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Adverse Effects of Analgesics Commonly Used by Older Adults with Osteoarthritis: Focus on Non-Opioid and Opioid Analgesics

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Abstract

Background—Osteoarthritis (OA) is the most common cause of disability in older adults, and while analgesic use can be helpful its use can also result in adverse drug events.

Objective—To review the recent literature to describe potential adverse drug events (ADEs) associated with analgesics commonly used by older adults with OA.

Methods—To identify articles for this review, a systematic search of English-language literature (January 2001 – June 2012) was conducted using PubMed, MEDLINE, EBSCO, and the Cochrane Database of Systematic Reviews for publications related to the medical management of osteoarthritis. Searches used a combination of the following search terms: *analgesics, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, pharmacokinetics, pharmacodynamics and adverse drug events*. We also restricted the search to those papers concerning humans 65 years of age. A manual search of the reference lists from identified articles and the authors' article files, book chapters, and recent reviews was conducted to identify additional articles. From these, the authors identified those studies that examined analgesic use in older adults.

Results—There are limited data to suggest that non-frail elders are more likely than their younger counterparts to develop acetaminophen-induced hepatotoxicity. However, decreased hepatic Phase 2 metabolism in frail elders may result in an increased risk of hepatotoxicity. Regarding NSAIDs, it is now well-established that older adults are at higher risk for NSAID-induced gastrointestinal toxicity and renal insufficiency. For opioids, the data suggesting an

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CONFLICT OF INTEREST STATEMENT

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increased risk of falls/fractures/delirium need to be tempered by the potential risk of inadequately treating severe chronic OA pain.

Conclusions—Acetaminophen is the mainstay frontline analgesic for OA pain in older adults. NSAIDs should be limited to short-term use only, and for moderate to severe OA pain, opioids may be preferable in those without substance abuse or dependence issues.

Keywords

aged; osteoarthritis; analgesics; adverse drug events

INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder in the United States (US) and is the leading cause of disability in the elderly.¹ OA pain may lead to decreased health-related quality of life, reduced sleep quality, interference with social relationships, diminished cognitive function, limitations in activities of daily living, reduced productivity, and increased anxiety and depression.² Thus, adequate pain control is an essential component of successful management of OA in older adults. Analgesics, including non-opioids and opioids, are the most common type of pharmacotherapy used in the treatment of OA.³ However, various adverse drug events (ADEs: injuries due to medication) have been reported with these analgesic classes.⁴

Several clinical guidelines are currently available for the management of OA. Most recently in April 2012, the American College of Rheumatology (ACR) published expert-guided consensus guidelines as an update to the 2000 guidelines.⁵ In addition, several other groups have published OA guidelines and recommendations, including: the American Geriatrics Society (AGS), the European League Against Rheumatism (EULAR), the National Institute of Clinical Excellence (NICE), the American Association of Orthopedic Surgeons (AAOS), and the Osteoarthritis Research Society International (OARSI).^{6–12} However, these guidelines primarily focus on analgesic efficacy with little attention paid to potential ADEs that may occur with analgesic use in older adults. Much of the pharmacoepidemiologic safety data available on analgesic use in older adults comes from primary literature. Thus, the objective of this project is to review the recent literature to describe the potential adverse drug events (ADEs) associated with analgesics commonly used by older adults with OA. In doing so, we hope to highlight the current gaps in the literature and suggest practical ways in which clinicians can optimize analgesic use by older adults with OA.

METHODS

A systematic search of English-language literature (January 2001 – June 2012) was conducted using PubMed, MEDLINE, EBSCO, and the Cochrane Database of Systematic Reviews for publications relating to the analgesic medication management of OA. The beginning date (2001) coincides with the time of a recent review of this topic written by one of the authors (JTH).⁴ Searches used a combination of the following search terms: *analgesics, acetaminophen, non-steroidal anti-inflammatory drugs, opioids, pharmacokinetics, pharmacodynamics and adverse drug events*. A manual search of the reference lists from identified articles and the authors' article files, book chapters, and recent reviews was conducted to identify additional articles. From these, the authors identified those studies that examined analgesic use in older adults. Of note, only those analgesics that are currently available in the US are discussed in this review. Those studies focused on adults < 65 years of age, analgesics other than acetaminophen, NSAIDs, or opioids, or focused just on efficacy/effectiveness were excluded.

