Nonsteroidal anti-inflammatory drugs and their effects in the elderly

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Management of chronic pain can often be a challenging task, especially in the elderly. Patients over the age of 65 years have altered metabolism and pharmacodynamics that increase their susceptibility to adverse side effects. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a common component of pain management in this population. Nonselective NSAIDs as well as selective Cox-2 inhibitors have been associated with side effects, including renal dysfunction, heart failure, gastrointestinal toxicity and increased risk of cardiovascular side effects. These adverse effects are particularly important in the elderly, and thus use of NSAIDs in this population must be scrutinized carefully. If NSAIDs are utilized, they should be tailored to the individual patient and administered in the lowest dose and for the shortest duration possible. It is hoped that future studies will provide further insight into the safety of these agents in elderly patients.

Chronic pain remains a significant source of distress and disability, particularly in the elderly population. It is estimated that 20% of individuals suffer from various forms of chronic pain worldwide [1]. Among this population, over 30 million people utilize nonsteroidal anti-inflammatory drugs (NSAIDs) for treatment of their discomfort. Approximately half of these patients are over the age of 65 years and use NSAIDs on a daily basis [2,3]. It is these patients that have the most comorbidities, which places them at highest risk of side effects. As the population ages, it is anticipated that the use of chronic pain medications for degenerative joint disease and other chronic ailments will only continue to increase. The most common pain medications used in these patients are NSAIDs as an alternative to opioid analgesics. Although initially viewed as a safer alternative in this particular population, emerging evidence suggests that the adverse effects on a variety of end organ systems may sometimes outweigh the analgesic benefits. Additionally, treatment costs of NSAID-induced cardiovascular (CV) and gastrointestinal (GI) side effects may negate the cost-effectiveness of oral administration of this class of medications when compared with topical preparations as measured by quality-adjusted life years [4]. The majority of elderly populations suffer from osteoarthritis; however, pain medication requirements can also stem from a variety of other conditions, including cancer-related discomfort and neuropathic pain from diabetes or zoster. Thus, the elderly often have unique requirements for treatment of pain, which could be compounded by a variety of medical conditions.

Although they are perhaps the population that can benefit the most from use of chronic pain medications, they are also the most susceptible to side effects due to altered pharmacodynamics secondary to changes in drug distribution dynamics, reduced metabolism and impaired absorption. NSAIDs, along with aspirin, have been implicated in increasing the risk of hospital admissions in elderly populations attributed to adverse drug reactions. In this review, we aim to discuss the current literature regarding the benefits and adverse effects of NSAID use in the elderly, in addition to highlighting future areas of study. Guideline recommendations from the American College of Cardiology/American Heart Association as well as the American Geriatric Society are included. We additionally queried the MEDLINE database as well as clinicaltrials.gov with keywords including elderly, nonsteroidal anti-inflammatory drugs, heart failure, myocardial infarction (MI), GI toxicity and renal dysfunction. We have synthesized these results in this review to provide a summary of the currently available literature on NSAID use in the elderly and the associated potential for adverse side effects.

Aspirin

Acetylsalicylic acid (ASA), better known as aspirin, was originally discovered in the 18th century although anecdotal use dates back to ancient Greek times. GI toxicity was noted as a use-limiting side effect early on, thus efforts to produce NSAIDs with improved efficacy and reduced toxicity led to the development of various forms of this medication. Although aspirin was one of the original NSAIDs developed for the
treatment of pain, there are limited data available on how often aspirin is used for this purpose. Instead, it is well validated role in primary and secondary prevention of CV disease places it in unique category compared with other NSAIDs. Multiple trials including a meta-analysis by the Antithrombotic Trialists’ Collaboration have demonstrated that anti-platelet therapy with aspirin reduces occurrence of major vascular events in patients with evidence of prior CV disease including MI, angina and stroke [5]. In patients with prior MI, aspirin therapy resulted in 36 fewer adverse events for every 1000 treated patients. For primary prevention, an updated meta-analysis in 2009 demonstrated a 12% risk reduction in major CV events primarily driven by reduction in MI; however, this benefit was mostly observed in men [6]. Although efficacy in reducing CV events is validated, aspirin still has an associated risk of bleeding. Unlike other NSAIDs, ASA irreversibly inhibits platelet function for the life of the platelet (7–10 days). The same 2009 meta-analysis also demonstrated a trend towards increased risk of hemorrhagic stroke and a 50% relative risk increase of major GI bleeding.

