

With a Summary of Guidelines from the American Geriatrics Society

Management of Cancer Pain in Geriatric Patients

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In the United States, 60% of all cancers and approximately 70% of cancer-related deaths occur in persons aged 65 and older [1–3]. These figures are expected to increase with the progressive expansion of the aging population. For instance, by the year 2030, more than 70% of all cancers will be diagnosed among those who are 65 and older.

Before discussing cancer and its associated pain in older patients, we first need to explore and define what we mean by aging. Aging involves a progressive decline in the functional reserve of multiple organs and systems [4], which may be associated with increased prevalence of comorbidity, waning social resources, and emergence of a number of conditions typical of older age and referred to as “geriatric syndromes” [5]. Altogether, these conditions lead to shorter life expectancy, increased prevalence of functional dependence, and reduced tolerance to stress [5].

Biology of Aging

Aging is associated with both systemic and organ-related changes. Of the systemic changes, an increased concentration of inflammatory substances, such as interleukin 6 [IL-6], tumor necrosis factor [TNF], and C-reactive protein [CRP] [6–9], has received special attention in recent years. This accumulation, which may result from a succession of inflammatory processes that fail to heal completely and may cause low-grade disseminated intravascular coagulation [DIC], appears to be responsible for many of the manifestations of aging. Inflammatory cytokines may induce a general catabolic status characterized by sarcopenia [6,10] and hypoproteinemia; they may cause osteoporosis [11] and cognitive decline [12]; and they also may compromise hemopoiesis [13] and

Abstract The management of cancer in the older person has become a central issue of oncology. At present, some 60% of all cancers in the United States and approximately 70% of cancer-related deaths occur in persons aged 65 and older, and these figures will continue to increase at a significant rate as the number of older people in our population grows. This review studies the management of pain, one of the most common and consequential symptoms of cancer and cancer treatment, in the older person. In particular, the article explores the influence of age on pain perception, assessment, and management. These questions will be addressed after attempting a definition of age in biological terms. In the conclusion, the American Geriatrics Society's guidelines for the management of pain in older individuals will be examined and a research agenda outlined.

the immune response [14]. In addition, endocrine senescence [15–17] may be responsible for reduced protein synthesis, whereas immune senescence [14] may accommodate the development of infection, leading to further accumulation of cytokines in the circulation.

Of special interest in the management of pain in older patients are changes that take place in the central and peripheral nervous systems and in drug pharmacokinetics. Though nerve conduction appears to be well maintained with age, the number of nociceptive receptors in the skin and the amount of afferent fibers decrease with age, which may alter the perception of pain [18–21]. Between ages 20 and 80, the brain may lose as many as 20% of its original neurons, a loss leading to a reduced number of opioid receptors and increased sensitivity to opioids [22]. It also has been suggested that this reduction in brain volume may result in altered ratios of μ and δ receptors and increased susceptibility to the complications of opioids.

Of the pharmacokinetic changes, two of the most important are the decline in glomerular filtration rate, which is progressive with age in the majority of persons over 65 [5, 23], and the reduction in activity of the cytochrome P450 system, which is responsible for the activation and the metabolism of a number of opioids [21–22, 24].

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Another factor that may contribute to enhanced opioid sensitivity is hypoalbuminemia [10], as the concentration of free drug in the circulation may increase in this circumstance. Furthermore, polypharmacy [25] may enhance the risk of drug interaction. The bioavailability of oral agents does not appear to be reduced with age [26], though absorption is reduced to some degree.

Clinical Evaluation of Older Patients

Age-related changes occur at different rates in different persons, and the extent of their presence is poorly reflected in chronologic age [5]. The clinical assessment of the older person must address questions of life expectancy, risk of functional decline and need of assistance, tolerance to stress, rehabilitation, and management of reversible conditions, such as depression, malnutrition, and polypharmacy, that may compromise survival, function, and quality of life if left untreated.

Since aging involves different living domains that are interwoven in generating the clinical picture of aging, the most reliable evaluation of aging in any given person is a multidimensional comprehensive geriatric assessment (CGA), account-

ing for function, comorbidity, social support, nutrition, presence of geriatric syndromes, and polypharmacy (Table 1).

COMPREHENSIVE GERIATRIC ASSESSMENT

A full discussion of the CGA is beyond the scope of this review, but some aspects of interest will be highlighted. Declining function is associated with progressive reduction in life expectancy [27–30]; in addition, dependence in the Instrumental Activities of Daily Living (IADL) indicates increased risk of dementia occurring over 2 years [31], and increased risk of chemotherapy-related toxicity [32]. Comorbidity has also been associated with decreased survival. Controversy lingers over the best method of evaluating comorbidity [33, 34], which may include assessing the number of comorbid conditions or trying to calculate a comorbidity index, accounting for the seriousness of each condition, with the use of comorbidity scales.

