

Safety Issues in the Pharmacologic Management of Chronic Pain in the Elderly

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Chronic pain is commonly encountered in elderly patients. About 20–50% of community-dwelling elderly experience it, and 45–80% of nursing home residents may be affected. Selection of pharmacologic therapy for the management of chronic pain must take into consideration the increased potential for adverse effects in this population. Major classes of drugs used to treat chronic pain (nonsteroidal antiinflammatory drugs, opioids, antidepressants) have adverse effects that occur more frequently in elderly than in younger patients. Given the often prolonged duration of therapy, optimal management requires minimizing the risk of adverse reactions. (Pharmacotherapy 1998;18(6):1313–1322)

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The high number of prescriptions for analgesic agents attests to the prevalence of pain-related conditions. Prescriptions for nonsteroidal anti-inflammatory drugs (NSAIDs) in the United States increased from approximately 28 million in 1973 to 67 million in 1983 and have remained relatively constant since then.¹ In 1991 approximately 70 million NSAID prescriptions were filled,² more than 40% for elderly patients.³ In addition, significant quantities of nonprescription analgesics are consumed, with more than \$900 million worth purchased annually in the United States.⁴ With such widespread use, it is clear that safety issues associated with these agents arise, particularly when they are given to treat elderly patients.

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Prevalence of Pain

Approximately 80% of visits to physicians are for conditions with a pain component. According to the National Institutes of Health chronic pain is the third largest health problem in the world, and in 1982 it afflicted approximately 65 million Americans.⁴ Common conditions are headache (40 million Americans suffer from chronic recurrent headaches), low back pain (about 15% of adults experience chronic low back pain at some time during their lives), and arthritis (affecting 20 million Americans).⁵

Chronic pain conditions are particularly prevalent among the elderly, occurring twice as often in persons 65 years of age and older as in younger individuals.⁶ As many as 20–50% of elderly people living in the community experience chronic pain,⁷ and the figures are 45–80% for those in long-term care institutions.⁸ This prevalence is largely due to disproportionate occurrence of conditions associated with chronic pain in this age group; for example, arthritis, which may affect as many as 80%, cancer, tic douloureux, and herpes zoster.^{5,8}

In addition to suffering, chronic pain takes a toll in terms of health care costs. It was estimated that the annual cost (both direct and indirect) in the United States is \$50 billion.⁵

Types of Pain

Pain is defined as “an unpleasant sensory and

emotional experience associated with actual or potential tissue damage, or described in terms of such damage.⁹ Chronic pain persists beyond the expected healing time¹⁰; according to the International Association for the Study of Pain, 3 or more months after an injury.¹¹ It is often associated with psychological or social factors, such as depression and anxiety, and other factors, such as disability and changes in personality (Figure 1).^{8,10}

Chronic pain can be categorized as nociceptive, neuropathic, or idiopathic.^{11,12} Nociceptive pain results from continuing damage to soft or bony tissues and is characterized by a localized, sharp, or aching quality. The nervous system is intact and pain is experienced secondary to tissue damage. Chronic pain associated with arthritis and cancer is classified as nociceptive. Neuropathic pain occurs after damage to or pressure on nerves or neural tissue of the central or peripheral nervous system. Examples are postherpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, and phantom limb pain. This type of pain typically follows the distribution of nerves and may be described as burning, tingling, pins and needles, deep aching, or numbness. Idiopathic pain has no underlying cause. More than one type of pain may be present in a patient with chronic pain.

Distinguishing the type of pain can assist in selecting the appropriate therapy. Nociceptive pain is responsive to traditional analgesic agents (NSAIDs, opioids), but neuropathic pain is generally not. Although more difficult to treat,

neuropathic pain may be relieved by adjunctive agents such as antidepressants and anticonvulsants.

