REVIEW ARTICLE

Persistent pain in the older adult

What should we do now in light of the 2009 American Geriatrics Society Clinical Practice Guideline?

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KEY WORDS

nonsteroidal anti-inflammatory drugs, older adults, persistent pain, treatment guidelines

ABSTRACT

The recent publication of revised guidelines for the management of persistent pain in the older adult (American Geriatric Society, 2009) has posed a dilemma for clinicians. In essence, these revised guidelines now downplay the use of nonsteroidal anti-inflammatory drugs (NSAIDs) relative to prior year's recommendations. The strong recommendation for caution when employing NSAIDs is because of the numerous, well-documented, potential adverse effects including renal failure, stroke, hypertension, heart failure exacerbations, and gastrointestinal complications. Nevertheless, physicians still have a substantial arsenal for combating chronic pain due to such conditions as degenerative arthritis and back problems. Options for intervention include physical therapy, topical nonsteroidals, capsaicin, topical lidocaine, intra-articular therapies, and judicious use of narcotics. In the future, cyclooxygenase-inhibiting nitric oxide-donating drugs may represent a technical improvement in the toxicity profile of traditional NSAIDs.

Introduction The recent publication of revised guidelines for the management of persistent pain in the older adult (American Geriatrics Society [AGS], 2009) has posed a dilemma for clinicians. In essence, these revised guidelines now downplay the use of nonsteroidal anti-inflammatory drugs (NSAIDs) relative to prior year's recommendations. Whereas NSAIDs have traditionally occupied a prominent role in the treatment of such conditions as osteoarthritis (OA) and low back pain, the AGS has called attention to the significant morbidity and mortality associated with their use in patients over the age of 65.

Throughout human history, these agents have been used for their analgesic and antipyretic properties. Ancient Greeks were known to chew bark from willow trees, which was later found to contain salicin, a precursor to salicylate. By the 1900s, salicylic acid was made into pill form, now known as aspirin. In more recent times, many other agents were discovered with similar properties, and the initialism, NSAIDs, was created.[1,2]

Over 30 million people use NSAIDs worldwide. The most common rheumatological disorder treated with this class of therapeutic agents is OA, which increases in prevalence with age.[3] Debility from OA may result in more sedentary, less productive lifestyles, and may contribute to missed work. Compound this issue with the high prevalence of low back pain, and it can be readily appreciated that healthcare providers treating older adults commonly confront chronic pain in their outpatient practices.

Before proceeding, it is important to emphasize that the AGS recommendations address management of only noninflammatory, noncancer pain, and only in patients older than 65 years (e.g., rheumatoid arthritis is excluded). Discussion is also limited to standard medical practice, and therefore complementary alternative medicine, herbal remedies, parenteral anesthetic agents, neurostimulatory pump technologies, biofeedback, and psychological interventions were not of relevance. In like manner, these topics are beyond the scope of our present discourse.

Caution with use of NSAIDs In 1998, the AGS specified the first set of guidelines to manage chronic pain in the elderly. This served to motivate clinicians to both address the issue of, and

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standardize the treatment of, persistent pain. The Journal of American Geriatrics Society published the latest set of guidelines in 2009 and this time the publication focused on the many cautions necessary when using NSAIDs and explored the latest alternative options.[4]

Unlike the younger population, persistent pain in the elderly is often confounded by multiple comorbidities, thereby making the target population more prone to adverse drug interactions from, for example, altered pharmacokinetics and pharmacodynamics.[4]

The strong recommendation for caution when employing NSAIDs derives from the numerous, well-documented, potential adverse effects including renal failure, stroke, hypertension, heart failure exacerbations, and gastrointestinal (GI) complications.[4,5] Specifically, NSAIDs have been associated with a 4-fold increase in mortality and for 10 to 20 of every 1000 hospitalizations.[6] One pharmacological concern was raised by the Food and Drug Administration in the United States with regard to ibuprofen in particular.[7] This agent can reduce the antiplatelet activity of cardioprotective aspirin.[2,8]