Although data is not definitive, there have been concerns raised over the potential for interaction between aspirin and NSAIDs. The belief is that concurrent NSAID use may interfere with the beneficial effects of aspirin, since nonselective NSAIDs compete with aspirin for binding to the Cox-1 enzyme. Studies have suggested the highest interaction to be with ibuprofen or naproxen, but this theoretical interaction could occur with any NSAID [7,8]. These studies mainly analyzed healthy subjects and have not clearly demonstrated that these interaction effects are clinically significant and results have been conflicting [9,10]. However, the US FDA suggests separating the time of administration of these compounds at least 2 h apart to avoid any possible interaction.

Although ASA has clearly been demonstrated to be effective in CV risk reduction, its use in the elderly population is not as clear. The US Preventive Services Task Force recommendations for use of ASA in patients 80 years or older state that the evidence is insufficient to determine the balance risks and benefits of aspirin for CV disease prevention [11]. An ongoing large, placebo-controlled trial of low-dose ASA in subjects over the age of 65 years without known CV disease is designed to assess the efficacy and safety of primary prevention of CV disease and dementia [12]. This study should significantly contribute to our understanding of ASA use in the elderly.

Nonselective NSAIDs
The primary mechanism of action of NSAIDs is inhibition of the Cox enzyme (prostaglandin synthase), thus impairing conversion of arachidonic acid to prostaglandins, prostacyclins and thromboxanes. Extent of enzyme inhibition varies by different NSAIDs and subclasses. Cox-1 and -2 are the primary isoforms of the Cox enzyme. They differ in the tissues in which they are present, which is important to understanding their different effects. Cox-1 is expressed in a wide variety of tissues, but to different degrees and is involved in regulation of gastric protection, kidney function and platelet function. Cox-2 is primarily upregulated in states of inflammation [13]. Although NSAIDs are deemed ‘nonselective’ they are known to differ in their affinity for Cox-1 versus -2 inhibition with older NSAIDs, including etodolac and nabumetone having relatively more selectivity for Cox-2. Concordantly, adverse effects between these more selective agents may be similar to selective Cox-2 inhibitors.

A wide variety of NSAIDs are available without prescription with six different classes, including over 20 different medications currently available in the USA (see Table 1). Currently available nonselective NSAIDs inhibit both Cox pathways and include ibuprofen, which is one of the most commonly used and widely available over-the-counter NSAIDs. This agent, although available over-the-counter, can still produce toxicity if administered at high doses and for extended periods of time. In the elderly, enterohepatic circulation is often reduced, thus increasing the length of mucosal exposure to NSAIDs leading to increased incidence of GI bleeding. Therefore, in this particular population it may be best to avoid long-acting NSAID preparations.

Selective Cox-2 inhibitors
Cox-2 inhibitors differ mainly in their tissue specificity and enhanced expression of Cox-2 during states of inflammation. Examples of these agents, along with those withdrawn from the market, are listed in Table 2. As inhibition of Cox-2 avoids interference with pathways protective of GI mucosa, selective Cox-2 inhibitors were originally developed to decrease potential GI side effects. Although they are selective for Cox-2 inhibition, they are generally felt to be as efficacious in regards to analgesia as nonselective NSAIDs [14,15]. The most commonly cited Cox-2 inhibitors are celecoxib, valdecoxib and rofecoxib. In 2004, rofecoxib was withdrawn worldwide after continued evidence of increased risk of CV events was observed.
Although Cox-2 inhibition is believed to have less GI toxicity [16,17], this reduction in GI risk compared with nonselective NSAIDs may not be present with concurrent use of ASA. In one study that analyzed ulcer occurrence, the incidence of ulcers was similar in patients taking either celecoxib or a nonselective NSAID if taken in conjunction with a low-dose ASA [16]. Therefore, the benefits of specific Cox-2 inhibition may be negated by ASA use for CV disease prevention in regards to GI side effects although another study by Altman et al. demonstrated benefit in reduction of adverse CV outcomes in acute coronary syndrome patients with meloxicam used in conjunction with heparin and ASA without excess GI effects [18]. Although evidence is inconclusive, it may be prudent to incorporate a proton pump inhibitor or other mucosal protective measures to prevent GI toxicity especially in the elderly who are at highest risk for GI complications.