Treatment

The goals of treating these patients are to determine the type of pain, relieve pain to the greatest extent possible, educate patients and family, and ensure maximum function and sense of autonomy and control for the patient.¹¹ Achieving these goals usually requires several pharmacologic and nonpharmacologic modalities. Applying both types is likely to result in greater pain control and reduce the risk of adverse drug effects.^{8,13}

Many clinicians stress the importance of differentiating between pain relief and resumption of function. It may be impossible to relieve chronic pain completely; rather, the goal should be to maintain the patient's function, mobility, and activities.¹⁴ In addition, these patients frequently experience anxiety and depression. It was estimated that 20–50% of have depressive symptoms that require treatment.⁷ Attention to these conditions is important because they may lower the pain threshold^{7,14} or decrease the patient's functional status.⁸

Treating elderly patients with chronic pain requires consideration of several additional factors including age-related alterations in pain sensation, cognitive status, and concurrent drug therapy. In a review of studies examining the perception of pain by the elderly, the authors concluded that no real consensus exists about age-related changes in pain perception.¹⁵ The expectation that older patients will experience less pain is inappropriate and may result in undertreatment and reduction in quality of life.⁸ In fact, these individuals may require specific attention to the presence and intensity of pain, the impact of pain on quality of life, and prompt and accurate diagnosis and treatment. The following are principles in managing pain in these patients⁸:

- Always ask them about pain.
- Accept their word about pain and its intensity.
- Never underestimate the potential effects of chronic pain on a patient's overall condition and quality of life.
- Be rigorous in assessing pain; an accurate diagnosis will lead to the most effective treatment.
- Treat pain to facilitate diagnostic procedures; do not wait for a diagnosis before relieving it.

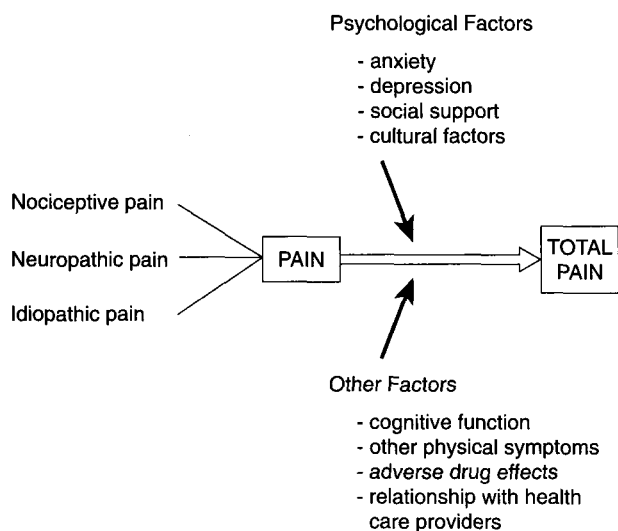


Figure 1. Factors contributing to chronic pain and suffering.

- Use a combined approach of drug and non-drug strategies when possible.
- Mobilize patients physically and psychosocially, and involve them in therapy.
- Administer analgesic drugs correctly, starting with low dosages and increasing them slowly; achieve adequate dosages and anticipate side effects.
- Anticipate and attend to anxiety and depression.
- Reassess responses to treatment; alter therapy to achieve maximum functional status and quality of life.

Cognitive status may influence therapy either by altering the amount or quality of information that the patient can supply or by limiting drug therapy due to adverse effects on cognition. Concurrent drug therapy also should be considered.

Behavioral and psychosocial therapies are often incorporated into protocols and improve the response to analgesics.¹⁶ Structured behavioral strategies, including psychologic counseling, relaxation techniques, and stress management, can provide therapeutic benefit.¹⁷

Drug Therapy

The choice of drugs is based on the type of pain and the patient's medical condition.¹⁸ Combinations of drugs often are appropriate, as they can provide synergistic action by relieving pain by different mechanisms or provide superior relief if more than one type of pain is present.

