 years of age, 9% and 7% have taken ibuprofen and acetaminophen, respectively, in the prior week.⁵ Among 3-year-old children, 53.7% have received an over-the-counter medication, two-thirds of which is acetaminophen.⁶ These medications are available over the counter, by prescription, and in myriad drug combinations; as such, their usage may increase even further as their potential role in decreasing mortality and malignancy is further investigated.^{7,8}

Hearing loss is the most common sensory disorder.^{9,10} More than 278 million people worldwide are affected by moderate to profound hearing loss.¹¹ While 31.5 million American adults self-reported hearing loss in 2000, that number increased to 37 million in 2006.⁹ In addition, serial data from the National Health and Nutrition Examination and Survey suggests that the prevalence of measured audiometric deficits has grown in recent years.¹⁰ In estimates looking forward to 2030, the World Health Organization expects that hearing disorders will rise within the top 10 causes of burden of disease in high- and middle-income countries and that the number of associated disability-adjusted life years will increase.¹²

While some hearing loss may result from genetic and congenital causes, a notable proportion is acquired.¹³ Remarkably, estimates suggest that half of hearing loss cases are preventable,^{14,15} making identification of related, modifiable risk factors a matter of clear importance for developing preventative strategies for public health. The widespread nature of hearing loss (20% of adolescents¹⁰ and 60% of septuagenarians¹⁶) suggests that causative exposures are far-reaching, crossing demographic, ethnic, and socioeconomic boundaries. Exposure to NSAIDs and acetaminophen is all but ubiquitous, and these agents have been available over the counter since 1983 and 1960, respectively. If data demonstrate that they play a role in the development of hearing loss, then the public health impact may be

enormous. If they are not, then the demonstrated audiologic safety is likewise important information for care-givers and consumers.

Patients may be driven to seek further information from their physicians after seeing health-relevant news broadcasts, and the potential relationship among NSAIDs, acetaminophen, and hearing loss is a topic that has made lay media headlines.^{17,18} With the desire to properly counsel patients and families with related inquiries, we embarked on a systematic review to evaluate the impact of NSAIDs and acetaminophen on hearing loss. Systematic reviews are distinct from traditional narrative reviews in that they are performed according to well-defined, rigorous procedures and provide a reproducible, thorough method to evaluate the current best evidence regarding a specific clinical question. As such, they often constitute the highest level of evidence available¹⁹⁻²¹ and form the foundation for high-impact documents, such as clinical practice guidelines.^{22,23} The objectives of this systematic review were to evaluate the association between hearing loss and (1) NSAIDs as a class, (2) NSAIDs available over the counter, (3) NSAIDs used in short intravenous courses, (4) prescription NSAIDs utilized by patients without systemic inflammatory conditions, (5) prescription NSAIDs in patients with arthritides, and (6) acetaminophen with and without concomitant narcotic usage.

Methods

Search Strategy

Computerized and manual searches were performed to identify all relevant data. A PubMed search of MEDLINE from 1965 to May 2014 was performed, updated through the latter date. Articles mapping to the exploded medical subject heading “hearing loss” or containing “hearing loss” in the title were combined into 1 group. Medical subject headings “anti-inflammatory agents,” “non-steroidal,” “ibuprofen,” “aspirin,” or “acetaminophen” were exploded, and the articles were collected into a second group. The 2 groups were then cross-referenced and limited to human studies in the English language. Parallel searches based on similar terms were performed in EMBASE and the Cochrane Library; the combined searches yielded 358 references. Titles and abstracts were then evaluated according to the inclusion and exclusion criteria described below. Reference lists for relevant narrative reviews and criteria-meeting publications were searched manually for additional studies. Two individuals blinded to each other's results performed searches independently. Topic experts were also contacted to determine if additional studies or unpublished data could be identified. Titles and abstracts for all identified studies were reviewed, and 23 articles were ultimately included in the analysis (**Figure 1**).

Inclusion and Exclusion Criteria

Articles identified by the strategy described above were evaluated relative to inclusion criteria: (1) patients of any age group, ethnicity, or socioeconomic background (patient population); (2) exposure to nonaspirin NSAIDs or acetaminophen of any dose, as confirmed via blood laboratory analysis, medical report, or self-report (intervention); (3) comparison to a control or non-NSAID/acetaminophen-exposed baseline data (comparison); and (4) hearing outcome measured via audiometry or related metric. Self-reported hearing

assessment was tracked in a separate group (outcomes). Any study design within the defined time frame was accepted.

Articles were excluded if (1) no hearing results were reported, (2) results focused on nonsensorineural hearing loss (eg, otitis media), (3) hearing results were unclear regarding the type of audiometric criteria used to determine hearing loss (ie, instances where it was unclear whether hearing results were determined via formal audiometry, self-reported hearing loss, or otherwise), (4) a population of solely nonhearing patients were evaluated (nonapplicable denominator), and (5) abstracts without subsequent full manuscript publication.

Data Extraction

Data extraction focused on items relevant to the study results, potential sources of heterogeneity among those results, and study identification (author, year of publication, full reference citation). Extracted data included (1) number or percentage with maintenance, improvement, or deterioration of hearing thresholds; (2) number of subjects in each group; (3) specific drug (or drugs) evaluated; (4) *P* value, confidence interval (CI), standard error of the mean, proportions, or descriptive statistics reported; and (5) follow-up time. Data collection also included multiple potential sources of heterogeneity among studies: dosing and duration of the drug regimen, control regimen details if applicable, audiologic criteria used for stratification of data, primary study end points, and study design. In accordance with data demonstrating that specific “study quality” ranking scales may be misleading or give heterogeneous results,²⁴⁻²⁷ rather than utilizing a summary scale, we focused on evaluation of data quality by consistent factual description of individual elements of study design with specific attention to the following: whether randomization was performed, prospective or retrospective analysis, incorporation of blinding (participants and/or assessors), whether hearing assessments were the primary outcome, and the type of hearing measurement.

Quantitative Data Analysis

An a priori plan was made to perform a meta-analysis if the data were permissive, with a goal of evaluating the following null hypotheses: (1) NSAIDs have no impact on the prevalence or pattern of sensorineural hearing loss; (2) acetaminophen has no impact on the prevalence or pattern of sensorineural hearing loss; and (3) any such impact of NSAIDs or acetaminophen is not dose or duration dependent. Ultimately, due to large variation in study designs, audiometric criteria, and reporting parameters, the data did not support a quantified pooled analysis.