One of the products of the Cox pathway is thromboxane, which is an important component of platelet function. Preferential blockade of Cox-2 avoids interaction with thromboxane production and, therefore, does not affect platelet function (as opposed to nonselective NSAIDs). This was seen in a study assessing very high doses of celecoxib compared with placebo and naproxen, which demonstrated no change in platelet function compared with significant increase in bleeding time and decreased platelet aggregation and adhesion with naproxen [19]. This preferential lack of effect may be beneficial when use of a NSAID is needed in the setting of additional anticoagulation for other conditions, such as atrial fibrillation or mechanical valves; both conditions that are more common in the elderly.

### Table 1. Nonsteroidal anti-inflammatory drugs available in the USA.

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Typical adult dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Oral: 325–650 mg every 4–6 h; maximum daily dose: 4 g; rectal suppository available</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>Oral: 500–1000 mg followed by 250–500 mg every 8–12 h; maximum daily dose: 1.5 g</td>
</tr>
<tr>
<td>Salsalate</td>
<td>Oral: 3 g/day in two to three divided doses</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Oral: 400–800 mg every 6 h as needed; maximum daily dose: 3.2 g</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Oral: 500 mg, then 250 mg every 6–8 h; maximum daily dose: 1.25 g</td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>Oral: 300–600 mg three- to four-times/day; maximum daily dose: 3.2 g</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Oral: 50 mg four-times/day or 75 mg three-times/day; maximum daily dose: 300 mg</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>Oral: 200–300 mg/day in two, three or four divided doses; maximum daily dose: 300 mg</td>
</tr>
<tr>
<td>Oxaprozin</td>
<td>Oral: 600–1200 mg/day</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Oral: 25–50 mg two- to three-times/day; maximum daily dose: 200 mg; iv. rectal suppository also available</td>
</tr>
<tr>
<td>Sulindac</td>
<td>Oral: 150 mg twice daily; maximum daily dose: 400 mg</td>
</tr>
<tr>
<td>Tolmetin</td>
<td>Oral: 600 mg to 1.8 g/day; maximum daily dose: 1.8 g</td>
</tr>
<tr>
<td>Etodolac</td>
<td>Oral: 400 mg twice daily or 300 mg two- to three-times/day or 500 mg twice daily</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Oral: 20 mg, followed by 10 mg every 4–6 h; maximum daily dose: 40 mg; oral dosing is intended to be a continuation of im. or iv. therapy only</td>
</tr>
<tr>
<td>Ind.: 60 mg as a single dose or 30 mg every 6 h; maximum daily dose: 120 mg</td>
<td></td>
</tr>
<tr>
<td>Iv.: 30 mg as a single dose or 30 mg every 6 h; maximum daily dose: 120 mg</td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Oral: 150–200 mg/day in three to four divided doses; Transdermal:</td>
</tr>
<tr>
<td></td>
<td>• Gel: apply 4 g of 1% gel to affected area four-times/day; maximum daily dose: 16 g/joint</td>
</tr>
<tr>
<td></td>
<td>• Solution: apply 40 drops to each affected knee(s) four-times/day</td>
</tr>
<tr>
<td></td>
<td>Topical patch also available</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>Oral: 1000 mg/day; maximum daily dose: 2000 mg</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Oral: 10–20 mg/day; maximum daily dose: 20 mg</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>Oral: 7.5–15 mg once daily; maximum daily dose: 15 mg</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>Oral: 500–250 mg every 4 h as needed; maximum therapy: 1 week</td>
</tr>
<tr>
<td>Meclofenamic acid</td>
<td>Oral: 200–400 mg/day in three to four divided doses; maximum daily dose: 400 mg</td>
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</table>

*im.: Intramuscular; iv.: Intravenous; NSAID: Nonsteroidal anti-inflammatory drug.