Acetaminophen

Acetaminophen is an effective analgesic for mild pain; when combined with opioid analgesics it can be given to manage more severe pain. It may be effective in patients with osteoarthritis. Its benefits compared with NSAIDs are a superior adverse effect profile (NSAIDs have increased frequency of toxicity in the elderly), significantly lower cost, and lack of potential to inhibit synthesis of proteoglycans, which are necessary for cartilage repair.^{19,20}

In general, acetaminophen is a safe agent; however, excessive short-term doses (≥ 15 g in an adult) or long-term use (> 5 g/day) can cause hepatotoxicity (Table 1).²¹⁻³³ In addition, evidence suggests that long-term ingestion of ethanol may predispose individuals to acetaminophen-related hepatotoxicity.^{34,35} Concern was raised regarding the potential for acetaminophen-induced hepatotoxicity after

modest doses (4–10 g/24 hrs) during fasting conditions (e.g., viral illness with gastrointestinal symptoms, dehydration).²³ These issues must be considered when recommending acetaminophen to any patient.

NSAIDs

These drugs are useful for mild to moderate pain, particularly that of musculoskeletal origin or caused by inflammation or cancer.¹⁸ Although NSAIDs vary in duration of action and adverse effect profiles, their analgesic efficacy is similar. Their effect is apparent within 0.5–4 hours after oral administration, although antiinflammatory effects may not be manifested for several days to weeks.²² The NSAIDs appear to have a ceiling for analgesic effect beyond which a dosage increase does not provide increased relief.^{18,36} Because this ceiling varies from patient to patient, slow dosage escalation can help determine this value.³⁶ Patients may respond differently to certain agents; therefore, a trial with another NSAID may be appropriate if the first one provides inadequate pain relief.³⁷

Although NSAIDs have a good overall safety profile, the sheer magnitude of their use puts them at the top of the list for serious adverse drug reactions in the United States and Britain.^{3,25,38} In 1985 a British study indicated that 25% of reported adverse reactions in men and 30% in women were attributed to these agents.²⁵ In 1990 the U.S. Food and Drug Administration imposed a class warning label because the risk of NSAID-induced ulcers and gastrointestinal bleeds was estimated to be 2–4% annually.³⁸ The drugs may cause a variety of adverse effects in the elderly, particularly gastrointestinal and renal toxicity.

Gastrointestinal Toxicity

The association between NSAIDs and gastrointestinal toxicity is well established. The agents are linked to increased risk for gastric ulcers, duodenal ulcers, upper gastrointestinal hemorrhage, and death from peptic ulcer disease or gastrointestinal hemorrhage.^{26,39-42} Results of a meta-analysis estimated the overall odds ratio for the risk of adverse gastrointestinal events related to NSAIDs to be 2.74 (CI 2.54–2.97).³⁹ The risk for a gastrointestinal-related hospitalization was estimated to be 6 times greater for patients with rheumatoid arthritis taking NSAIDs compared with those not taking the drugs.³⁸

Results of a case control study in elderly patients reported similar findings.²⁶ The