Among the comorbid conditions, anemia deserves special attention [35], as it is associated with shortened survival [36–40], decline in function [41], increased risk of heart failure [42], dementia

Table 1
Example of a Comprehensive Geriatric Assessment (CGA)

ASSESSMENT	IMPLICATIONS
Functional status	
<i>Activities of Daily Living (ADL)</i> : transferring, continence, dressing, bathing, grooming, eating	Relation to life expectancy, tolerance of chemotherapy, dependence ^{27–31,34}
<i>Instrumental Activities of Daily Living (IADL)</i> : shopping, using transportation, providing for one's meals, money management, ability to take medications	Relation to life expectancy and tolerance of treatment ^{27–31,34}
Comorbidity	
Number of comorbid conditions and comorbidity indices	Relation to life expectancy and dependence ^{33,34}
Mental status	
Folstein minimal status	Relation to survival; may indicate motivation to receive treatment ^{50,51}
Emotional conditions	
Geriatric Depression Scale (GDS)	Relation to survival; may indicate motivation to receive treatment ^{50,51}
Nutritional status	
Mininutritional assessment (MNA)	Reversible condition; possible relationship to survival ^{50,51}
Polypharmacy	
Number and types of drugs being taken concomitantly	Risk of drug interactions ^{25,26}
Geriatric syndromes	
Delirium, dementia, depression, falls, incontinence, spontaneous bone fractures, neglect and abuse, failure to thrive	Relationship to survival and functional dependence ⁵

[43], coronary death [44], and drug-related toxicity [45–46].

Depression is common in older people and is associated with shortened survival, even when it is subclinical [47–49]; the detection of this condition is very important because, in general, it is fully reversible.

Of several approaches to the estimate of life expectancy, the one proposed by Walter et al [34] is probably the most practical and best validated.

In general geriatrics practice, application of the CGA has resulted in reduced disability rates [50–57], reduced hospitalization rates [50–57], reduced admissions to adult living facilities [50–57], improved management of “in hospital” delirium, and possibly improved survival [52]. In addition, on the basis of the CGA, different nosologic groups of older individuals may be recognized, with different life expectancy and tolerance to stress [58–59]. These groups include:

- the fully independent;
- the so-called frail, who have negligible functional reserve and tolerance to stress; and
- an intermediate group, among whom fall the majority of cancer patients whose condition may be improved by appropriate rehabilitation and special provisions, such as assignment of a home-caregiver.

A common definition of frailty involves at least one of the following: dependency in one or more Activities of Daily Living (ADL), one or more geriatric syndromes, or one or more serious comorbid conditions [60].

In geriatric oncology, the CGA allows an individualized approach to older cancer patients that includes catering to the special health, social, and rehabilitative needs of each patient and estimating the benefits and risks of treatment [61–64]. It is reasonable to expect some form of geriatric assessment to be helpful even for the management of cancer-related pain [21, 65]. Potential benefits include:

- Management tailored to the patient’s life expectancy. In an otherwise healthy elderly person whose life expectancy exceeds the cancer-related survival, the most effective management may include chemotherapy or other forms of aggressive treatment to induce the remission of the disease. Life expectancy may be critical to the decision to institute intrathecal infusion of opioids [66].
- Recognition of conditions that may alter the clinical picture of pain. In the presence of dementia, pain may present as confusion, delirium,

withdrawal, or outbursts [18, 21, 67–72]. In addition, cognitive impairment may interfere with the assessment of pain [65, 73–74]. Comorbid conditions causing chronic pain or hypertension may blunt the perception of new pain [75–79], whereas other conditions, such as depression or anxiety, may aggravate pain [80–82].

- Identification of the clinical consequences of pain, including decreased function [18, 21, 65, 83]; sleep deprivation [21, 65]; and decreased attention span and ability to perform complex tasks [18, 21, 65, 84]. These signs may reveal the extent of disruption to the patient’s lifestyle and intimate the urgency of treatment; they may also be used to monitor the success of treatment.

- Identification of the risks of pharmacologic managements. Clearly, patients who are functionally dependent or cognitively impaired are at increased risk of complications from opioids and may need some safety provision, such as a home-caregiver, when treatment is initiated [65]. Frail patients usually have reduced function of the cytochrome P450 enzymes and may be more subject to the complications of treatment than other patients [60].