DATA SYNTHESIS

Below, in separate sections for both non-opioid (i.e., acetaminophen and non-steroidal anti-inflammatory drugs [NSAIDs]) and opioid analgesics, we provide an overview, information about age-related pharmacokinetics/pharmacodynamics, data about specific adverse drug events, and provide a section summary.

Non-Opioids

Acetaminophen

Overview: Acetaminophen (APAP) is recommended in current guidelines as a first-line analgesic for mild to moderate pain due to OA of the knee and hip.^{6–12} The analgesic activity of APAP results from the central inhibition of prostaglandin synthesis. However, the primary mechanism of prostaglandin synthesis inhibition by APAP remains unknown.¹³

Recently, there has been increasing concerns raised about APAP hepatotoxicity. Due to these concerns, the FDA commissioned a working group within the Center for Drug Evaluation and Research to recommend interventions to reduce APAP-induced liver toxicity.¹⁴ An assembly of three advisory panels reviewed the report of the working group and endorsed the following three recommendations: a reduction of the maximum daily dose from 4 grams to possibly 3250 mg daily; a ban on prescription narcotic-APAP combinations; and a reduction of the maximum single nonprescription dose from 1 gram to 650 mg, thus relegating the 500mg dosage strength prescription status.¹⁴ While the FDA has not implemented all of the suggestions of the advisory panel, they have required expanded warnings about hepatotoxicity on nonprescription products containing APAP, required companies to limit the APAP component of combination analgesic prescription products to 325 mg per dosage form, required a black box warning regarding liver injury, and mandated one concentration of APAP liquid (160 mg/5ml). The question remains as to whether the data support a greater risk of hepatotoxicity in older adults.

Acetaminophen is a dose-dependent hepatotoxin, and excessive doses (intentional or unintentional) may lead to irreversible acute liver failure. Glucuronidation and sulfation are the major metabolic pathways for APAP metabolism in usual doses in healthy adults.¹⁵ These Phase II pathways become saturated after an APAP overdose, causing a shift to Phase I metabolism and creation of a toxic metabolite, N-acetyl-p-benzoquinone (NAPQI), that binds to glutathione. When glutathione is depleted, NAPQI accumulates, binds to hepatic cells, and causes hepatic necrosis. Even in therapeutic doses, APAP may still cause transient liver enzyme elevations and possibly hepatotoxicity, particularly in people who are malnourished (due to glutathione reduction) and among those using hepatic enzyme inducers (e.g., regular and heavy alcohol use, rifampin, phenytoin, carbamazepine, and barbiturates), which increase Phase I metabolism and NAPQI concentrations.¹⁵

Age-related changes in acetaminophen pharmacokinetics: Several studies have investigated the pharmacokinetics of APAP in healthy older adults, reporting variable effects of age.^{16–21} It has been shown that APAP is rapidly and completely absorbed from the gastrointestinal (GI) tract, and neither the rate nor the extent of absorption appears to be age-dependent.²² The volume of distribution decreases with age and female gender, which is consistent with the drug's hydrophilic nature as well as age-associated changes in body composition; no differences have been reported in the volume of distribution between healthy and frail older people.¹⁸ In general, increased age does not alter the clearance of APAP, which is metabolized by Phase II hepatic conjugative metabolism.^{16,17,19} For example, a study involving 11 women, aged 89±4 years, who received multiple doses of APAP 1 gram three times daily for 5 days showed no drug accumulation.²⁰ However, some

studies of older adults have investigated the impact of frailty on clearance. For example, Wynne et al examined the effect of frailty on specific conjugative pathways and demonstrated a reduced clearance of the glucuronide metabolite, while clearance of the sulfate metabolite was unaffected.¹⁸ Furthermore, in a study of intravenous APAP in patients aged 80 to 90 years, the oldest patients had a 1.3 to 1.5 fold greater exposure to APAP metabolites than patients aged 20 to 40 years.²¹ As seen, these results suggest that metabolism of APAP in older patients is highly variable and that the intrinsic conjugative activity of the liver maybe preserved in healthy older people, but may be compromised in frail elderly. It is unknown whether these changes in pharmacokinetics are responsible for increases in APAP hepatotoxicity described below.