Table 1. Management of Common Adverse Effects of Analgesics

Analgesic	Adverse Effect	Management
Acetaminophen ^{22, 23}	Hepatotoxicity	Avoid long-term administration of more than 4 g/d. Avoid when patient is ingesting limited food or consumes long-term ethanol.
NSAIDs ^{3, 24-29}	Gastrointestinal toxicity	Give lowest effective dosage; periodically reassess required dosage. Begin therapy with drugs least likely to cause gastrointestinal toxicity (etodolac, ibuprofen, ketoprofen, nabumetone, naproxen). Administer with misoprostol in at-risk patients. Periodically monitor for gastrointestinal blood by hematocrit and stool guaiac.
	Renal toxicity	Give lowest effective dosage; periodically reassess required dosage. Avoid concurrent diuretics. Begin therapy with drugs least likely to cause renal toxicity (salsalate, sulindac); avoid fenoprofen, indomethacin, naproxen. Assess high-risk patients (renal function, electrolytes, weight) when therapy is begun and 2 wks later.
Traditional opioids ^{7, 8, 10, 30, 31}	Sedation, confusion	Tolerance usually develops; begin or increase dose in stepped doses; decrease dose and increase dosing frequency. Discontinue other therapy with potential additive adverse central nervous system effects. Switch to another opioid or decrease opioid dose and try combination therapy with another type of analgesic.
	Nausea, vomiting	Tolerance usually develops. Administer antiemetic agents (cisapride, hydroxyzine, prochlorperazine) selected by mechanism of nausea.
	Constipation	Increase dietary fluids and fiber. Administer laxative (stool softener, stimulant laxative; lactulose).
Tramadol ^{8, 10, 30, 32}	Sedation, dizziness	Tolerance usually develops. Begin or increase dose in stepped doses; decrease dose and increase dosing frequency. Discontinue therapy with potential additive central nervous system effects. Switch to another opioid or decrease opioid dosage and give in combination with another type of analgesic.
	Nausea, vomiting	Tolerance usually develops. Administer antiemetic agents (cisapride, hydroxyzine, prochlorperazine) selected by mechanism of nausea.
	Constipation	Increase dietary fluids and fiber. Administer laxative (stool softener, stimulant laxative; lactulose).
Antidepressants ^{10, 33}	Sedation, delirium	Avoid most sedating antidepressants (amitriptyline); give dose at bedtime. Discontinue other therapy with potential additive central nervous system effects.
	Anticholinergic effects (dry mouth, decreased visual accommodation, constipation)	Administer dose at bedtime. Switch to drug with weaker anticholinergic effects (desipramine, trazodone). Discontinue other therapy with anticholinergic effects. Dry mouth: frequent sips of water, artificial saliva. Constipation: dietary fluids and fiber.
	Orthostatic hypotension	Instruct patient about sudden shift in posture. Switch to drug with less potential for effect (desipramine, nortriptyline). Administer therapy for orthostatic hypotension (liberal sodium intake; fludrocortisone).

estimated relative risk for developing peptic ulcer disease was 4.1 (CI 3.5–4.7) among NSAID users compared with control patients, and the association with increased risk was consistent for subpopulations (e.g., gender, race, age). Furthermore, the increased risk occurred for several other diagnoses including gastric ulcer (relative risk 5.5, CI 4.4–6.9), duodenal ulcer (relative risk 4.3, CI 3.5–5.2), and upper gastrointestinal hemorrhage (relative risk 2.4, CI

1.8–3.2). In a similar case control study, death from peptic ulcer disease and gastrointestinal hemorrhage was 4 times more likely in elderly patients currently taking NSAIDs than in elderly not taking them.⁴²

Risk Factors. Numerous patient characteristics are linked to an increased risk for gastrointestinal toxicity, including age, female gender, and history of gastrointestinal disease. The relative risk for

serious gastrointestinal events was more than 3 times greater among elderly than younger users.³⁹ Similarly, the hazard ratio for gastrointestinal death in elderly patients (> 60 yrs) with rheumatoid arthritis and taking NSAIDs was almost 3 times greater than for younger patients.³⁸

Several reasons explain why the elderly, especially women, may be at greater risk for this type of toxicity. First, elderly patients have a high rate of exposure to the drugs because they have a high prevalence of chronic pain conditions. Specifically, elderly women may have greater exposure simply because they outnumber elderly men (particularly in the oldest age groups), because of differences in prescribing (60% of NSAID users are women), or because certain painful conditions (e.g., rheumatoid arthritis) are more common in women.^{38, 40, 41} The elderly, especially women, may be at greater risk by virtue of lower body weight; gastric ulcers appear to be related to systemic changes in prostaglandin production by NSAIDs, and the lower ratio of body mass to dose may amplify systemic effects.⁴¹ Furthermore, the greater prevalence of *Helicobacter pylori* gastritis in the elderly may be related to increased risk.⁴¹