If the primary study reported a statistical analysis, it was included in the extracted data. If the primary study did not describe a statistical comparison, post hoc calculations for the 95% CI of proportions were calculated according to the binomial distribution.

Results

The 23 criterion-meeting studies included a total of 92,532 participants. **Table 1** provides an overview of included studies; **Tables 2-10** describe their results and designs in detail. Two

studies evaluated multiple NSAIDs as a class, while 5 focused solely on those available over the counter (eg, ibuprofen, naproxen). Six reports evaluated either NSAIDs utilized perioperatively (ketorolac) or in brief intravenous courses (indomethacin). A range of studies evaluated oral NSAIDs, which were prescribed for systemic conditions (indomethacin, piroxicam, sulindac, diflunisal, pirofen, fenoprofen). Acetaminophen, either alone or in combination with narcotics, was evaluated in 6 publications. Studies designs spanned the range from randomized controlled trials to case reports. Audiometric evaluations included standard pure tone thresholds and speech discrimination scores, otoacoustic emissions, and psychophysical measurements. Nonaudiometric data consisted of self-reported hearing loss via survey results.

NSAIDs as a Class

Two studies evaluated multiple NSAIDs as a class, considering multiple agents in 1 analytic group (**Table 2**). The first of these was one of the largest of the criterion-meeting studies: an evaluation of a prospective observational cohort from the Health Professionals Follow-up Study (n = 26,917 adult males) with regard to general nonaspirin NSAID usage regularly (2 times per week) or nonregularly (2 times per week).²⁸ Self-reported hearing loss was measured every 2 years beginning in 1986; standard pure tone audiometry and speech scores were not collected. NSAID utilization was characterized by frequency and duration, without specific dose or agent information. Multivariable adjusted hazard ratio demonstrated that hearing loss was associated with NSAID consumption more than twice weekly (1.21; 95% CI, 1.11-1.33). The risk of hearing loss was increased with longer duration of regular usage (1-4 years: 1.23; 95% CI, 1.12-1.34; >4 years: 1.33; 95% CI, 1.18-1.49).²⁸

The second study was a prospective analysis of rheumatoid arthritis patients who were exposed to nonaspirin NSAIDs (exact agents not specified), along with methotrexate, D-penicillamine, Plaquenil, or a combination thereof. Standard pure tone and impedance audiometry were measured. There was no significant difference in hearing thresholds between the NSAID-exposed and unexposed groups; hearing was the primary outcome, although the sample size was limited (n = 45).²⁹

Individual NSAIDs

NSAIDs Available Over the Counter

Ibuprofen: Three publications addressed the impact of ibuprofen on hearing loss (**Table 3**). The first of these was the largest criterion-meeting study, conducted through the prospective Nurses' Health Study II cohort; it evaluated 62,261 adult women's self-reported hearing loss and consumption of ibuprofen.³⁰ Subjects responded to survey questions every 2 years from 1995 to 2009. Standard pure tone audiometry or speech scores were not measured. Those reporting tinnitus more than twice weekly were excluded from the analysis. The results demonstrated a significant association with self-reported hearing loss: multivariate adjusted risk ratio, 1.13 (95% CI, 1.06-1.19) for 2 to 3 days per week, 1.21 (95% CI, 1.11-1.32) for 4 to 5 days per week, and 1.24 (95% CI, 1.14-1.35) for 6 days per week.

The second study of ibuprofen was one of the few randomized controlled trials. This parallel study evaluated the impact of a 3-day course of oral versus intravenous ibuprofen in low

birth weight infants with patent ductus arteriosus, and it measured audiologic results as a dichotomous outcome: presence or absence of bilateral loss requiring amplification.³¹ None of the study subjects (n = 102 at outset, 57 at completion) required amplification at the 18- to 24-month follow-up. Hearing was not the primary outcome, and details of subsequent audiometry were not provided; however, it suggested that a 3-day course of ibuprofen was not associated with subsequent need for amplification.

The third publication focusing on ibuprofen was a simple case report; it was, however, the only relevant article that described standard pure tone audiometry results. Specifically, it described a 66-year-old woman who ingested ibuprofen (dose not specified) every 6 hours for 3 months and developed a sudden bilateral 30-dB worsening of pure tone thresholds, which was inferred to have occurred in a setting of an ibuprofen-induced aseptic meningitis.

Naproxen: Publications relevant to naproxen were limited to 2 case reports of sudden loss (**Table 4**). One occurred after just 4 doses of 500 mg at 12-hour intervals in an otherwise healthy young adult; this bilateral decrease to pure tone thresholds of 35 to 70 dB was unresponsive to prednisone and ultimately proved irreversible over a 6-month follow-up. The second occurred in an elderly man treated for seronegative arthropathy. He had a severe bilateral worsening of pure tone thresholds to 70 to 100 dB, which also proved irreversible over a 12-month follow-up.

NSAIDs Utilized Perioperatively: Ketorolac—Three case reports described hearing loss after ketorolac administration (**Table 5**). In each case, hearing loss occurred quickly after ketorolac administration, as measured by pure tone audiometry. Concurrent conditions included polyarteritis nodosa, end-stage renal disease, and general anesthetic exposure. One case was reversible (4 days after discontinuing ketorolac); 1 case was partially reversible; and 1 case was irreversible.