Adverse drug events (focus on hepatotoxicity): Acetaminophen hepatotoxicity has been examined in multiple studies, but unfortunately age has been the focus of only a few studies. For example, the impact of frailty on hepatotoxicity of short-course APAP treatment was evaluated in an observational study of young (18–55 years, n=19), healthy older (≥ 70 years, n=24), and frail older (n=28) inpatients.²³ Treatment group participants received APAP 3 to 4 grams per day; control group participants received no APAP. Plasma alanine aminotransferase (ALT) concentrations were obtained at baseline and on day five; a random APAP concentration was measured at day five. Older patients, particularly frail older patients, had a lower incidence of ALT elevation compared to younger patients despite having significantly higher mean APAP concentrations after five days of treatment.²³ One possible explanation for this finding is that reduced Phase I hepatic metabolism with old age may result in less efficient production of NAPQI, thereby protecting healthy older people from APAP toxicity and suggesting that older frail people may not be at increased risk of hepatotoxicity. However, future studies are needed to confirm this finding.

In a prospective study of more than 600 patients (mean age 37 years; range 17–76 years) from 22 US tertiary care centers, APAP-induced liver damage was the leading cause of acute liver failure, and approximately half of the cases were due to unintentional overdose.²⁴ The mean daily dose of APAP was 7.5 grams (range 1.0–78 grams), and 38% of cases used multiple APAP products whereas 63% used an APAP/opioid combination product.²⁴ Another analysis of ED visits in the US between 1993 and 2007 revealed that APAP overdoses accounted for 0.05% of all visits.²⁵ The annual rate per 100,000 persons significantly decreased from 1993 to 2007 (20.1 visits in 1993–1999 vs. 15.2 visits in 2000–2007; $p = 0.017$). Rates were highest in young children under 5 years (72.4 visits, 95% CI 49.1–95.8) and for adolescents between 15 and 17 years (61.8 visits, 95% CI 35.4–88.3). Those ≥ 65 years accounted for 0.88 visits per 100,000 persons per year.²⁵ This low rate of APAP-overdose detected on ED visits is surprising and suggests that older adults may be at lower risk of APAP overdose, at least those that were treated in ED. The authors also suggest that the low rate may be due to lack of documentation of APAP toxicity due to polypharmacy issues, or that older, institutionalized patients may not be transferred to the ED for treatment of APAP toxicity. Another recent analysis of the National Electronic Injury Surveillance System (NEISS) data from 2006 to 2007 specifically focused on the ED visits for non-abuse related APAP overdose and characterized patient demographics, treatments, and type and amount of APAP-containing product ingested.²⁶ This analysis revealed that most ED visits for APAP-toxicity were due to self-directed violence (69.8%, 95% CI 66.4%–73.2%), with the highest rate among patients aged 15 to 24 years (46.4 per 100,000 patients per year). Older patient over 64 years accounted for 2.2% (95% CI 1.4–3.1) of intentional APAP overdose and 14.6% (95% CI 9.5–19.7) of therapeutic misadventures.²⁶

Summary: Since the pharmacokinetic profile of APAP is highly variable with age and frailty, dosing should be individualized. In light of the limited clinical data about liver toxicity in older adults taking 4 grams per day and considering pharmacokinetic data,

routine dosage reductions may not be necessary in healthy elderly patients; however, malnutrition, pre-existing liver disease, concomitant use of enzyme-inducing drugs, and chronic alcohol use may warrant lower maximum doses of 2 grams to 3 grams per day.

Non-steroidal Anti-inflammatory Drugs

Overview—NSAIDs are commonly used in older adults with OA.²⁷ In patients, in which APAP does not provide adequate analgesia or if an anti-inflammatory effect is needed, an NSAID should be considered.²⁸ The primary mechanism of action of salicylates and other nonselective NSAIDs is the inhibition of COX-1 and COX-2 pathways, which inhibits the production of prostaglandins and other factors that cause pain and inflammation.²⁹ The analgesic effects of NSAIDs have been attributed to the inhibition of COX-2, while the GI side effects and antiplatelet effects are thought to be secondary to the inhibition of COX-1. Thus, the selective COX-2 inhibitor celecoxib is thought to have fewer GI side effects compared to other NSAIDs.^{4,28}

Age-related changes in NSAID pharmacokinetics—There have been several publications that have been reviewed the pharmacokinetics of NSAIDs. In general, most of these agents are extensively hepatically metabolized by Phase I cytochrome P450 isoenzymes.^{4,29,30} Most NSAIDs are well-absorbed and highly plasma protein bound. Therefore, frail elders with hypoalbuminemia are likely to have higher free drug concentrations. Some agents have longer half-lives in older adults when compared to those determined in younger adults (i.e., celecoxib, diflunisal, naproxen, oxaprozin, piroxicam, sulindac).^{4,29,30} It is unknown whether these changes in pharmacokinetics are responsible for increases in NSAID ADEs described below.