Certain characteristics of NSAIDs also may predispose select patients to gastrointestinal toxicity. The risk for peptic ulcer disease increases as NSAID dosage increases.³⁹ Duration of therapy is inversely related to risk of related gastrointestinal toxicity. A compilation of data from 10 studies suggests that the risk is highest during the first 3 months of therapy.^{26, 39} This seemingly backward association is thought to be a result of mucosal adaptation that occurs after prolonged therapy.^{39, 41} Another explanation may be compliance; if compliance is better when therapy is begun, the risk may be greatest shortly after the drug is prescribed.³⁹

Variability among NSAIDs. Limited data suggest that the risks incurred with different agents may vary.^{26, 39} In two studies, ibuprofen was associated with the lowest risk for NSAID-related gastrointestinal toxicity. In addition, reports of this condition were fewer for two relatively new agents, etodolac and nabumetone, which may pose less risk both with short- and long-term therapy.²⁷ However, confidence intervals for various NSAIDs tend to be broad and overlapping, and more studies are necessary to determine if differences in risk among agents truly exist.

Renal Toxicity

Renal toxicity is not as frequent as gastropathy,⁴³ occurring in perhaps as many as 5% of persons taking an NSAID.⁴⁴ However, by virtue of age-related changes in kidney function and concurrent drug therapy, the group most likely to be at risk is the elderly.^{24, 28, 29} Types of NSAID-induced renal toxicity include acute reversible renal failure; impaired renal excretion of sodium, potassium, and water; acute interstitial nephritis; and analgesic nephropathy.⁴³ Acute renal failure secondary to decreased vasodilatory prostaglandins is the most common form of NSAID-induced renal toxicity and is rapidly reversible.²⁸ For most patients, even the elderly, these vascular effects are minimized by other forces.^{29, 43} However, the presence of disease or concurrent drugs may result in toxicity.

Risk Factors. Patients susceptible to NSAID inhibition of prostaglandins include the elderly and those with volume depletion (e.g., diuretics), congestive heart failure, hepatic cirrhosis, diabetes mellitus, infections, and preexisting renal insufficiency.⁴³ Concurrent diuretic and NSAID therapy may decrease renal blood flow and glomerular filtration rate, and cause sodium retention. As a result, clinically important fluid accumulation may develop in patients with congestive heart failure, arteriosclerotic heart disease, or renal impairment. A decline in renal function occurred in 20% of patients with arteriosclerotic heart disease who took a diuretic and an NSAID.²⁹ Similarly, the actions of NSAIDs on prostaglandins and renin may cause a clinically important elevation in serum potassium, especially if the patient is concurrently receiving an angiotensin-converting enzyme inhibitor or potassium-sparing diuretic.^{24, 43} The likelihood of acute renal failure increases with higher NSAID dosages and perhaps with drug accumulation in the elderly because of impaired clearance resulting in greater prostaglandin effects.^{29, 43, 45}

In high-risk patients, all NSAIDs are likely to cause acute renal failure.²⁹ In an elderly patient with chronic renal insufficiency, renal function deteriorated further in the presence of three sequentially prescribed NSAIDs, sulindac, piroxicam, and ibuprofen.²⁸ In patients with moderate risk (i.e., fewer or milder degrees of medical conditions noted above), either lower dosages or certain agents (e.g., salsalate, sulindac) may decrease the risk of NSAID-

induced nephropathy.^{29, 43} In all elderly patients, therapy should be preceded by assessment of renal function, electrolytes, and weight; these measurements should be repeated 1–4 weeks after start of therapy.^{3, 24, 29}

Both acute interstitial nephritis and analgesic nephropathy are rare forms of NSAID-induced renal toxicity. Duration of therapy is the only identified risk factor; this condition is reported most commonly with fenoprofen.^{28, 37}

Traditional Opioid Analgesics

Opioid analgesics are administered to treat moderate to severe pain. They are effective against all types of pain, although their effectiveness in neuropathic pain is limited.^{8, 30} Traditional opioid analgesics are generally classified as agonists, mixed agonist-antagonists, or partial agonists. This classification is based on their actions at three central opioid receptors (μ , δ , κ). Most clinically used opioids are μ agonists.