Data taken from [68,69,101].
This was demonstrated in a study assessing bleeding in patients on warfarin in a case–control study. Patients with bleeding were much more likely to have used a nonselective NSAID compared with patients without bleeding who were more likely to have used a Cox-2 inhibitor [20].

**NSAIDs & potential adverse side effects**

In the elderly, a variety of factors can play into elevated risk of adverse end-organ effects, which may outweigh any benefits with regards to NSAIDs. Altered mechanisms of drug metabolism may prolong exposure to the harmful end products of the Cox pathways. Most analgesic doses are not adjusted for age; therefore, the most prudent way to prescribe these medications is to start at the lowest dose and titrate up as needed for effect.

In patients with swallowing difficulties, alternative forms of NSAID therapy (i.e., transdermal preparations) can be considered, although absorption may be more variable. Although NSAIDs can provide significant pain relief, the risks and benefits, particularly in the elderly, must be considered carefully. We review the most common known adverse side effects in this section.

**Hypertension**

All NSAIDs elevate blood pressure to some degree in both normotensive and hypertensive individuals [21]. Elevation in blood pressure varies, but ranges from 2 to 5 mmHg across a wide range of studies. Hypertensive effects of NSAIDs are most likely due to Cox-2 inhibition and subsequent effects on renal physiology. In the kidneys, Cox-2 inhibition leads to decreased sodium excretion and increased intravascular volume. Aspirin has minimal effect on Cox-2, and does not elevate blood pressure [22,23].

Multiple meta-analyses have studied the association between NSAIDs and hypertension. In one study by Pope et al., subjects with a mean duration of NSAID therapy for 15 days experienced an increase in mean arterial pressure of 3.3 mmHg with noticeable differences between specific NSAIDs. After adjustment for sodium intake, naproxen demonstrated the highest increase in blood pressure (3.7 mmHg) [23]. Another meta-analysis by Johnson et al. evaluated 50 randomized control trials with the mean age of participants being 47 years [22]. In two-thirds of these trials the duration of NSAID use was at least 1 week and was associated with an increase in blood pressure of 5 mmHg. However, sub-analyses demonstrated significant increases in only those with controlled hypertension, with piroxicam, ibuprofen and indomethacin all demonstrating the highest increases in mean arterial pressure when compared with placebo. Overall, these two analyses showed elevation in blood pressures that varied by specific NSAID and presence of underlying hypertension.

The SUCCESS VI and VII studies analyzed the relationship between blood pressure and Cox-2 inhibition in a large group of patients with hypertension. These studies included a large proportion of elderly subjects over the age of 65 years and demonstrated a significant increase in number of patients with blood pressure elevation with rofecoxib compared with celecoxib [24,25]. Additionally, the CRESCENT trial evaluated changes in blood pressure among diabetics with controlled hypertension (mean age 63 years old). Patients on rofecoxib demonstrated the highest elevations in blood pressure [26].

**GI toxicity**

Prostaglandins and prostanoids are critical in maintaining gastric mucosal integrity. The GI

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**Table 2. Selective Cox-2 inhibitors.**

<table>
<thead>
<tr>
<th>Selective Cox-2 inhibitors</th>
<th>Typical adult dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib (Celebrex®)</td>
<td>Oral: 200 mg/day as a single dose or in divided doses twice daily</td>
</tr>
<tr>
<td>Rofecoxib (Vioxx®)</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Valdecoxib (Bextra®)</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Parecoxib (Dynastat®)</td>
<td>Im., iv.: 40 mg, followed by 20–40 mg every 6–12 h; maximum daily dose: 80 mg Withdrawn, available in Europe</td>
</tr>
<tr>
<td>Lumiracoxib (Prexige®)</td>
<td>Oral: 400 mg once daily Withdrawn, available in Mexico</td>
</tr>
<tr>
<td>Etoricoxib (Arcoxia®)</td>
<td>Oral: 30–60 mg once daily Withdrawn, available in Europe</td>
</tr>
</tbody>
</table>