NSAIDs Utilized in Short Intravenous Courses in Infants: Indomethacin—Three related studies (2 randomized controlled trials and 1 inception cohort) evaluated the impact of a 3-day exposure to intravenous indomethacin in infancy (**Table 6**).³²⁻³⁴ The main study was a randomized placebo-controlled trial that evaluated low birth weight neonates (n = 1202) 12 to 21 months after treatment. Hearing loss was a secondary outcome, and the authors reported, “Audiometry was performed to determine the presence or absence of hearing loss. A central adjudication committee that was unaware of the group assignments reviewed the results of audiologic tests for all infants with potential deafness whose hearing had not been amplified.”³³ There was no difference in this hearing outcome between groups: 2% required amplification whether indomethacin or placebo was received (odds ratio, 1.0; 95% CI, 0.4, 2.5; $P = .93$).³³ A post hoc analysis of a subgroup of infants with antenatal corticosteroid exposure also demonstrated no difference in deafness 18 months after 3 days of indomethacin administration.³⁴ Another analysis of this group as an inception cohort determined that bronchopulmonary dysplasia and retinopathy were associated with hearing loss in both study arms combined.³²

Prescribed Oral NSAIDs in Patients without Inflammatory Systemic Disease—Six publications focused on NSAIDs available only by prescription (**Tables 7, 8**). Two

evaluated the impact of 1 NSAID on normal-hearing subjects without known inflammatory conditions (**Table 7**). The first of these was a phase III randomized placebo-controlled trial (n = 290) that evaluated a regimen of both sulindac (NSAID) and difluoromethylornithine (ornithine decarboxylase inhibitor) in patients with previously resected colonic adenomas.³⁵ Hearing was the primary outcome and was assessed via standard audiometry. Hearing loss was more frequent in the treatment arm versus placebo in the unadjusted analysis (9.3% vs 2.9%; relative risk, 3.2; 95% CI, 1.09-9.55; $P = .02$), but there was no difference between groups at 18 to 36 months in the multivariate analysis (0.99-dB difference between groups; CI, -0.17, 2.14; $P = .09$). Perhaps most important, there were no significant differences in clinically meaningful hearing loss, as there was a very small decibel difference between groups in the latter analysis.

The second study, based on a crossover design, evaluated the impact of sulindac or diflunisal on hearing results after noise exposure.³⁶ Intense sounds were presented to 11 normal-hearing subjects with administration of diflunisal (750 mg/d) or sulindac (400 mg/d). Psychophysical measurements were utilized to measure outcomes. There was no increase in audiometric thresholds noted beyond the temporary noise-induced hearing loss. In general, both drugs produced <5 dB of change in hearing sensitivity at any frequency prior to noise exposure.

Prescribed Oral NSAIDs in Patients with Arthritides—Two prospective studies evaluated the impact of NSAIDs on hearing in comparison to aspirin (**Table 8**). One of these was a randomized trial (n = 40) that compared the effects of pirofen to aspirin in rheumatoid arthritis patients on standard audiometric measurements.³⁷ There was no difference in new or progressive hearing loss between the 2 groups, although hearing loss was not the primary outcome.³⁷ The second study was a prospective double-blind controlled study of patients with rheumatoid arthritis, and it evaluated fenoprofen in comparison to placebo and aspirin. Subjects were interviewed to determine a related “auditory side effect score,” which was not further defined but was based on patient self-report.³⁸ The relative risk of hearing symptoms of fenoprofen relative to placebo was not reported. When fenoprofen and aspirin were compared, however, ear-related symptoms were significantly worse in the aspirin group. The remaining relevant publications were 2 case reports; each reported irreversible hearing loss after either indomethacin or piroxicam.

NSAIDs: Reversibility of Hearing Loss

NSAIDs with Reported Irreversible Hearing Loss—Indomethacin, naproxen, and piroxicam had reported episodes of irreversible sensorineural hearing loss.³⁹⁻⁴³ A flat, profound deficit that occurred 5 days into exposure was attributed to indomethacin,³⁹ as were 2 moderate to severe sensorineural hearing losses after 2 to 5 days; prednisone did not result in improvement.^{40,41} Piroxicam resulted in a moderate to severe loss 30 minutes after exposure.⁴² One episode of unilateral sudden loss occurred immediately after dental extraction under general anesthesia with postoperative ketorolac and morphine, so multiple agents may have been responsible.⁴³ In all cases, the medications were utilized within their accepted dosage parameters.

NSAIDs with Reported Reversible Hearing Loss—There have been reported episodes of reversible sensori-neural hearing loss after ketorolac and ibuprofen exposure.⁴⁴⁻⁴⁶ Hearing symptoms occurred 25 minutes to 48 hours after exposure to ketorolac at dosages within established ranges of clinical practice, and they returned at least partially within 4 to 9 days.^{44,45} Ibuprofen-related bilateral loss occurred after 3 months of taking the medication every 6 hours (milligram per dose not specified).⁴⁶

Acetaminophen

Acetaminophen: Audiometric Data—Published results with formal audiometric data surrounding acetaminophen ingestion are limited to 4 small case series and case reports (**Table 9**).⁴⁷⁻⁵⁰ In all instances, the affected subjects were also taking concomitant narcotics. One case series with chart review described 10 subjects who took acetaminophen with codeine for several years, often at doses exceeding standard recommendations; all experienced precipitous irreversible sensorineural hearing loss that progressed to the need for cochlear implantation.⁴⁷ Another report of 3 patients described similar findings with acetaminophen and codeine, although the reversibility of the hearing loss was not specifically recorded.⁴⁸ Excess usage of acetaminophen with hydrocodone and with oxycodone has also been associated with irreversible sensorineural loss in case reports.^{49,50} Thus, relevant publications with standard audiometric measurements are limited to small retrospective noncomparative series and case reports, but they have audiometric data showing a potential for a profound loss of hearing when acetaminophen is utilized in combination with narcotics. In addition, none of the reported cases were determined to be reversible.

Acetaminophen: Self-reported Hearing Loss—While there are no studies that evaluate the impact of acetaminophen in isolation on standard audiometry, there were 2 prospective observation cohort studies suggesting that regular acetaminophen usage was associated with an increased risk of self-reported hearing loss (**Table 10**).^{28,30} The Nurses' Health Study II evaluated the impact of acetaminophen on hearing in adult females and found that ingestion for 2 to 3 days per week and 4 to 5 days per week was statistically associated with self-reported hearing loss—multivariate adjusted analysis risk ratio, 1.11 (95% CI: 1.02, 1.19), 1.21 (95% CI: 1.07, 1.37), respectively—but usage on >6 days per week showed no significant difference: 1.08 (95% CI, 0.95-1.22 CI). Thus, there was not a clear dose-dependent effect.³⁰

The Health Professionals Follow-up Study demonstrated a multivariate hazard ratio of 1.22 (95% CI, 1.07-1.39) for regular use of acetaminophen in adult males. This risk of self-reported hearing loss increased with at least 4 years of regular acetaminophen use (hazard ratio, 1.33; 95% CI, 1.14-1.56). Thus, both female and male groups had similar results,^{28,30} but there are no correlating findings with standard audiometric measurements as of yet.