Gastrointestinal adverse drug events—Recently, an evidence-based table was published as part of the updated 2012 Beers criteria for the risk of GI toxicity associated with NSAID use.³¹ However, there are some additional studies worth discussing, which are summarized in Table 1. The incidence of serious GI side effects associated with the use of oral NSAIDs (and acetaminophen) was assessed in a large population-based study of elderly patients in Canada.³² The adjusted hazard ratio (HR) for GI-related hospitalization (perforation, ulcer, bleeding) was higher in patients receiving oral non-selective NSAIDs (1.63, 95% CI 1.44–1.85) than in patients being treated with low dose (3g/day) acetaminophen. It was also shown that patients receiving high dose (>3g/day) had a higher risk of GI hospitalization compared to those receiving low dose APAP (1.20, 95% CI 1.03–1.40). However, the HR was highest among those patients treated with NSAIDs plus high dose APAP (2.55, 95% CI 1.98–3.28).³² Multiple studies support this finding of an increased risk of GI-related adverse drug events due to non-selective NSAIDs.^{33–35} However, the compounded deleterious effect of APAP on NSAID-related GI side effects is less well-established, and future research is needed.

While the COX-2 inhibitor celecoxib is thought to cause fewer GI side effects compared to non-selective NSAIDs, it is important to note that it is not without GI risk. For example, it was shown in a population-based study in Taiwan that among older adults (65–79 years and 80+ years) celecoxib use significantly increased the odds of hospitalization for an upper GI adverse drug event (Table 1).³⁵ Moreover, Rahme et al found that celecoxib plus aspirin significantly increased the risk of a hospitalization for a GI bleed.³⁴ However, there is mixed evidence showing that celecoxib did not increase the risk of hospitalization for upper GI bleeding (adjusted rate ratio 1.0, 0.7–1.6)³³ and even that celecoxib significantly reduced the risk of GI bleeding compared to non-selective NSAIDs (adjusted HR 0.60, 0.35–1.00).³⁶ A major limitation of some of these studies is the lack of data on over-the-counter medications as well as information on pain severity.

Cardiovascular/cerebrovascular adverse drug events—Lévesque et al conducted a population-based, retrospective cohort study in Québec, Canada of 113,927 older adults without previous MI and newly started on an NSAID to assess the effect of NSAIDs on the risk for a first MI.³⁷ They reported that celecoxib use was not significantly associated with an increased risk of first MI (rate ratio 0.99, 0.85–1.16), and neither were the other NSAIDs (eg, naproxen) studied. In a separate study using the same cohort, the investigators found that neither repeated exposure to celecoxib nor treatment duration of celecoxib was associated with an increased risk of first MI.³⁸ Conversely, Rahme et al found a significant risk of hospitalization for AMI with celecoxib plus aspirin use compared to APAP alone use in older adults in Québec (adjusted HR 1.17, 1.01–1.35).³⁴

Another negative cardiovascular event associated with NSAID use is heart failure (HF). Mamdani et al conducted a population-based cohort study of NSAID-naïve older adults who were started on celecoxib and non-selective NSAIDs, assessing the association between such use and admissions rates for HF.³⁹ Compared to non-NSAID users, patients on non-selective NSAIDs but not celecoxib had an increased risk of admission for HF (adjusted rate ratio 1.4, 1.0–1.9; 1.0, 0.8–1.3, respectively).³⁹ Furthermore, a recent systematic review and meta-analysis assessed the stroke risk associated with NSAIDs and reported an increased risk of all subtypes of incident stroke with current diclofenac use (relative risk 1.27, 1.08–1.48).⁴⁰ However, due to a small sample size (n=6 studies included), the authors were not able to assess the independent effect of age using meta-regression in this study. Finally, Solomon et al assessed the relative effects of non-selective and COX-2 selective (i.e., celecoxib, rofecoxib, and valdecoxib) NSAIDs on a composite cardiovascular outcome (MI, stroke, HF, revascularization, and out of hospital cardiac death).³⁶ These investigators detected a significantly higher risk of the composite outcome among COX-2 selective NSAID users compared to non-selective NSAID users (adjusted HR 1.28, 1.01–1.62).³⁶ The independent effect of celecoxib (the only coxib currently available in the US) was not specified.