NSAIDs cause clinically significant increases in blood pressure in an already hypertension-prone population, thereby measurably increasing cardiovascular risk.[9] Furthermore, they are implicated in the disruption of the prostacyclin to thromboxane ratio, which in turn disrupts the prothrombotic/antithrombotic balance leading to more severe complications, such as myocardial infarction and stroke.[8] This risk has been especially documented in patients using rofecoxib but may also be an issue for nonselective nonsteroidals such as diclofenac.[10] In addition, patients with heart failure experience increased frequency of exacerbations from NSAIDs likely secondary to effects on the kidneys.[1,11,12] Most NSAID-related effects are time-dependent. For example, adverse GI events may be observed after as little as 2 to 3 months of continuous use.[13] In fact, they are the 15th most common medication offenders in the United States for deaths related to the upper GI tract. The cyclooxygenase (COX)-1 enzyme pathway, which is inhibited by nonselective NSAIDs, allows for mucus and bicarbonate production and gastroduodenal tract perfusion.[6] Many randomized controlled trials (VIGOR, CLASS, MEDAL, TARGET, etc.) have compared traditional NSAIDs with the COX-2 inhibitors and have shown decreased ulcer risk in the selective NSAID group. However, when COX-2 inhibitors are combined with cardioprotective aspirin, upper endoscopy assessment reveals that the incidence of ulcers is the same as that seen with nonselective NSAIDs.[2]

In light of these adverse effects, not only the AGS but others have expressed concern as well. The World Health Organization (WHO) issued a consensus statement to avoid NSAIDs in high-risk populations and to rely more heavily on opiates as first-line therapy.[14] Other organizations have issued similar cautions including the American Heart Association, American College of Rheumatology (ACR), and the American College of Gastroenterology.[6]

Based upon the currently available research literature, it is difficult to ascertain at what point NSAIDs should ideally be prescribed in elderly patients with persistent pain. Some researchers say that NSAIDs can be given to those patients at low risk of GI adverse events and the other enumerated toxicities. According to the ACR, risk factors for GR bleeding include age ≥75, peptic ulcer disease, GI bleeding, or concomitant glucocorticoid use. With regard to the kidney, risk factors for renal insufficiency associated with NSAID use include age ≥75, diabetes mellitus, hypertension, angiotensin converting enzyme inhibitor use or diuretic use.[15] Clearly, patients who rely upon these medications for the management of persistent pain must be informed of potential cardiovascular, renal, and GI adverse effects.[1,16]

According to the ACR, if older patients are prescribed either nonselective NSAIDs or COX-2 inhibitors along with aspirin, then they should also receive GI prophylaxis with misoprostol or a proton pump inhibitor. In addition, it may be reasonable to test patients for (and eradicate) *Helicobacter pylori* prior to initiating chronic NSAID therapy.[1,17] Moreover, a baseline complete blood count and creatinine should be performed with follow-up tests annually. Finally, the creatinine should be repeated within 3 months of initiating long-term NSAID therapy.[6]

In summary, the decision to employ NSAIDs in the management of chronic pain in older adults demands individualized consideration. Comorbidities, concomitant medications, and associated risk factors (including genetics) all impact the decision to introduce such treatment. Medical decision making must weigh the potential benefits of the improved function and health status that NSAIDs may provide.[18] Key issues in the selection of NSAID therapy are pain amelioration, cardiovascular risk, nephrotoxicity, drug interactions, and GI toxicity. In those individuals in whom NSAID therapy is needed, and where GI risk is considered low, it may be reasonable to emphasize ibuprofen or naproxen. These agents appear to have the strongest research suggesting relative neutrality from the standpoint of potential cardiovascular risk. If GI risk is significant, many authors favor coprescribing with a proton pump inhibitor. Finally, if there exists significant GI risk and significant cardiovascular concern, then again, low-dose aspirin with either naproxen or a COX-2 inhibitor seem to be among the most reasonable therapeutic compromises.[19]

Treatment options other than NSAIDs It should be kept in mind that physical therapy is noninferior to NSAID therapy for OA of the knee. Isometric exercises improve muscle strength without requiring painful joint motion. Assistive devices, in the form of a cane or brace, can

sometimes improve ambulation. Obesity is considered a modifiable risk factor for OA. Weight loss and exercise are recommended by the ACR for patients with knee OA. Weight loss has been shown to improve knee function in patients with OA. For every pound of weight lost there corresponds a 4-pound reduction in joint load forces in the knee per step. Hence, there is a larger force reduction than the actual weight reduction. Higher internal or external knee joint moments during walking are related to increased compressive loads on the knee. Subtalar pronation initiates medial tibial and knee rotation, and threatens knee stability. There appears to be a significant association between weight loss and reduced internal medial rotation moment. Inversion in late stance locks the intertarsal joints and provides a firm base on which to toe off. It is theorized that weight loss leads to improved subtalar stability and subsequent reduced stress on the knee.[20,21] Rehabilitation also helps patients adjust to their debility physically.[21]