Study Designs and Risk of Bias

Among the 23 criterion-meeting publications (**Table 1**), 11 studies had a prospective design, and 4 trials were randomized. Eight studies employed blinding of the assessors, subjects, or both. Formal audiometry was measured as the primary outcome in only 3 instances, with the

remainder of reports describing audiometry as a secondary outcome or focusing on self-reported hearing. Self-reported hearing results inherently contain additional risks of bias, as described below.

Discussion

This systematic review evaluated the impact of NSAIDs and acetaminophen on sensorineural hearing loss. Overall, the data were frequently limited, by the method of hearing evaluation or sample sizes. These data also varied, demonstrating a measurable effect on self-reported symptoms from NSAIDs as a class, ibuprofen, and acetaminophen but without audiometric data to confirm this suggested audiometric effect. The specific agent sulindac was the only one to have been studied with formal audiometry in a randomized double-blind placebo-controlled trial in which hearing was the reported primary outcome: while an effect was seen in the unadjusted analysis, the effect dissipated in the adjusted analysis. Bilateral profound effects on hearing were noted in case reports of patients ingesting high doses of acetaminophen with narcotics.

When multiple NSAIDs were evaluated together, self-reported hearing results suggested an approximately 20% risk increase, but audiometric data have yet to corroborate these findings; the extent of the potentially associated hearing loss also remains uncharacterized. Similarly, self-reported hearing results regarding ibuprofen suggest a 13% to 24% associated increase in risk of hearing loss in large prospective studies, but studies with formal audiometric measurements have yet to confirm this finding. The relevant randomized trial showed no difference after a 3-day course of ibuprofen in infants but tracked the more extreme dichotomous outcome of bilateral hearing loss requiring amplification, making it unclear whether mild, moderate, or unilateral cases arose; in addition, hearing results were not the primary outcome, so the potential for a type II error for hearing results was not delineated. Thus, higher-level studies with formal audiometric data would be ideal; future dose-specific data could help determine whether an effect is seen at levels available over the counter or by prescription only and what duration of treatment may induce risk. Such audiometric results regarding commonly available NSAIDs will provide more meaningful data on which to assess the public health impact and counsel patients.

With regard to naproxen and ketorolac, there were no data exceeding the level of a case report that suggested either was associated with hearing loss. Thus, while the limited literature suggests a potential for irreversible hearing loss, the incidence, dose dependence, and whether any such association would remain after adjustment for potential confounders remain unknown.

Data from related randomized and prospective studies suggest that a short intravenous course of indomethacin in infants is not associated with a subsequent need for amplification. Although hearing was not the primary outcome in this cluster of studies, sample sizes were large, and randomization reduced selection bias. Neonates treated for patent ductus arteriosus are typically very low birth weight infants, usually born at <32 weeks and, frequently, <28 weeks of gestational age; their stay in the neonatal intensive care unit is thus multiple weeks, which often prompts vigilant audiologic follow-up regardless.

With regard to NSAIDs prescribed to adults without systemic inflammatory conditions, the data included the single instance of a randomized double-blind placebo-controlled trial in which audiometry was the reported primary outcome, making it the most relevant data with the least risk of bias. This study had somewhat mixed results in that there was a statistically significant 3-fold increase in risk of 15-dB HL in 2 frequencies with sulindac in the unadjusted analysis, but the effect did not persist when multivariate linear regression was applied for the adjusted analysis, and the magnitude of observed hearing differences was small. No a priori power calculations were reported, but the sample size was large, suggesting that a type II error was less probable. This study also had one of the longest follow-up periods, and the overall results suggested that if sulindac does have an effect on audiometry, it is quite limited.

Among adults with arthritides, NSAIDs scored better than aspirin in self-reported hearing symptoms, but there was no significant difference in standard audiometry measurements, although these were not the primary outcome. Hearing data after treatment versus no treatment in this subgroup were limited, and underlying conditions may have already predisposed toward hearing changes, affecting the baseline risk in these studies.

When acetaminophen ingestion was considered, data from large-scale, carefully executed longitudinal studies suggested a significant effect on self-reported hearing loss in men and women, but formal audiometric data were limited to small case series and case reports with the concomitant usage of narcotics. Reports of hearing loss with such combination usage have suggested that the resulting deficits are typically profound and irreversible. It is unknown whether the accompanying conditions that might prompt frequent acetaminophen ingestion have an underlying increased risk of hearing loss as well.

Formal audiometry is the ideal reference standard for audiologic evaluation, as it determines the type, degree, and configuration of hearing loss. Self-reported hearing results have been studied in relation to the gold standard of pure tone thresholds in multiple studies with a range of results. Sensitivity ranged from 26% to 90%, while specificity ranged from 50% to 96%.⁵¹⁻⁵⁶ Positive predictive values ranged from 5% to 71%, while negative predictive values ranged from 7% to 99%. The diagnostic test metrics varied according to age, smoking status, threshold cutoff defining hearing loss, sound frequency tested, and occupation.^{52-54,57} Thus, self-reported hearing results may be concordant with audiometry results, but they have not been demonstrated to be so consistently parallel that they forgo the need for audiometric confirmation in high-level evaluations. In addition, there may be an uncontrolled association between self-reported hearing loss and medical care utilization; those who seek medical care more frequently may be more likely to take medications and be aware of hearing deficits due to surveillance bias.⁵⁸ Subjects with increased self-focused and somatic attention report worse perceived symptom handicap and utilize more medical resources, even in instances where objective findings are no different from their less somatically aware counterparts.^{59,60} This potential bias is particularly of concern in studies of subjects who are not blinded to their exposure status, and blinding was utilized in just one-third of studies.