Rational Prescribing

Initially designed as a guide for the treatment of cancer pain, the World Health Organization's analgesic ladder provides a rational basis for pain management with these drugs.³⁶ Although the agents are effective, many clinicians have reservations about administering them to treat chronic nonmalignant pain.^{32, 46, 47} Despite evidence to the contrary, fear of dependence is the major barrier to their appropriate prescription.^{30, 36} Psychologic dependence is rare in patients receiving long-term therapy for pain with opioids, with frequency estimated to be about 0.1%.³⁶ In one report, only four cases of dependence were reported among 11,882 hospitalized patients treated with opioid analgesics.⁴⁸

Addiction, Physical Dependence, and Tolerance

Confusion among addiction, physical dependence, and tolerance contributes to apprehension about prescribing opioids for long periods of time. Physical dependence to the drugs, demonstrated by adverse effects on sudden withdrawal, is a common phenomenon. However, dependence is not synonymous with addiction, which is craving for the drug.³⁶ Long-term opioid therapy in patients without a history of drug dependence did not produce psychologic dependence.^{30, 31, 47, 49} Unfortunately, inappropriate prescription (e.g., inadequate dosages, excessively long dosage

intervals) may create a picture of drug craving by patients in pain.^{30, 47}

Tolerance is the need to increase the dosage of an opioid to maintain adequate analgesia.³⁶ However, a request for a higher dosage may not necessarily reflect tolerance (decreased effect of the drug to the same pain intensity); rather, it may indicate a change in pain intensity.⁵⁰ Tolerance is not a clinically significant problem in patients receiving long-term opioid therapy.^{47, 49} Dosages remained stable for more than 80% of patients with cancer receiving long-term therapy.³⁰ Long-term therapy with little or no dosage adjustment also was reported by other authors,⁴⁷ and a survey found that 60% of patients reported increasing their opioid dosage a little or not at all over time.⁵¹ Because dosage requirements can vary dramatically,⁴⁶ individualized dosing is critical.

Adverse Effects

Common adverse effects of opioid analgesics occur with all agents in the class and are extensions of their pharmacologic effect. They include sedation, respiratory depression, nausea and vomiting, and constipation. Fortunately, most patients develop tolerance to sedation, respiratory depression, and nausea usually within days of starting therapy; tolerance to constipation is uncommon.⁵² Central nervous system (CNS) adverse effects, including sedation and confusion, often manifest on starting therapy or after a dosage increase and persist for several days to several weeks. If they do not subside, management may include discontinuing concurrent drugs that cause CNS effects, reducing opioid dosage, or adding agents such as stimulants or antipsychotics to counter the adverse effect.⁵² Switching a patient to another opioid analgesic may also be effective. A series of case reports demonstrated that patients may have dissimilar side effects depending on the drug, and switching from one opioid to another may eliminate side effects and provide better analgesia.⁵³

The frequency of respiratory depression during long-term opioid therapy is reduced by two mechanisms. First, tolerance to the respiratory depression usually develops, and second, it appears that pain, as a respiratory stimulant, continues despite relief.^{50, 52} However, dosages greater than those required for analgesia may cause clinically important respiratory depression.⁵⁰

Traditional opioids cause nausea and vomiting by stimulating the chemoreceptor trigger zone, and they also increase vertigo and delay gastric

emptying. Some tolerance may develop to these symptoms.^{52, 54} Nausea and vomiting can occur in up to 40% of ambulatory patients.⁵² Persistence of these symptoms is usually managed by adding an agent to counter the mechanism of nausea. Metoclopramide or cisapride may relieve gastric stasis, meclizine or scopolamine may alleviate nausea related to dizziness, and prochlorperazine can be prescribed for other types of nausea.⁵² Unfortunately, addition of these agents can be a particular problem in elderly patients who are likely to develop anticholinergic adverse effects, confusion, or extrapyramidal effects.⁸