First-line pharmacological therapy of persistent pain should be acetaminophen (in the absence of hepatic disease). Judicious dosing can provide pain relief that is comparable to higher analgesics. However, a major concern is to ensure that dosing does not exceed 4 g in 24 h, and is less in cases of hepatic disease. Older patients are known to take many over-the-counter medications that may also contain some acetaminophen (cough suppressants, etc.) and these additional dosing sources must be considered in the overall acetaminophen calculation.

Topical capsaicin has proved to reduce pain in patients with OA, as well as other musculoskeletal disorders. It should not be used for treating acute pain, but more for its prolonged effects. Unfortunately, some patients are not able to tolerate the burning sensation even though it is usually only present for the first few weeks.[4,22]

Another topical therapy for those that are not able to tolerate capsaicin are topical NSAIDs. Topical therapies are preferred for alleviating pain as they have less systemic side effects.[22] There are many different topical NSAIDs worldwide: aspirin, indomethacin, diclofenac, piroxicam, ketoprofen. Most studies suggest that topical NSAIDs are as efficacious as oral NSAIDs for persistent knee pain secondary to OA in the short term (6 weeks or less).[23,24] Prolonged therapy beyond 6 weeks has yet to be evaluated for safety and efficacy.

A controlled trial of lidocaine 5% patch showed efficacy in treating postherpetic neuralgia. Moreover, recent trials have also shown efficacy with other neuropathic pain disorders. Patients seemed to prefer it over placebo most likely because it suppresses various different pain sensations including those described as sharp, dull, or deep.[21,25]

Traditionally, glucosamine chondroitin has been thought to have low efficacy but a few trials have shown that 40% of patients have a significant clinical response.[22] Although this agent does not improve joint space structurally as is popularly construed, it is potentially a worthwhile agent to try for mild persistent pain.

A novel form of therapy for OA of the knee is intra-articular injection of hyaluronic acid. The beneficial effects may last up to 6 months without additional interventions.[21,22] In clinical trials, 60% of patients noted significant pain improvement compared to placebo. Local corticosteroid injections are generally safe as well, but it should be recognized that they possess rare side effects of infection, depigmentation or dimpling of skin, avascular necrosis, and cartilaginous destruction.[26] Patients with a tense effusion of the knee often significantly benefit from these injections especially when coupled with drainage in order to debulk the joint.[22]

Some interventions have a long history of interest within the general rheumatological community. Irrigation of joints removes particulates and macromolecules that may be proinflammatory. However, sham-controlled studies of joint irrigation reveal no benefit above and beyond a placebo effect. Furthermore, the presence of chondrocalcinosis, synovial fluid crystals, and arthroscopic severity does not reliably predict response to irrigation.[27]

Because of their adverse effect profile, low-dose oral corticosteroids have been used short term for their analgesic effects. They have been used in bone, neuropathic, and bowel obstruction pain.[4] Rheumatologists generally shy away from long-term use of glucocorticoids for degenerative diseases owing to their many well-known adverse effects.

A recent study by Pergolizzi et al. demonstrated that patients over the age of 65 often benefit more from opiates than the younger population.[14] This may partially alleviate the anxiety of practitioners to use this class in the older population. Moreover opiates are advocated as first-line therapy in patients with persistent pain by the WHO 2008 Consensus Statement. Despite all this, most elderly patients are underprescribed because of the fear of dependence. To the contrary, prevalence of dependence has been very low in patients with no prior history of substance abuse.[4] In fact, in a study involving transdermal fentanyl, older patients were found to have an improvement in their SF-36 mental health summary scales, pain, perceived debility, and total pain summary scales over 3 to 6 months. Rather than dependency, the adverse effect profile of constipation, sedation, nausea, respiratory depression, and impaired balance perception are what may make opioids an unfavorable choice in some individuals. Novel strategies are under investigation in order to overcome these issues. In one study, patients were given oxycodone prolonged release and naloxone prolonged release when necessary. By using this combination, patients were able to offset some of the adverse effects related to opioids, such as constipation.[28]