Future studies quantifying the relative risk of audiometric impact (beyond that of self-reported hearing loss) of NSAIDs would be beneficial to our understanding of any adverse effects associated with over-the-counter ingestion, long-term usage, and the profound bilateral effects that may be observed after acetaminophen/narcotic overuse. There would be also be benefits from similar studies of aspirin, another ubiquitous exposure with suggested impact on hearing.⁶¹ The true contribution of ototoxic exposures to the epidemiology of hearing loss is unknown, and more than 130 chemicals have reported hearing effects.^{62,63}

The basic science that could underlie an audiologic effect of NSAIDs and acetaminophen has been investigated. NSAIDs have been implicated as potentially harmful to outer hair cells and cochlear blood flow.^{64,65} They have also been linked to cases of aseptic meningitis.⁶⁶ Acetaminophen and its metabolite, N-acetyl-p-benzoquinone imine, have been implicated as causing primary ototoxicity via oxidative and endoplasmic reticulum stress-dependent pathways in auditory cells.⁶⁷ In vitro studies suggest that the sensory hair cells undergo apoptosis after exposure to acetaminophen and that the potentially profound deleterious effect results from this medication, rather than a narcotic exposure, although a narcotic can potentiate the acetaminophen-associated effect.⁶⁸ In addition, acetaminophen and narcotic metabolism both involve the CYP3A4 enzyme, which might be overwhelmed in high-dose situations or result in atypical metabolites in those with inborn enzyme alterations.^{69,70} Thus, although an association has yet to be demonstrated via formal audiometry, the mechanism by which such an effect could occur at a cellular level has been described.

Conclusions

The overall data varied, demonstrating a measurable effect on self-reported symptoms from NSAIDs as a class, ibuprofen, and acetaminophen, but there are no audiometric data to confirm or refute this suggested effect. Sulindac was the only specific agents to have been studied with formal audiometry as a primary outcome in a randomized double-blind placebo-controlled trial, and the significant effect seen in the unadjusted analysis dissipated in the adjusted multivariate regression.

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Figure 1.
Flow diagram showing the stages of identification of studies.

Table 1Study Designs.^a

Author	Randomized	Prospective	Blinding of Participants	Blinding of Assessors/ Outcome Measurement	Hearing Is the Primary Outcome	Standard Pure Tone Audiometry Reported	Self-reported Hearing Loss Reported
NSAIDs evaluated as a class							
Curhan ²⁸	—	X	—	—	X	—	X
Kastanioudakis ²⁹	—	X	X	X	X	X	—
NSAIDs available over the counter: Ibuprofen							
Curhan ³⁰	—	X	—	—	X	—	X
Eras ³¹	—	X	—	X	—	—	—
Davison ⁴⁶	—	—	—	—	—	X	X
NSAIDs available over the counter: Naproxen							
McKinnon ⁴⁰	—	—	—	—	—	X	X
Chapman ⁴¹	—	—	—	—	—	X	X
NSAIDs utilized perioperatively: Ketorolac							
Schaab ⁴⁴	—	—	—	—	—	X	X
Otti ⁴⁵	—	—	—	—	—	X	X
Srinivasan ⁴³	—	—	—	—	—	X	X
NSAIDs utilized in short intravenous courses in infants: Indomethacin							
Schmidt ³³	X	X	X	X	—	X	—
Schmidt ³⁴	X	X	X	X	—	X	—
Schmidt ³²	—	X	—	X	—	X	—
Prescribed oral NSAIDs in patients without inflammatory systemic disease							
McLaren ³⁵	X	X	X	X	X	X	—
McFadden ³⁶	—	X	—	—	X	—	—
Prescribed oral NSAIDs in patients with arthritides							
Davis ³⁷	X	X	X	X	—	X	—
Huskisson ³⁸	—	X	X	X	—	—	X
Ahmad ³⁹	—	—	—	—	—	X	X
Vernick ⁴²	—	—	—	—	—	X	X
Acetaminophen: Audiometric data							
Freeman ⁴⁷	—	—	—	—	X	X	X
Blakely ⁴⁸	—	—	—	—	—	X	X
Oh ⁴⁹	—	—	—	—	—	X	X
Rigby ⁵⁰	—	—	—	—	—	X	X
Acetaminophen: Self-reported hearing loss							
Curhan ³⁰	—	X	—	—	X	—	X
Curhan ²⁸	—	X	—	—	X	—	X

Abbreviations: X, characteristic present; —, characteristic absent; NSAID, nonsteroidal anti-inflammatory drug.

^aPrimary outcome assignments were not considered applicable to case reports.

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Table 2

NSAIDs as a Class.

Author	Study Design and Sample	Evaluation and Follow-up	NSAID Exposure Results	Additional Comments
Curhan ²⁸	Prospective observational cohort study, n = 26,917 Health Professionals Follow-up Study Age: 40-74 y; all men	NSAID: Combination of NSAIDs; regular use defined as 2 or more times per week Hearing: Self-reported HL in response to survey question Follow-up: Survey every 2 y from 1986 onward	Multivariable adjusted HR: 1.21 (CI, 1.11-1.33) for 21 times/wk The risk of HL increased with longer duration of regular use (>4y) For men <50 y, the HR for HL was 1.61 (CI, 1.15-2.26). Time from exposure to outcome: NR	Excluded if malignancy, other than nonmelanoma skin cancer.
Kastanioudakis ²⁹	Prospective cohort study, n = 45 42 female, 3 male with RA Mean age: 52.5 ± 10.7 y Mean disease duration: 8.5 ± 7.3 y	NSAID: n = 33 (not including ASA); 19 Plaquenil; 25 methotrexate; 20 D-penicillamine Hearing: Standard pure tone audiometry and impedance audiometry	44.4% (40 of 90) of ears tested had hearing loss >20 dB HL at least 2 frequencies 35.5% (16 of 35) had bilateral symmetric SNHL No significant difference with NSAID vs no NSAID (<i>P</i> > .05, Mann-Whitney) Time from exposure to outcome: NR	Some patients were taking a combination of drugs.

Abbreviations (Tables 2-10): ABR, auditory brainstem response; AD, right ear; ASA, acetylsalicylic acid (aspirin); AU, bilaterally; BID, twice daily; BPD, broncho-pulmonary dysplasia; CHL, conductive hearing loss; CI, confidence interval; DFMO, difluoromethylornithine; DPOAE, distortion product otoacoustic emissions; ESRD, end-stage renal disease; HL, hearing loss; HR, hazard ratios based on Cox proportional hazards regression models; IM, intramuscular; IV, intravenous; L, left; MRI, magnetic resonance imaging; NICU, neonatal intensive care unit; NR, not recorded; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PAN, polyarteritis nodosa; PTA, pure tone average; R, right; RA, rheumatoid arthritis; ROP retinopathy; RR, relative risk; SNHL, sensorineural hearing loss; SRT, speech reception threshold; TEOAE, transient evoked otoacoustic emissions; TID, 3 times per day; VNG, videonystagmography.