Renal adverse drug events—Schneider et al assessed the association of non-selective and COX-2 selective NSAIDs with acute renal failure in a population-based, nested case-control study using a cohort of new NSAIDs users aged 66 years or older from Québec.⁴¹ These investigators found that the risk of hospitalization for acute renal failure for all NSAIDs combined was highest within 30 days of treatment initiation (adjusted rate ratio [ARR] 2.05, 1.61–2.60), which then decreased over time. For individual NSAIDs, the risk of acute renal failure was statistically significant for non-selective, non-naproxen NSAIDs (ARR 2.30, 1.60–3.32), naproxen (ARR 2.42, 1.52–3.85), and celecoxib (ARR 1.54, 1.14–2.09).⁴¹ Furthermore, the effect of non-selective and COX-2 selective NSAIDs on the progression of chronic kidney disease (CKD) was assessed in a community-based cohort of older adults in Calgary.⁴² The primary outcome was a decrease in estimated glomerular filtration rate of 15 mL/min/1.73². After following a total of 10,184 subjects for a median of 2.75 years, it was reported that high-dose NSAID users experienced a 26% increased risk of progression of CKD (adjusted odds ratio 1.26, 1.04–1.53).⁴² Of note, a differential effect between selective and non-selective NSAIDs was not seen.

Other adverse drug events—Kerr et al examined the risk for all-cause mortality in elderly Australian veterans receiving non-selective and COX-2 selective NSAIDs.⁴³ They determined hazard ratios through Cox proportional hazards regression modeling of all-cause mortality in individuals starting treatment with an NSAID, relative to individuals supplied with an unrelated medication (i.e., glaucoma or hypothyroidism medications). Patients receiving a non-selective NSAID had the highest increased mortality risk (adjusted HR 1.76, 1.59–1.94). However, all individuals receiving NSAIDs had a significantly higher mortality risk relative to those receiving a glaucoma/hypothyroid medication. The individual HRs

detected are as follows: celecoxib (1.39, 1.25–1.55); meloxicam (1.49, 1.25–1.78); diclofenac (1.44, 1.28–1.62).⁴³ A strength of this study was the use of a time-to-event approach, which attributes mortality risk only during the drug exposure period. Yet, this study is limited by the fact that non-selective NSAIDs were treated as a single group, preventing the assessment of individual non-selective NSAID mortality risk.

Summary—NSAIDs have been shown to increase the risk of several outcomes in older adults. These include GI, cardiovascular/cerebrovascular and renal adverse drug events as well as cognitive effects.⁴⁴ The risks of NSAIDs need to be balanced by their analgesic effectiveness for pain not controlled by APAP, and diligent monitoring and patient education is essential to preventing adverse drug events. In general, if an NSAID is required one should consider the use of nonacetylated salicylates as they rarely cause GI bleeding, and they do not interfere with platelet function, even in patients taking aspirin.⁴⁵

Opioids

Overview—For patients who do not respond to APAP or NSAIDs or cannot tolerate the side effect profiles of these agents, opioid analgesics may be useful.^{6,45,46} Opioids inhibit pain pathways by binding to the mu opioid receptors in the central nervous system.⁴ The selection of an opioid analgesic for older patients with chronic pain is influenced by factors such as pain intensity, age-related alterations in pharmacokinetics/pharmacodynamics, comorbid conditions and adverse drug events. While randomized trials may be the best study design to assess pharmacokinetics/pharmacodynamics and efficacy, observational studies are best in determining risks associated for more rare events.^{47,48}

Age-related changes in opioid pharmacokinetics/pharmacodynamics—

Evidence shows that there is an age-related decline in the clearance of high hepatic extraction opioids (i.e., meperidine, morphine).⁴⁹ There are several recent studies showing an age-related decrease in clearance of oxycodone.^{50–52} The pharmacokinetics of tramadol and fentanyl in older adults have also been well studied but revealed mixed effects of age on clearance.^{53,54} Both codeine and tramadol are prodrugs and are metabolized by CYP2D6 to active metabolites.^{54,55} Therefore, use of these agents in those who are slow metabolizers or taking medications that inhibit CYP2D6 (e.g, amiodarone, bupropion, fluoxetine, quinidine, ritonavir) can reduce efficacy. Many opioids have active renally-cleared metabolites (i.e., codeine, fentanyl, hydromorphone, meperidine, morphine, oxycodone, tramadol).⁴ In particular, normeperidine can accumulate in older adults and result in neurotoxicity resulting in recommendations that the parent drug (meperidine) be avoided in older adults.³¹ Given the long half-life of methadone and potential QT interval effects, this medication is generally not recommended for use in older adults.⁵⁶ It is also clear that there is an age-related increase in the pharmacodynamic activity of opioids that maybe independent of changes in pharmacokinetics.⁴ This is part of the reason why pentazocine, which can cause increased psychomimetic reactions, should be avoided in older adults.³¹