There are many different types of opiates on the market. Tramadol is a mixed analgesic with

inhibition at both μ opiod receptor and serotonin and norepinephrine uptake sites. It has been used for mild to moderate pain and has decreased incidence of constipation. On the other hand, methadone is a potent μ opioid agonist, whose use is discouraged in the elderly. It has a varied half-life making dose titration difficult.[16] In clinical studies, oxycodone and morphine have been found to be equianalgesic. Furthermore, transdermal fentanyl has been found to be effective and with a more favorable adverse effect profile than other opiates. Patients experience less constipation, nausea, and somnolence.[14]

Transdermal buprenorphine, available in most European countries, is a very attractive choice as it has demonstrated a ceiling effect of respiratory depression. In clinical trials, respiratory rate rarely dropped below 10 breaths per minute.[14] Furthermore, inhibition of μ and κ receptors is thought to contribute to its antihyperalgesic effect.[14,29] Finally, buprenorphine does not require dosage adjustment for renal failure, which is unlike other opiates. However, dosage should be decreased with hepatic failure as it is also known for its long duration of action.[30]

The future of NSAIDs and miscellaneous points Hypertension and OA commonly coexist in the older adult.[31] Moreover, the treatment for OA may cause clinically significant increases in blood pressure and may as well be prothrombotic. As a result, physicians are cautioned to balance the risk--benefit profile of high dose nonsteroidal anti--inflammatory agents against potential benefits.[32] Of interest, in this regard, is the role of the diffusion of nitric oxide (NO) into the vascular endothelium. For this reason, cyclooxygenase-inhibiting NO-donating drugs have been developed.[33] Such agents may avoid the adverse vascular effects associated with NSAID use in vulnerable populations.

Even though OA is often termed degenerative, this name does a disservice to the biologically active cytokine environment of regional OA. Cytokines, including interleukin 1 (IL-1) and tumor necrosis factor, may induce NO within the inflamed joint. Because chondrocytes express inducible NO synthase (iNOS) (for example under the influence of IL-1), then the chondrocyte microenvironment for NOS production (which relates to constitutive and inducible NOS) may endure both beneficial and harmful effects to the joint. Finally, vascular pathology leading to subchondral bone ischemia may also play a role in the generation of OA.[34]

Pain medications should be individualized to each patient and there should be continued exploration of each medication's indication, tolerability, and potential. There is significant evidence cautioning the use of NSAIDs in older patients with persistent pain. Therefore, multiple different pharmacologic and nonpharmacologic modalities must be employed. Further advances in research will allow physicians to continue to treat pain with reduced risk of cardiovascular, renal, and GI side effects.

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ARTYKUŁ POGLĄDOWY

Ból przewlekły u chorych w starszym wieku

Jak postępować w świetle wytycznych American Geriatrics Society 2009?

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SŁOWA KLUCZOWE

ból przewlekły, niesteroidowe leki przeciwzapalne, osoby w starszym wieku, wytyczne postępowania

STRESZCZENIE

Niedawno opublikowane zaktualizowane wytyczne American Geriatrics Society 2009, dotyczące postępowania w bólu przewlekłym u osób w starszym wieku, stawiają lekarzy przed dylematem. W skrócie – obecne wytyczne zmniejszają rolę niesteroidowych leków przeciwzapalnych (NSLPZ) w stosunku do ubiegłorocznych zaleceń. Silne zalecenie zachowania ostrożności podczas stosowania NSLPZ wynika z wielu dobrze udokumentowanych potencjalnych skutków niepożądanych, takich jak niewydolność nerek, udar mózgu, nadciśnienie tętnicze, zaostrzenie niewydolności serca i powikłania żołądkowo-jelitowe. Niemniej jednak lekarze wciąż dysponują solidnym arsenałem do zwalczania bólu przewlekłego spowodowanego takimi stanami, jak choroba zwyrodnieniowa stawów czy choroby grzbietu. Możliwe interwencje obejmują fizykoterapię, preparaty NSLPZ do stosowania miejscowego, kapsaicynę, miejscowe stosowanie lidokainy, wstrzyknięcia dostawowe oraz rozważne stosowanie narkotyków. W przyszłości inhibitory cyklooksygenazy dostarczające tlenku azotu mogą stanowić postęp techniczny w aspekcie profilu toksyczności tradycyjnych NSLPZ.

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