Table 3

NSAIDs Available over the Counter: Ibuprofen.

Author	Study Design and Sample	Evaluation and Follow-up	NSAID Exposure Results	Additional Comments
Curhan ³⁰	Prospective observational cohort study, n = 62,261 Nurses' Health Study II Age, 31-48 y; all women	NSAID: Ibuprofen; frequency of use categorized as < 1, 1,2-3, 4-5, or 6 d/wk Hearing: Self-reported response to survey Follow-up time: Survey every 2 y from 1995 to 2009	Multivariate adjusted analysis RR Ibuprofen: 1.13 (CI, 1.06, 1.19) for 2-3 d/wk; 1.21 (CI, 1.11, 1.32) for 4-5 d/wk; 1.24 (CI, 1.14, 1.35) for 6 d/wk Time from exposure to outcome: NR	Excluded if tinnitus on 2 d/wk or malignancy other than nonmelanoma skin cancer.
Eras ³¹	Prospective cohort from a prior randomized placebo-controlled trial, n = 102 Infants with birth weight 1500 g and gestational age 32 wk receiving oral vs IV ibuprofen for patent ductus arteriosus	NSAID: Oral or IV ibuprofen, 10 mg/kg of body weight, followed by 5 mg/kg at 24 and 48 h Hearing: Presence or absence of bilateral hearing loss needing amplification Follow-up time: 18 and 24 mo after dosing	0% (0 of 30) were diagnosed as deaf in the oral ibuprofen group 0% (0 of 27) was diagnosed as deaf in the IV ibuprofen group. Time from exposure to outcome: NR	3 infants excluded for death before discharge, 42 infants excluded for incomplete follow-up
Davison ⁴⁶	Case report, n = 1 66-y-old female with suspected NSAID-induced aseptic meningitis	NSAID: Ibuprofen every 6 h × 3 mo (mg per dose NR) Hearing: Standard pure tone audiometry Follow-up time: 6 mo	Sudden bilateral 30-dB decrease in pure tone thresholds and a substantial increase in baseline tinnitus Time from exposure to outcome: 3 mo	Reversible: Hearing loss and tinnitus resolved. No abnormalities on MRI when NSAID was discontinued

Abbreviations: See **Table 2** note.

Table 4

NSAIDs Available over the Counter: Naproxen.

Author	Study Design and Sample	Evaluation and Follow-up	NSAID Exposure Results	Additional Comments
McKinnon ⁴⁰	Case report, n = 1 35-y-old woman treated for low back pain	NSAID evaluated: Naproxen, 500 mg, BID × 48 h Hearing evaluation: Standard pure tone audiometry Follow up time: 6 mo	Moderate SNHL bilaterally (pure tone thresholds, 35-70 dB), VNG showed left-sided unilateral vestibular weakness, MRI results were normal Time from exposure to outcome: 48 h	Irreversible: Treated with prednisone with no notable improvement in hearing, tinnitus, or noise intolerance.
Chapman ⁴¹	Case report, n = 1 70-y-old man on naproxen for seronegative arthropathy	NSAID evaluated: Naproxen, 250 mg, BID, long-standing, then 4 d after an interval off for renal deterioration. Hearing evaluation: Standard pure tone audiometry Follow up time: 12 mo	Sudden, severe bilateral SNHL (pure tones thresholds, 70-100 dB). Calorics were normal. Time from exposure to outcome: 5 d	Irreversible: No improvement in HL after naproxen was discontinued, although renal function recovered.

Abbreviations: See **Table 2** note.

Table 5

NSAIDs Utilized Perioperatively: Ketorolac.

Author, y	Study Design and Sample	Evaluation and Follow-up	NSAID Exposure Results	Additional Comments
Schaab ⁴⁴	Case report, n = 1 20-y-old woman with PAN	NSAID evaluated: Ketorolac, 30 mg, IV Hearing evaluation: Standard pure tone audiometry Follow-up time: 18 mo prior, day of onset, 48 h after onset, and 9 d after onset	Sudden HL AU (10-80 dB, worse in higher frequencies), tinnitus, vertigo with nausea and vomiting. Received 50 mg of diphenhydramine IV, and nausea and vertigo were attenuated Bilateral hearing loss (R>L) persisted Time from exposure to outcome: 25 min	Partially reversible: 18 mo prior to receiving ketorolac, she had sudden severe SNHL in her left ear that was considered an effect of PAN. Sudden right mild to profound SNHL that partially recovered by 9 d after NSAID was discontinued. Patient also was taking methotrexate for PAN
Otti ⁴⁵	Case report, n = 1 38-y-old woman treated for ESRD with continuous ambulatory peritoneal dialysis	NSAID evaluated: Ketorolac, 60 mg, IM, and 10 mg, oral, every 6 h for a total of 8 oral doses Hearing evaluation: Standard pure tone audiometry Follow-up time: 4 d	Sudden bilateral HL and tinnitus and headache Time from exposure to outcome: 48 h	Reversible: HL and tinnitus resolved 4 d after discontinuing ketorolac
Srinivasan ⁴³	Case report, n = 1 30-y-old man who underwent general anesthesia for multiple dental extractions	NSAID evaluated: Ketorolac (dosage not specified) after general anesthesia (morphine, propofol, isoflurane, and nitrous oxide) Hearing evaluation: Standard pure tone audiometry Follow-up time: 3 wk after the extraction of 4 third molars and the lower first molars, 8 mo	High-frequency SNHL in left ear (70- to 80-dB pure tone threshold). MRI and neurologic examination results were normal Time from exposure to outcome: "immediately after" the operation	Irreversible: Morphine and ketorolac were given for pain relief. The procedure resulted in minimal blood loss. Bupivacaine 0.5% infiltration was used for local analgesia. Postoperative recovery was uneventful.

Abbreviations: See **Table 2** note.

Table 6

NSAIDs Utilized in Short Intravenous Courses in Infants: Indomethacin.