*im.: Intramuscular; iv.: Intravenous.
Data taken from [68,69,101].
mucosa uses local Cox-1 to produce these protective prostaglandins. Inhibition of Cox pathways by aspirin doses as low as 10 mg per day have been associated with subclinical mucosal damage with higher doses associated with increased risk of clinically apparent toxicity [27]. Aspirin has also been shown to increase the incidence of duodenal ulcers [28, 29] with concurrent Helicobacter pylori infection potentially playing an independent role in ulcer formation in the setting of NSAID use [30]. Multiple studies have sought to identify additional risk factors for GI hemorrhage associated with NSAID use. Duration of treatment appears to be an important risk factor, along with older age, prior history of NSAID-induced GI toxicity, history of peptic ulcer disease, concurrent use of steroids or antiplatelet agents, such as clopidogrel and use of other anticoagulants [31].

Renal dysfunction
Nonselective NSAIDs may induce both acute and chronic renal injury. Acute injury is secondary to prostaglandin-mediated vasoconstriction [32]. Although injury can occur with any NSAID, a large study conducted in an elderly population demonstrated an increased risk of acute kidney injury within 30 days of initiation of naproxen, rofecoxib and celecoxib [33]. It has been suggested that low-dose ASA, ibuprofen and sulindac are safer agents [34, 35]; however, low-dose ASA in the elderly may still have an associated risk of renal dysfunction [36].

In relatively healthy patients, large clinical trials have not demonstrated a significant risk of renal dysfunction with use of Cox-2 inhibitors; however, in high-risk patients with underlying renal disease and other precipitating factors, such as heart failure and volume depletion, these agents can affect renal function. In several studies, older patients seemed to be particularly susceptible to significant reductions in glomerular filtration rate [37, 38]. Thus, elderly patients with underlying renal function or other conditions that may predispose to renal dysfunction should avoid selective Cox-2 inhibitors.

Heart failure
Several large cohort studies have looked at the association between heart failure and NSAID use. In one study, relative risk for first occurrence of heart failure was not significantly different among NSAID users compared with nonusers [39]. However, risk of rehospitalization for heart failure appears to be significantly increased with NSAID use, specifically diclofenac and ibuprofen, and appears dose dependent [40]. In another study, ibuprofen given in total doses of at least 1200 mg/day and naproxen at least 500 mg day, were associated with increased risk of death as well [41]. The primary mechanism of NSAID-induced heart failure may be due to increased afterload from NSAID-induced vasoconstriction [42]. Although patients with pre-existing hypotension appear to be at greatest risk, this likely serves more as a marker for those patients with more severe heart failure who are thereby more susceptible to fluid and sodium shifts induced by NSAIDs as opposed to an actual risk factor for heart failure [43].

Selective Cox-2 inhibitors have also been studied in relation to heart failure. In patients older than 66 years of age without known heart failure, rofecoxib was associated with increased risk of hospitalization for heart failure [44]. In patients with known heart failure, there appears to be a dose-dependent relationship between risk of death with rofecoxib, celecoxib and diclofenac [41]. High-dose ibuprofen (1200 mg) and naproxen (>500 mg daily), were associated with increased risk of death [41]. NSAID-induced vasoconstriction may also negate the beneficial afterload reducing effects of angiotensin-converting enzyme inhibition [40, 45].