Delirium adverse drug events—A systematic review of medications (including opioids) that may increase the risk of delirium in older adults was published in 2011.⁵⁷ Data regarding opioids were pooled from two moderate quality observational studies of 866 hospitalized patients. Those patients with orders for opioids had more than a two-fold increased risk of delirium (OR 2.50; 95% CI 1.2–5.2).⁵⁷ One of the included cohort studies by Morrison et al examined delirium, measured using the reliable and valid Confusion Assessment Method (CAM), in older hip fracture inpatients from four hospitals.⁵⁸ Opioid use was converted to parenteral morphine equivalents (PME) per day. They found that the risk of delirium in previously cognitively intact older inpatients actually decreased as the PME per day increased (<10 mg PME, adjusted RR 25.2; 10–30mg PME, adjusted RR

4.4).⁵⁸ Of all the individual opioids used, meperidine had the highest increased risk of delirium. Of note, those who had severe pain measured by a 5-point Likert scale had a 9-fold increased risk of delirium. This latter point suggests that while opioids do have an increased risk of delirium, under treating severe pain may be riskier. This issue of controlling for confounding by indication/severity is an important consideration that will be revisited below. Further studies examining the risk of opioids on cognitive function in older adults in other care settings are needed.

Injuries adverse drug events—Takkouche et al (in 2007) published the results of a meta-analysis that included pooled data for six observational studies.⁵⁹ They found that those exposed to opioids had a 38% increased risk of fractures (OR 1.38, 95% CI 1.15–1.66). Since that time, five additional studies have been published. Miller and colleagues (2011) compared the risk of fracture (i.e., hip, humerus, ulna, wrist) associated with initiating treatment with opioids to that of NSAIDs in older adults with arthritis.⁶⁰ Controlling for a number of potential risk factors, new opioid users compared to new NSAID users had nearly a fivefold increased risk of fracture (adjusted HR 4.9, 95% CI 3.5–6.9). They also demonstrated that the risk further increased with higher opioid doses. Saunders et al., (2010) examined the risk of opioids with fractures (excluding vertebral) in older Health Maintenance Organization patients.⁶¹ They found a non-statistically significant increased risk with opioid use and fractures (adjusted HR 1.28, 95%CI 0.99–1.64). They did, however, demonstrate a dose-response relationship where those taking 50mg or higher oral morphine equivalents (OME) had a two-fold increased risk of fractures (adjusted HR 2.00, 95%CI 1.24–3.24). Solomon et al examined the risk of individual oral opioid receptor agonist (i.e., tramadol, oxycodone, codeine) use compared to hydrocodone use and a variety of outcomes in older adults with nonmalignant pain.⁶² They found that those exposed to tramadol were less likely to experience a fracture than those exposed to hydrocodone (rate ratio 0.21, 95%CI 0.16–0.28). No dose response relationship was found in tramadol users. Moreover, there were no differences in fracture risk between users of hydrocodone and codeine or oxycodone. This same group examined the risk of fracture (i.e., hip, humerus, ulna, wrist) associated with any opioid use compared to non-selective NSAID use in older adults with arthritis.³⁶ Of interest, this study used the same databases used by the Miller et al⁶⁰ study but uniquely matched on propensity scores. Another difference was taking COX-2 selective NSAIDs out of the comparison exposure group and extending the follow-up period one year. As one might expect, this manuscript reported a similarly higher increased risk of fracture in opioid users (adjusted HR 4.47, 95% CI 3.12–6.41).⁶² No dose or duration response analyses were conducted, but they did report the number of subjects that would need to be exposed to opioids to observe one excess fracture (i.e., number needed to harm) was 47. It is not clear that such a common rate of fracture (2 in every 100 older adults using opioids) is clinically sensible.