Author	Study Design and Sample	Evaluation and Follow-up	Exposure Results	Additional Comments
Schmidt ³³	Randomized placebo-controlled trial, n = 1202 Newborn infants with birth weight ranging from 500 to 999 g	NSAID evaluated: Indomethacin, 0.1 mg/kg, IV, every 24 h × 3d; placebo: equivalent volume of saline Hearing evaluation: Audiometry to determine HL presence or absence. Adjudication committee unaware of assignment reviewed audiometry for all infants whose hearing had not been amplified. Follow-up time: Baseline and follow-up evaluation at the corrected age of 12-21 mo	NSAID: 2% (10 of 456) HL requiring amplification; no significant difference between NSAID and placebo: OR, 1.0 (CI, 0.4, 2.5; <i>P</i> = .93) No NSAID: 2% (10 of 466) HL requiring amplification	13 children were lost to follow-up. If audiometry was difficult to obtain, deafness requiring amplification was assumed to be absent, if there was no indication of HL during the clinical examination and the Bayley test (n = 27).
Schmidt ³⁴	Post hoc analysis of a randomized placebo-controlled trial, n = 670 Newborn infants with birth weights ranging from 500 to 999 g and known exposure to antenatal corticosteroid at least 24 h before delivery	NSAID evaluated: Indomethacin, 0.1 mg/kg, IV, every 24 h × 3d; placebo: equivalent volume of saline Hearing evaluation: Audiometry to determine HL presence or absence. Adjudication committee unaware of group assignment reviewed the audiometry for all infants whose hearing had not been amplified. Follow-up time: Baseline and follow-up at the corrected age of 18 mo	NSAID: Adequate antenatal steroid: 2.7% (7 of 264) HL requiring amplification OR 1.48 (CI, 0.46-4.72; inadequate antenatal steroid: 1.6% (3 of 188) HL requiring amplification; OR, 0.59 (CI, 0.14-2.52) No NSAID: HL requiring amplification in 1.8% (5 of 276) of those with adequate antenatal corticosteroid exposure and 2.7% (5 of 188) of inadequate antenatal corticosteroid exposure.	
Schmidt ³²	Inception cohort, n = 910 Infants with birth weights of 500-999 g who were admitted to NICU and survived to a postmenstrual age of 36 wk	NSAID evaluated: Indomethacin, 0.1 mg/kg, IV, every 24 h × 3d Hearing evaluation: Sound field audiometry was conducted to determine presence or absence of HL. HL requiring amplification Follow-up time: Baseline and follow-up evaluation at the corrected age of 12-21 mo	2% (20 of 876) of both groups combined had HL requiring amplification. Subjects were followed from their baseline. Hearing loss was associated with worse general health outcome at 18 mo	Study concluded that concomitant BPD, brain injury, and severe ROP predicted the risk of neurosensory impairment.

Abbreviations: See **Table 2** note.

Table 7

Prescribed Oral NSAIDs in Patients without Inflammatory Systemic Disease.

Author	Study Design and Sample	Evaluation and Follow-up	Exposure Results	Additional Comments
McLaren ³⁵	Randomized, double-blind, placebo-controlled phase III trial, n = 290 Age, 40-80 y, history of 1 resected 3-mm colorectal adenoma within 5 y of study start. All subjects fell within 20 dB of normal age-adjusted hearing levels at baseline	NSAID evaluated: Sulindac, 150 mg, daily with DFMO, 500 mg daily; control: placebos Hearing evaluation: Standard pure tone audiometry: hearing loss defined as 15 dB decrease in thresholds from baseline testing at any frequency Follow-up time: Baseline, 18 and 36 mo after randomization, or off study, and 6 mo afterward	NSAID exposure results: DFMO + Sulindac: 9.3% (14 of 151) had 15 dB of hearing loss from baseline in 2 frequencies No NSAID exposure results: placebo—2.9% (4 of 139) had 15 dB of hearing loss from baseline in 2 frequencies RR of 15-dB HL in 2 frequencies: 3.2 (95% CI, 1.09, 9.55; <i>P</i> = .02, unadjusted) DFMO + Sulindac associated with a 0.99-dB greater hearing loss than placebo (95% CI, -0.17, 2.14 dB; <i>P</i> = .09, multivariate linear regression); no significant difference in the proportion with clinically significant HL. Time from exposure to outcome: NR	Temporary hearing loss side effect of DFMO; 6 mo after treatment was stopped, hearing loss was not significantly different between groups
McFadden ³⁶	Prospective crossover study, n = 11 Study also evaluated effect of noise exposure: all sessions were conducted with sound intensity necessary for a 10-min 2500-Hz tone to produce ~12dB of temporary threshold shift 11 men, 19 to 23 y old with normal hearing	NSAID evaluated: Sulindac, 200 mg, BID ± 4 d; Diflunisal, 375 mg, BID Hearing evaluation: Psychophysical methods: >5-dB shift in audiometric thresholds, as measured by a 2-interval forced choice method Follow-up time: 4 d	NSAID exposure results: Sulindac and Diflunisal generally produced <5 dB of change in hearing sensitivity at any frequency prior to noise exposure. Subjects were compared to their own baseline and to their own performance in other drug regimens. No NSAID exposure results: 2.8 min Time from exposure to outcome: Sulindac and diflunisal had no effect	

Abbreviations: See **Table 2** note.

Table 8

Prescribed Oral NSAIDs in Patients with Arthritides.