Adverse CV events
In 2004, rofecoxib was withdrawn from the market due to evidence of increased CV events. Additionally, valdecoxib (and its intravenous prodrug parecoxib) were withdrawn from the market in 2005 over similar concerns. Although celecoxib remains on the market, caution has been advised with regard to dose-dependent CV risks associated with these agents. Although many trials have highlighted the risks associated with selective Cox-2 inhibitors, CV events are not just limited to these agents. Nonselective NSAIDs, particularly those that are more selective for Cox-2, such as diclofenac, have been associated with adverse CV events, primarily MI [46, 47]. However, other studies have been less conclusive [48, 49]. In a recent post-hoc analysis from the INVEST trial, patients with coronary artery disease and hypertension who endorsed chronic use of NSAIDs over an average length of 2.7 years were found to have a significant (47%) increase in adverse CV events (death, nonfatal MI or nonfatal stroke). The exact data on the type of NSAID was not collected, thus it was presumed to be a class effect. The results of this analysis are particularly important as the average age of study subjects was 65 years.
Various studies have demonstrated increased risk of CV events with Cox-2 inhibition although the extent of elevated risk appears to depend on dose [51] and may differ among specific NSAIDs [52]. A recent meta-analysis from Trelle et al. assessed CV safety of NSAIDs in 31 trials in over 100,000 patients. The investigators found that rofecoxib was associated with the highest risk of MI and ibuprofen was associated with the highest risk of stroke. Celecoxib and diclofenac were associated with the highest risk of CV death, while naproxen was associated with the least harm [52]. After MI, short-term use of celecoxib and rofecoxib has been associated with an increase in risk of death [53]. In a study of patients older than 65 years of age, first-time use of rofecoxib was associated with significant increased risk of MI [54]. In 2011, a large meta-analysis found risk of MI with Celebrex® (Pfizer, NY, USA) to be lower than rofecoxib or ibuprofen, but greater than naproxen [52]. The ACP trial for polyp prevention was terminated prematurely due to increased CV events and risk of CV death [55]. However, although these trials suggest an association between celecoxib and CV risk, several other studies including CLASS and SUCCESS-1 did not support these assertions [16,56].

The ADAPT was developed to test the hypothesis that use of naproxen or celecoxib in a healthy elderly population would reduce the incidence of dementia [57]. This trial, however, was stopped in 2004 after increasing concerns over CV toxicity associated with Cox-2 inhibitors in general in light of the withdrawal of rofecoxib from the market and suspension of celecoxib use in clinical trials.

**Guidelines**

Several different advisory guidelines have been published addressing NSAID use and the association between various adverse side effects (Table 3). These include the American Heart Association, the American College of Cardiology and the American College of Rheumatology. All of these agencies advise caution with prolonged use of any NSAID. Specific caution is recommended by the American College of Cardiology/American Heart Association against use of NSAIDs in heart failure patients and in those presenting with acute MI or unstable angina [58,59]. However, the American College of Rheumatology does acknowledge that, in patients with severe arthritis, the potential risks associated with NSAIDs use may be outweighed by the benefits of adequate pain management and therapy should be tailored to the individual patient [60].

The most recent guidelines from the American Geriatrics Society Panel on the management of persistent pain in the elderly published in 2009 focused primarily on discussion of pharmacotherapeutic options [61]. They advise that alternate routes of administration including transdermal preparations may be suitable option in some patients. Additionally, as the elderly often demonstrate varied absorption of medications, the shortest acting form of any pain medication should be used for intermittently occurring pain. Acetaminophen is recommended as a first choice as it is not associated with adverse side effects, such as GI bleeding, renal or CV toxicity. However, it is not a targeted anti-inflammatory, which often makes acetaminophen less effective for treatment of chronic pain conditions, such as osteoarthritis or rheumatoid arthritis. If NSAIDs are used it is recommended that the lowest dose for the shortest duration be utilized and that consideration be given for concurrent administration of a mucosal protective agent, such as a proton pump inhibitor or H2-receptor antagonist.

Additionally, although the FDA has released warnings on the use of selective and nonselective NSAIDs, there is a lack of specific information on use of these agents in the elderly. As the literature highlights, there are significant specific CV, GI and other end-organ side effects that are heightened in the elderly population. Future public health campaigns by the FDA and other government agencies should focus on highlighting these various potential harmful side effects in the elderly as use of NSAIDs in this population will only continue to increase as the population ages.

**Alternative analgesics & nonpharmacologic therapies**

Due to the previously discussed potential for side effects, particularly prominent in the elderly, alternative therapies for treatment of chronic pain should be considered. As discussed previously, acetaminophen may be considered as a first-line therapy for pain. Acetaminophen penetrates the CNS and produces analgesia by altering pain perception resulting in a higher pain threshold.