OTHER FORMS OF GERIATRIC ASSESSMENT

The CGA is complex and time consuming and not always practical in face of a shortage of health-care personnel. In addition, there is no universal agreement over the most productive form of CGA. Alternative forms of geriatric assessment include screening questionnaires, tests of physical activity, and laboratory tests.

Several forms of screening questionnaires have been proposed. The main use of these questionnaires is to establish which patients are at risk for death and functional dependence and need a more comprehensive evaluation through a CGA. The Vulnerable Elders Survey 13 (VES-13) (Fig. 1) is one of the best validated and practical screening questionnaires [85]. This 13-item questionnaire can be easily completed by the patient or family members in a short time; each answer is scored, and the scores of each answer are summed into a final score. A final score of 4 or higher is associated with a fourfold increased risk of dependence and mortality (Fig. 1).

Tests of physical performance are also used to identify patients in need of a more in-depth CGA. Probably the most frequently used of these tests is called the “get up and go” test. It consists of asking an older individual to rise from an arm chair, walk

Vulnerable Elders Survey 13 (VES-13)

1. Age: _____

Score 1 point for age 75–84, 3 points for age 85+

2. In general, compared to other people your age, would you say that your health is:

poor fair good very good excellent

Score 1 point for "fair" or "poor"

3. How much difficulty, on average, do you have with the following physical activities?

	No difficulty	A little difficulty	Some difficulty	A lot of difficulty*	Unable to do*
a. stooping, crouching, or kneeling?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. lifting or carrying objects as heavy as 10 pounds?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. reaching or extending arms above shoulder level?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. writing, or handling and grasping small objects?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e. walking a quarter of a mile?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f. heavy housework, such as scrubbing floors or washing windows?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Score 1 point for each * response (maximum, 2 points)

4. Because of your health or a physical condition, do you have any difficulty:

a. shopping for personal items (like toilet items or medicines)?

Yes. If so, do you get help with shopping? Yes* No

No

Don't do. If so, is that because of your health? Yes* No

b. managing money (like keeping track of expenses or paying bills)?

Yes. If so, do you get help with managing money? Yes* No

No

Don't do. If so, is that because of your health? Yes* No

c. walking across the room? (*use of a cane or walker is OK*)

Yes. If so, do you get help with walking? Yes* No

No

Don't do. If so, is that because of your health? Yes* No

d. doing light housework (like washing dishes, straightening up, or light cleaning)?

Yes. If so, do you get help with light housework? Yes* No

No

Don't do. If so, is that because of your health? Yes* No

e. bathing or showering?

Yes. If so, do you get help with bathing or showering? Yes* No

No

Don't do. If so, is that because of your health? Yes* No

Score 4 points for one or more * responses

Figure 1 Vulnerable Elders Survey 13 (VES-13)

The Vulnerable Elders Survey 13 (VES-13) is a simple tool for identifying older persons at risk for health deterioration. A score of 4 or higher is associated with a 4.2-fold higher risk of functional decline or death, compared with elders scoring 2 or less. Adapted from Saliba et al.⁸⁵ © 2001 by RAND.

10 feet, and come back [86]. Negative prognostic factors include use of an arm to get up, more than 10 seconds to complete the full action, and uncertain gait. This test is also simple to administer and perform and has been validated for the prediction of early functional dependence and death.

Recent studies have demonstrated that elevated concentrations of inflammatory cytokines in the circulation of home-dwelling older individuals are associated with increased risk of functional dependence and mortality. Of special interest, Cohen and others [9] have demonstrated that the simultaneous increase of IL-6 and d-dimer in the circulation predicts an almost threefold increase of mortality and functional dependence. These tests are currently not part of standard geriatric assessment, but it is reasonable to expect that they may add important predictive information and may also be used as markers to monitor the effectiveness of treatment and rehabilitation of older individuals.

How Age May Influence the Clinical Presentation of Pain

In exploring the influence of age on the clinical presentation of pain, three questions will be addressed:

1. Does age alter the perception of pain?
2. Are the manifestations of pain different in younger and older individuals?
3. What are the effects of pain on function and quality of life in the elderly?

AGE AND THE PERCEPTION OF PAIN

This issue has been studied in both the research and clinical settings, with inconclusive results. In the laboratory, at least 40 studies have tried to establish whether the threshold for mechanical, thermal, and electrical painful stimuli to the skin is increased with age, with the majority of studies suggesting a trend toward a higher threshold [18]. The main criticism of all of these studies is that the painful stimulus used to cause pain in the laboratory is so low that lack of its perception may be irrelevant to the recognition of clinically meaningful pain. Also, a wide range of individual variations was observed, indicating that age was, at most, just one of the variables affecting perception of pain.