Author	Study Design and Sample	Evaluation and Follow-up	NSAID Exposure Results	Additional Comments
Davis ³⁷	Cohort within a randomized controlled double-blind trial, n = 40 Age, 22-68 y, with rheumatoid arthritis	NSAID evaluated: Pirprofen, 200 mg, every 6 h (800 mg/d) for 1 y; or ASA, 900 mg, every 6 h (3600 mg/d) for 1 y Hearing evaluation: Pure tone audiometry—hearing loss defined as a “threshold shift” Follow-up time: 20 wk, 1 y	Pirprofen was compared to ASA. 16% (3 of 19) of pirprofen group had new hearing loss. 16% (3 of 19) of pirprofen group had progression of hearing loss. 11.1% (2 of 18) of ASA group had new HL 27.8% (5 of 18) of ASA group had progression of hearing loss. No significant difference (post hoc) Subjects were followed from their baseline. Time from exposure to outcome: NR	53% (10 of 19) of pirprofen subjects had CHL or SNHL at the outset. HL was a secondary outcome. ⁵ subjects withdrew from the study.
Huskisson ³⁸	Prospective double-blind controlled study, n = 60 Outpatients with classical or definite rheumatoid arthritis	NSAID evaluated: Fenoprofen, 2.4 g/d; n = 29; ASA, 6 g/d; n = 31 Hearing evaluation: Patient self-report: they were asked about side effects (mild, moderate, severe) Follow-up time: Weekly intervals for 4 weeks, moly intervals through the 24th week of treatment	Week 1: Fenoprofen: 3% (1 of 29) reported tinnitus of deafness ASA: 66% (19 of 29) reported tinnitus of deafness, $P < .01$ Time from exposure to outcome: 1 wk	3 patients did not complete study
Ahmad ³⁹	Case report, n = 1 41-y-old man treated for gout	NSAID evaluated: Indomethacin, 25 mg, TID × 5d Hearing evaluation: Standard pure tone audiometry Follow-up time: 3 mo	R: normal hearing at 250 Hz sloping to a profound SNHL L: flat profound SNHL Irreversible: No improvement in SNHL since cessation of NSAID Time from exposure to outcome: 5 d	Also taking furosemide at the time NSAID was initiated. Tinnitus, dizziness preceded HL.
Vernick ⁴²	Case report, n = 1 63-y-old woman treated for degenerative arthritis	NSAID evaluated: Piroxicam, 20 mg × 3 doses (symptoms after the first dose) Hearing evaluation: Standard pure tone audiometry Follow-up time: 1 mo, 6mo	Tinnitus, aural fullness, SNHL AD, ABR showed delayed waves I, III, and V in AD Irreversible: No improvement after cessation. Time from exposure to outcome: 30 min	First case of permanent hearing loss and tinnitus associated with use of the drug.

Abbreviations: See **Table 2** note.

Table 9

Acetaminophen: Audiometric Data.

Author	Patient Characteristics	Acetaminophen Ingestion and Follow-up Time	Results with NSAID Exposure and Time Lag between Exposure and Hearing Impact	Additional Comments
Freeman ⁴⁷	10 patients: 6 women, 4 men, age 26-64 y. All had sudden or rapidly progressive bilateral profound SNHL and were evaluated for cochlear implant (n = 10)	Acetaminophen, 500 mg, and codeine phosphate, 30 mg, in combination for several years, usually at greater-than-recommended daily dose; 4-10 tabs/d for 1-30 y Follow-up time: Variable	Results: 100% (10 of 10) patients had profound sensorineural hearing loss bilaterally Time lag: Variable up to 11 y	Irreversible; all patients underwent cochlear implant surgery
Blakely ⁴⁸	Three patients: (a) 37-y-old man, (b) 45-y-old woman, (c) 37-y-old woman	Acetaminophen, 300 mg, with codeine, 8-60 mg; 14-100 tablets daily Follow-up time: NR	Results: Large dosages of acetaminophen-codeine were associated with deafness in 3 individuals: (a) SRTs (R: 30 dB; L: 85 dB), 1 y later: SRTs (R: 90 dB; L: 80 dB), 1 y 9 mo later: no response; (b) SRTs (R: 85 dB; L: 90 dB), 2 mo later: PTA (105 dB); (c) SRTs (R: 25 dB; L: 15 dB), 1 y later: SRTs (R: 95 dB; L: 110 dB) Time lag: (a) 15 y, (b) 22 y, (c) 2 y	Reversibility not reported: (a) occupational welder; (b) occasionally used oxycodone; (c) HL, tinnitus, and imbalance
Oh ⁴⁹	Two patients: (a) 34-y-old woman, (b) 32-y-old man	Acetaminophen, 500 mg, with hydrocodone, 5 mg: (a) 15 tablets, 4 times daily; (b) "Up to 35" tablets daily Follow-up time: NR; both had progressive HL from initial symptoms	Results: (a) flat, profound bilateral SNHL, absent TE/DPOAEs; (b) moderate to profound SNHL, absent TE/DPOAEs, normal caloric Time lag: (a) 3 y, (b) NR	Irreversible: Neither improved with high-dose prednisone. Despite the profound effect on hearing, vestibular function was relatively spared. (a) Underwent cochlear implant.
Rigby ⁵⁰	55-y-old woman	Acetaminophen, 325 mg, with oxycodone, 5 mg, exceeding 20-30 tablets daily for 1.5 y Follow-up time: Initial presentation of HL, 6 mo, and 8 mo after initial presentation of HL	Results: Initial: R: moderate to severe / L: moderate; 6 mo later: R: profound / L: severe to profound; 8 mo later: R: profound / L: severe to profound Time lag: 2-3 mo	Irreversible: HL remained stable at 6-and 8-mo follow-up since discontinuing Percocet. Mild tinnitus in right ear at presentation

Abbreviations: See **Table 2** note.

Table 10

Acetaminophen: Self-reported Hearing Loss.

Author	Study Design and Sample	Evaluation and Follow-up	NSAID Exposure Results	Additional Comments
Curhan ³⁰	Prospective observational cohort study, n = 62,261 Nurses' Health Study II Age, 31-48 y; all women	Agent evaluated: Acetaminophen; frequency of use categorized as < 1, 1, 2-3, 4-5, or 6 d/wk. Hearing evaluation: Self-reported response to survey Follow-up time: Survey every 2 y from 1995 to 2009	Multivariate adjusted analysis RR Acetaminophen: 1.11 (CI, 1.02, 1.19) for 2-3 d/wk; 1.21 (CI, 1.07, 1.37) for 4-5 d/wk; 1.08 (CI 0.95, 1.22) for 6 d/wk Time from exposure to outcome: NR	Excluded if tinnitus on 2 d/wk or malignancy other than nonmelanoma skin cancer.
Curhan ²⁸	Prospective observational cohort study, n = 26,917 Health Professionals Follow-up Study Age, 40-74 y; all men	Agent evaluated: Acetaminophen; regular use defined as 2 or more times per week. Hearing evaluation: Self-reported hearing loss in response to survey question, Follow-up time: Survey every 2 y beginning in 1986	Age and multivariable adjusted HR Acetaminophen: 1.22 (CI, 1.07-1.39) for 2+ times/wk; for acetaminophen, the risk of HL increased with longer duration of regular use (>4 y); for men <50 y, the HR for HL was 1.99 (CI, 1.34-2.95) for acetaminophen use. Time from exposure to outcome: NR	Excluded if malignancy, other than nonmelanoma skin cancer.

Abbreviations: See **Table 2** note.