Opioid therapy is another alternative for pain treatment. Although these agents are still associated with some risk of cardiac events as compared with NSAIDs [62], opioids are associated
with less GI toxicity. However, other side effects such as constipation, respiratory depression and sedation can be use limiting. Still, opioids are a reasonable option for treatment of chronic pain, especially in the elderly who demonstrate the lowest risk of abuse of these agents [61]. However, if concerns over abuse potential or side effects exist, tramadol may be another alternative agent. Tramadol is a centrally acting analgesic alternative with both monoaminergic and opioid effects [63]. In fact, this dual mechanism of pain control gives tramadol some advantages in the management of neuropathic pain. However, the use of tramadol is limited because abuse potential still exists, and serious drug interactions are possible due to its metabolism. Tapentadol is a newer similar analgesic with combined opioid and noradrenergic actions that has been found to be as effective for the management of osteoarthritis and lower back pain as oxycodone and morphine. It also has superior GI tolerability [64]. Since no metabolic activation is necessary, tapentadol has less drug interactions than tramadol and may be a preferred analgesic in patients with mild hepatic or renal impairment.

Unlike oral therapies, targeted topical administration of analgesics can minimize systemic side effects. Topical NSAIDs are designed to provide analgesia, but with much lower systemic exposure. Specifically, topical ibuprofen has been shown to have similar efficacy to oral ibuprofen, and was in fact the preferred administration method by patients [65]. In another small study, lidocaine 5% transdermal patch was found to be no different than celecoxib in effectiveness and tolerability for treatment of osteoarthritic knee pain [66]. Although these topical/transdermal agents are not always feasible, they may present a reasonable option for chronic management of mild-to-moderate pain, especially in the elderly.

As an additional option, a variety of nonpharmacotherapy-based therapies for treatment of chronic pain have also been studied. Examples of more targeted local therapies include pulsation-based thermal therapy, localized nerve blockade and radiofrequency neurotomy. Such therapies, along with many other nonpharmacologic therapies currently being developed, have demonstrated significant promise and further advancements in these techniques may lead to reduced need for chronic oral therapies, such as NSAIDs.

**Conclusion & future perspective**

Although advances have been made in understanding the potential for adverse effects of NSAIDs in the elderly population, opportunities exist to further expand our knowledge in this area. Future trials should focus on improving our understanding of the safety of NSAID use in the elderly. One such trial currently underway is the PRECISION trial. This is a multicenter, multinational study designed to assess the CV safety of celecoxib relative to ibuprofen and

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**Table 3. Summary of nonsteroidal anti-inflammatory drug guidelines.**

<table>
<thead>
<tr>
<th>Writing group</th>
<th>Patient population</th>
<th>Position on NSAIDs</th>
<th>Additional recommendations on NSAIDs</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Geriatrics Society</td>
<td>Age ≥65 years</td>
<td>Acetaminophen recommended as first-line therapy in the elderly</td>
<td>If NSAIDs are used, it should be for the shortest time period and lowest dose. Consider use of concurrent mucosal protective agent</td>
<td>[61]</td>
</tr>
<tr>
<td>American Heart Association/American College of Cardiology</td>
<td>Heart failure</td>
<td>Recommends against use of NSAIDs in patients with heart failure</td>
<td>Consider gastroprotection therapy for patients on concurrent ASA and NSAID</td>
<td>[59]</td>
</tr>
<tr>
<td>American Heart Association/American College of Cardiology</td>
<td>Patients hospitalized for MI, unstable angina</td>
<td>Recommends immediate cessation of all nonaspirin NSAIDs upon hospital admission</td>
<td>Upon hospital discharge, can consider naproxen if acetaminophen is ineffective</td>
<td>[58]</td>
</tr>
<tr>
<td>American College of Gastroenterology</td>
<td>Age ≥65 years</td>
<td>Helicobacter pylori infection increases the risk of NSAID-related GI complications</td>
<td>Testing and treatment for Helicobacter pylori in high-risk patients prior to the initiation of NSAID therapy may reduce the risk of GI complications</td>
<td>[70]</td>
</tr>
<tr>
<td>American College of Rheumatology</td>
<td>Patients with chronic arthritis</td>
<td>Benefits of NSAIDs in patients with severe arthritis may outweigh risks</td>
<td>Naproxen is the NSAID of choice in patients at increased CV risk</td>
<td>[60]</td>
</tr>
</tbody>
</table>