Buckeridge and colleagues from Canada examined the risk of injuries (i.e., soft tissue laceration/subluxation that can be due to falls or motor vehicle accidents and/or fracture excluding vertebral) with time-varying exposure to opioids categorized by potency.⁶³ The only exposure group with an adjusted hazard ratio above two was seen in those taking codeine combined with non-opioid analgesics (adjusted HR 2.27, 95% CI 2.21–2.34). However, the exposure to any low potency opioid (i.e., codeine, oxycodone, pentazocine, or butorphanol) had a much lower risk of injuries (adjusted HR 1.36, 95% CI 1.33–1.39). It is important to note that this group was able to control for important potential confounders (e.g., gait and balance problems, cognitive impairment, and other CNS active agents). This latter point is important as seen in a cohort study that found that the combined use of CNS active agents (i.e., antidepressants, antipsychotics, benzodiazepine receptor agonists, and opioids) had an increased risk of recurrent falls even after controlling for the most common indications/pain in community dwelling elders.⁶⁴

The studies by Miller et al⁶⁰ and Solomon et al⁶² are to be commended for addressing potential confounding by indication by restricting the study samples to those with arthritis. It is important to note, however, the inability to control for pain severity by these studies and the others described above could have had an important confounding effect similar to what was seen in the delirium study by Morrison et al.⁵⁸ From several studies, compared to no exposure, the point estimates (OR/HR/RR) for opioid use with various forms of injuries in older adults are less than 1.5 and confounding (especially for pain severity) cannot be ruled out. Future studies that control for pain severity along with other important factors not typically found in administrative databases (e.g., depression, cognitive impairment, mobility) are needed to better assess the risk/benefits of opioid use.

Other adverse drug events—The study described above by Solomon et al also reported an increased risk of opioid use with hospitalization and mortality compared to non-selective NSAIDs.³⁶ The second study by this group suggests that the increased risk of mortality may only be seen with either codeine or oxycodone use.⁶² In addition, they found that codeine use may also increase the risk of cardiovascular events.

An interesting nested case-control study by Dublin et al found nearly a 38% increased risk of pneumonia (adjusted OR 1.38; 95% CI 1.08–1.76) in community dwelling immunocompetent elders exposed to opioids.⁶⁵ This group also categorized the following opioids as immunosuppressive: codeine, morphine, fentanyl, and methadone; they determined that the risk of pneumonia was greatest in this exposure group (adjusted OR 1.88, 95% CI 1.26–1.79). They also found higher risks in those taking long-acting agents (sustained-released forms of morphine or oxycodone, transdermal fentanyl, methadone, levorphanol) but not with benzodiazepine use.⁶⁵ Furthermore, a recent meta-analysis of randomized controlled trials found that constipation, nausea and dizziness occur in at least one in five older subjects receiving opioid analgesics.⁶⁶ Future studies that replicate these findings are necessary to more firmly establish the risk of opioids with these miscellaneous events.

Summary—Opioids may increase the risk of a number of important events in older adults. These include cognitive impairment/delirium and injuries (i.e., falls and fractures). In addition, there is emerging literature suggesting that opioid use in the elderly may increase the risk of cardiovascular events, pneumonia, and perhaps hospitalization/death. These potential risks need to be balanced by their effectiveness with improving functional status and reducing moderate/severe pain not controlled by non-opioids. In most cases, tramadol may be preferred in those without a seizure disorder or taking drugs that might increase the risk of serotonin syndrome or block the activation of this medication.⁴ In general, long-acting opioids should be avoided in older adults naïve to previous shorter-acting agents.⁶⁷

DISCUSSION

As reviewed, there are limited data to suggest that non-frail elders are more likely than their younger counterparts to develop APAP-induced hepatotoxicity. However, given the fact that older adults are more likely than younger adults to use enzyme inducing agents and are more likely to be frail (both of which may cause an accumulation of the APAP toxic metabolite), it is reasonable to use less than 4 grams per day in these subgroups. Regarding NSAIDs, it is now well-established that older adults are at higher risk for NSAID-induced GI toxicity and renal insufficiency. In addition, similar to their younger counterparts, NSAIDs can increase the risk of adverse CV drug events. Finally, the data for opioids increasing the risk of delirium/falls/fractures need to be tempered by the risk of inadequately treating severe chronic pain.