Constipation is experienced so often by patients taking long-term opioids that many clinicians recommend prophylactic laxatives at the start of therapy.^{8, 52, 54} Combinations of laxative agents may be required for maximum effectiveness; a stool softener is frequently combined with a cathartic.^{8, 52}

Some opioid analgesics have distinctive adverse effect profiles. Pentazocine is likely to cause delirium and agitation in the elderly.^{8, 10} More than 20% of patients experience dysphoria with pentazocine and butorphanol; other opioids cause dysphoria in only about 3% of patients.⁵⁰ Long-term meperidine therapy is hampered by production of a toxic metabolite that may cause agitation, tremor, or convulsions.^{10, 50} As a result, pentazocine, butorphanol, and meperidine have limited application in the management of chronic pain in the elderly.

Tramadol

Tramadol, is a new synthetic, centrally acting analgesic with antinociceptive activity produced by two mechanisms: opioid receptor binding and inhibition of norepinephrine and serotonin reuptake.⁵⁵ Both mechanisms are involved in the drug's analgesic action. In studies in healthy volunteers, the analgesic effect was only partly reversed by naloxone (a μ opioid receptor antagonist),⁵⁶ and was almost completely reversed by yohimbine (an α_2 -adrenergic receptor antagonist).⁵⁷ This dual action may make tramadol particularly effective in treating neuropathic pain; however, additional studies are required to examine its usefulness for this indication.⁵⁸

Tramadol is effective for moderate to moderately severe pain; its analgesic potency is generally comparable to that of meperidine, pentazocine, and codeine,^{30, 59, 60} but its analgesic effect in higher dosages may be similar to that of morphine.³²

Adverse Effects

Although tramadol is generally well tolerated, it commonly causes dizziness, nausea, vomiting, sedation, constipation, dry mouth, sweating, and headache.⁶¹ When it is administered orally, the frequency of nausea and dizziness is 5%, sedation and dry mouth 3%, and vomiting 1%.³² Adverse effects are dose related; accumulation of the drug can occur with repeated administration and dosage adjustment may be warranted, particularly in patients with renal or hepatic impairment.^{58, 62} Tramadol reportedly causes less of some opioid-induced adverse effects, such as respiratory depression, urinary retention, and constipation.^{32, 59, 63} With long-term therapy, equianalgesic doses of tramadol, oxycodone with acetaminophen, and codeine with acetaminophen were associated with constipation in 35%, 41%, and 58% of patients, respectively.³² After short-term intravenous administration, tramadol produced significantly less respiratory depression than morphine.^{63, 64}

Abuse Potential

Tramadol may have less potential to cause drug dependence than traditional opioid analgesics; sensation of euphoria is uncommon. In a study of abuse potential, the drug was compared with morphine by administering each agent and placebo to subjects who were previously opioid dependent.⁶⁵ Subjects were asked to describe the effect of each drug on three scales: feel the drug, high, and like the drug. Morphine significantly increased scores on all three scales. In contrast, the highest dose of tramadol (300 mg) produced a significant elevation only for feel the drug; the two lower doses (75 and 150 mg) were not significantly different from placebo. Another study examined the effect of naloxone to test for physical dependence in patients who had received tramadol for pain relief.⁶⁶ Most patients (94%) showed no signs of dependence; the rating for those who had withdrawal symptoms was slight to marginal. This property may make tramadol a good choice for the treatment of chronic pain. Furthermore, the agent has comparable efficacy to acetaminophen with codeine and is unlikely to induce euphoria or tolerance with continued use.⁶⁷ Combined, these attributes make it an appropriate analgesic for the management of chronic pain in elderly patients.