ASA: Acetylsalicylic acid; CV: Cardiovascular; GI: Gastrointestinal; MI: Myocardial infarction; NSAID: Nonsteroidal anti-inflammatory drug.
It is targeted to patients with rheumatoid arthritis or osteoarthritis. In addition, patients had established or were at high risk for CV disease. Although targeting a diverse population, this trial should have a substantial number of elderly subjects enrolled due to the high prevalence of osteoarthritis in this population. As the PRECISION study was designed for assessment of safety, lack of early termination of the trial suggests no difference in end points but final results should shed further light on the safety of NSAID use in the elderly population, which is often excluded from clinical trials. Further research efforts should also focus on targeting the management of pain in the elderly to create safer medications for the treatment of chronic pain. Additionally, alternate approaches to pain management, including nonpharmacologic therapies, should continue to be developed.

Management of chronic pain in the elderly remains a challenge and will become increasingly prominent as the population ages. Although NSAIDs produce significant analgesia, they are not without significant risk of adverse CV and other end-organ side effects. Use of NSAIDs in the elderly should be monitored carefully and individualized to each patient’s needs for maximal efficacy in pain management and minimal risk of adverse effects.

Financial & competing interests disclosure
AA Bavry has received research support from Novartis Pharmaceuticals and is a contractor for the American College of Cardiology’s Cardiosource. Publication of this article was funded, in part, by the University of Florida Open-Access Publishing Fund. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Considerations for pain therapy in the elderly
• A significant proportion of patients treated for chronic pain are over the age of 65 years.
• Elderly patients often have multiple comorbidities making treatment of chronic pain challenging.
• Elderly patients have altered metabolism and pharmacodynamics, which can alter drug metabolism.
• Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used agents for chronic pain therapy, but can cause significant end-organ damage, particularly in the elderly.

Aspirin
• Aspirin was originally designed for the treatment of pain but also has proven benefit in primary and secondary prevention of cardiovascular disease.

Nonselective NSAIDs
• Wide variety of prescription and over-the-counter preparations available for the treatment of acute and chronic pain.

Selective Cox-2 inhibitors
• Designed to provide equivalent analgesia but less gastrointestinal toxicity compared with nonselective NSAIDs.

NSAIDs & potential adverse side effects
• All NSAIDs, to varying degrees, can elevate blood pressure in both normotensive and hypertensive patients.
• Inhibition of Cox pathways leads to mucosal compromise and increase in gastrointestinal toxicity with increased risk of bleeding.
• Both nonselective NSAIDs and Cox-2 inhibitors may induce renal dysfunction, particularly in the elderly.
• NSAIDs appear to increase the risk of hospitalization in patients with known heart failure.
• Selective Cox-2 inhibitors and nonselective NSAIDs have been associated with an elevated risk of adverse cardiac events, such as myocardial infarction.

Guidelines
• Published guidelines from a variety of sources advocate caution with use of NSAIDs in those with heart failure, acute myocardial infarction and the elderly. Acetaminophen is recommended as first-line therapy in the elderly and, if NSAIDs are used, they should be prescribed in the lowest dose for the shortest duration possible.

Alternative analgesics & nonpharmacologic therapies
• Nonpharmacologic treatments for the management of chronic pain should be considered as an alternative to NSAIDs, particularly in the elderly.

Future perspective
• Future trials such as the PRECISION study should significantly contribute to our understanding of NSAID safety, particularly in the elderly.
References

Papers of special note have been highlighted as:

• of interest
•• of considerable interest


** Important meta-analysis demonstrating the benefits of aspirin in the reduction of cardiovascular events.


• Study in progress that will contribute significantly to our understanding of safety and efficacy of acetylsalicylic acid therapy in the elderly.


31. No authors listed. Final report on the aspirin component of the ongoing physicians’ health

NSAIDs in the elderly – REVIEW

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Aging Health (2012) 8(2) 175


•• Key statement from the American Geriatrics Society highlighting challenges in management of chronic pain in the elderly.


•• Study designed to assess safety of celecoxib in patients either with known cardiovascular disease or at high risk of adverse cardiovascular events.


Website


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