In conclusion, we are in agreement that APAP is the mainstay frontline analgesic for OA pain, that NSAIDs should be limited to short-term use only, and that for moderate to severe pain opioids (in combination with APAP) may be preferable in those without substance abuse or dependence issues.^{46,49} Future research should focus on determining the pharmacokinetics and pharmacodynamics of common analgesics not previously studied (e.g., hydrocodone) as well as observational studies to determine the risk of individual analgesics in older adults with consideration of dose- and duration-response relationships and controlling for indication and severity of pain.^{47,49}

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Table 1
Observational studies of gastrointestinal adverse drug events from NSAIDs in older adults^{32–36}

Study	NSAIDs assessed	Design	Patient Population	Safety Outcome	Findings
Chang	Celecoxib nsNSAIDs: indomethacin, sulindac, diclofenac, ketorolac, piroxicam, flurbiprofen, mefenamic acid	Case-crossover study	Patients aged 20 years in 2006 in Taiwan (mean age 61.4 years)	Hospitalization for upper GI adverse events (peptic ulcer and bleeding, gastritis, and duodenitis)	Adjusted OR (relative to no NSAID use): Celecoxib use in those aged 65–79: 1.97 (1.53–2.54) Celecoxib use in those aged 80+: 1.63 (1.18–2.24) Oral nsNSAID use in those aged 65–79: 3.42 (3.14–3.72) Oral nsNSAID use in those aged 80+: 4.35 (3.85–4.93)
Mamdani	nsNSAIDs (e.g., naproxen, ibuprofen, diclofenac) Diclofenac + misoprostol Rofecoxib Celecoxib	Observational cohort	Older adults (aged 66+) in Ontario, Canada who initiated therapy with one of the four NSAID categories; control group of older adults who did not use any NSAID	Hospitalization for upper GI bleed	Adjusted Risk Ratios (relative to control): nsNSAIDs 4.0 (2.3–6.9), diclofenac + misoprostol 3.0 (1.7–5.6), rofecoxib 1.9 (1.3–2.8), and celecoxib 1.0 (0.7–1.6) Adjusted Risk Ratios (relative to celecoxib): nsNSAIDs 4.4 (2.3–8.5), diclofenac + misoprostol 3.2 (1.6–6.5), rofecoxib 1.9 (1.2–2.8) Adjusted Risk Ratios (relative to rofecoxib): nsNSAIDs 1.9 (1.0–3.5), diclofenac + misoprostol 1.4 (0.7–2.7)
Rahme (a)	tNSAIDs (not specified)	Observational cohort	Older adults (aged 65+) in Quebec, Canada who filled a prescription for APAP or a tNSAID between January 1998 and December 2004	Hospitalization for upper and lower GI events	Adjusted Hazard Ratios (relative to APAP 3g/day): APAP >3g/day 1.20 (1.03–1.40), tNSAIDs 1.63 (1.44–1.85), and APAP + tNSAIDs 2.55 (1.98–3.28) Adjusted Hazard Ratio (relative to tNSAIDs): APAP + tNSAIDs 1.55 (1.20–2.00)
Rahme (b)	nsNSAIDs: ibuprofen, diclofenac, naproxen Rofecoxib Celecoxib	Observational cohort	Older adults (aged 65+) in Quebec, Canada who filled a prescription for one of the analgesic medications specified between April 1999 and December 2002	Hospitalization for GI bleeding	Adjusted Hazard Ratios (relative to APAP alone): Naproxen 2.75 (2.05–3.69), celecoxib + ASA 1.85 (1.48–2.31), diclofenac + ASA 3.06 (2.16–4.35), naproxen + ASA 2.37 (1.40–3.99), APAP + ASA 1.56 (1.31–1.87)
				Combined outcome of AMI/GI bleeding	Adjusted Hazard Ratios (relative to APAP alone): Naproxen 1.59 (1.31–1.93), celecoxib + ASA 1.34 (1.19–1.52), diclofenac + ASA 1.69 (1.35–2.10), APAP + ASA 1.29 (1.17–1.42)
Solomon	Non-selective NSAIDs: diclofenac, etodolac, flurbiprofen, ketorolac, ibuprofen, indomethacin, meloxicam, naproxen, piroxicam, sulindac COX-2 selective NSAIDs: celecoxib, rofecoxib, valdecoxib	Observational cohort	Older Medicare beneficiaries from Pennsylvania and New Jersey who qualified for pharmaceutical assistance for low-income older adults and who initiated therapy with an nsNSAID, a COX-2 selective NSAID, or an opioid from January 1, 1999 through December 31, 2005	Upper or lower GI tract bleeding	Adjusted HR (COX-2 selective NSAID vs. nsNSAIDs) 0.60 (0.35–1.00)

Abbreviations: AMI: acute myocardial infarction; APAP: acetaminophen; ASA: aspirin; COX: cyclooxygenase; GI gastrointestinal; HR: hazard ratio; NSAID: non-steroidal anti-inflammatory drug; nsNSAID: non-selective non-steroidal anti-inflammatory drug; OR: odds ratio; tNSAID: traditional non-steroidal anti-inflammatory drug