Antidepressants

The antinociceptive effect of antidepressants is

thought to result from an intrinsic analgesic effect⁶⁸ rather than mood elevation.^{69, 70} Placebo-controlled studies^{33, 69, 71, 72} and two meta-analyses^{68, 70} examined the effectiveness of antidepressants in the treatment of chronic pain conditions. The agents were less effective for the treatment of pain than for the treatment of depression; approximately 57–65% of patients obtained pain relief compared with 70% of those who usually responded to the antidepressant effects of these drugs.^{68–70} In 70–87% of trials, antidepressants were more efficacious than placebo for treating pain.^{33, 68–70}

The dosage at which analgesia occurs is lower than that given to treat depression, and the time to onset of pain relief is often shorter than that required for antidepressant effects.^{33, 68, 70, 71} The duration of analgesia is not well studied but is believed to persist with continued therapy. In two trials that investigated the long-term analgesic efficacy of antidepressants, more than half of patients still experienced analgesic benefit after 1 year of therapy. Furthermore, a decrease in dosage can be attempted 1 month after maximum benefit is obtained, and after 3–6 months of therapy, slow tapering of dosage.³³ Some patients may even be able to discontinue therapy and maintain pain relief.³³

Although these drugs are potentially effective for a wide variety of chronic pain syndromes, questions still arise about which conditions respond the best and which antidepressants may provide best efficacy. Some evidence suggests that head pain (headache, facial pain) may be more responsive than other types of pain^{33, 68}; other conditions that may respond are osteoarthritis, rheumatoid arthritis, diabetic neuropathy, postherpetic neuralgia, low back pain, and fibromyalgia.^{33, 69, 71} Both serotonin and adrenergic systems are probably involved in the perception of pain; antidepressants that selectively act at serotonin receptors may not be as effective as those that possess mixed neurotransmitter activity.^{33, 68, 69} Preferred drugs are amitriptyline, clomipramine, and doxepin.^{68, 70}

Adverse Effects

Common adverse effects of tricyclic antidepressants are sedation, orthostatic hypotension, anticholinergic effects (dry mouth, blurred vision, constipation), and cardiac conduction effects. Sedation may be an adverse effect in one patient or useful in another patient who has difficulty sleeping. In two trials investigating

amitriptyline 25 mg for the treatment of chronic pain, the most common adverse effects were drowsiness (23–36%) and dry mouth (27–31%).^{73, 74} Their frequency was dose related. Amitriptyline 75 mg produced drowsiness in 52% of patients and dry mouth in 63%; however, only 10% of patients discontinued therapy because of adverse effects.⁷³ Drowsiness (8–13%) and delirium (3–18%) were the two most common reasons for patients to discontinue therapy.³³

Orthostatic hypotension is a particular concern in elderly patients because it is linked to falls resulting in hip fractures. Measuring blood pressure in sitting and standing positions before beginning therapy and 1–2 hours after the initial dose can help determine if it is likely to be a problem.³³

Anticholinergic adverse effects are also of concern in the elderly who may be more susceptible to them because of age-related changes (e.g., slowed gastrointestinal motility) or concurrent drug therapy. Central anticholinergic effects may cause confusion or agitation, and the drug regimen in a disoriented elderly person should always be suspect.

Cardiac conduction defects may preclude prescription of tricyclic antidepressants. However, if such therapy is warranted, desipramine may be the drug of choice. Cardiac toxicity can be monitored by serial electrocardiograms; widening of the QRS complex is a sign of the disorder. Table 1 summarizes adverse effects of frequently prescribed analgesics.

Conclusion

Chronic pain is frequently encountered in the geriatric population and can have significant ramifications with regard to patients' ability to function and enjoy life. Drug therapy for chronic pain is usually long term and many agents may be taken concurrently. Selecting the best drug or drug combination for elderly patients should include analysis of benefits and risks. The goal is to increase the likelihood of benefit (relief of pain) and limit the risks (adverse effects) associated with therapy.

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