A number of clinical studies indicate that age may be associated with reduced perception of visceral pain [18]. The prevalence of silent exertional myocardial ischemia and of silent myocardial

infarction increases with age [87–89]. In addition, the absence of abdominal pain during peritonitis is more common among older people than among younger individuals [90–91]. Of special interest, Wroblewski and Mikulowski [92] reported that of 212 patients aged 60–99 with acute peritonitis, only 55% reported pain.

In the postoperative setting, there appears to be a reduction in pain intensity by 10%–20% for each decade of life after age 60 [18, 93–94]. It has been suggested, however, that these differences may be due, at least in part, to alterations in the cognitive status of older adults and in the inadequacy of some pain scales to accurately assess pain in these patients [95].

In regard to cancer-related pain, a number of studies have indicated that the prevalence and the intensity of pain may decline with age. For instance, Cheng et al reported that among 1,500 patients with metastatic cancer, 55% of those younger than 45 complained of pain; 35% of those aged 45–55 complained of pain, but only 26% of those over 65 complained of pain [96]. According to Curless et al [97], pain from rectal cancer was fourfold more common among individuals younger than 65 than in those older than 65. In another study, among 1,000 cancer patients in different centers in the Western world, persons younger than 65 were 50% more likely to score their pain 7 or higher on a visual analog scale than those older than 65 [98]. At least one large study, however, failed to report any difference in pain intensity among younger and older cancer patients [99].

While the majority of studies suggest that the perception of somatic and visceral pain decreases with age, no report can be considered definitive, for several reasons. First, the majority of these studies were subject to the limitation of retrospection, which is of particular concern when assessing an exquisitely individual variable such as pain. Second, no attempt was made to account for the decline in cognitive status and other difficulties older patients may have in communicating their pain [21]. Third, it has become clear that the report of pain by elderly individuals may vary with the scale used to measure pain. For example, Corran et al [100] and Gagliese and Melzack [101] demonstrated that older individuals reported the same intensity of chronic pain as younger individuals on a visual analog scale. However, the pain intensity was significantly lower for older individuals when it was measured with the McGill

Pain Questionnaire (MPQ), which also accounts for the emotional dimensions of pain. These differences may be explained in different ways, including the fact that the MPQ may be too complex for cognitively impaired elderly people or the fact that the emotional component of pain is less pronounced in these individuals. The important observation, however, is the fact that age-related differences in pain report may be scale-specific.

Regardless of whether the perception of pain by older individuals is different from that of younger ones, numerous studies have shown that pain is common and undertreated in elderly individuals, both those living at home and those in institutions [65, 102–103], and that pain is a potentially reversible cause of deconditioning and disability. In the older cancer patient, deconditioning and disability may lead to immobilization, sarcopenia, and poor functional status and also may compromise the effectiveness of antineoplastic treatment. Effective management of pain should be part of any program of cancer management in older individuals and be aimed at prolonging survival and maintaining function and quality of life.

MANIFESTATIONS OF PAIN IN YOUNGER AND OLDER INDIVIDUALS

Atypical manifestations of pain are more common in older individuals than in younger ones [18, 21, 65, 68–69] and may include delirium, confusion, fatigue, withdrawal, and depression [67, 80, 104–106]. Although these manifestations may be more common in cognitively impaired persons, previously depressed patients, and patients with multiple comorbidities, they may occur also in individuals who appear functionally, cognitively, and emotionally intact. The pathogenesis of these atypical manifestations is poorly understood but certainly reflects the multidimensional nature of aging and the involvement of different domains in the response to stress. Other age-related factors may further complicate the manifestations of pain, including:

- Some comorbidities, including hypertension [21, 65, 76–79] and other conditions causing pain [75], may blunt the perception of new pain.
- Older individuals may ascribe new pain to an aggravation of preexisting conditions, such as arthritis, and may fail to relate them to cancer;
- Older individuals may have difficulties in verbalizing pain [107–109]. They may preferentially refer to pain as “discomfort,” a term that may not

catch the attention of unprepared staff. Older patients may be concerned about being perceived as whining and a nuisance, especially in a busy hospital or nursing home setting, or they may simply believe that pain is a normal consequence of aging and does not deserve special attention or treatment. They may also be in denial about the possibility that pain signifies worsening of their neoplasm.

- Misconceptions about the use of pain medications may also play a role [21]. Older individuals may still be influenced by the old beliefs about pain treatment—that opioid medications need to be reserved for terminal pain, because otherwise they won’t work when they are most needed. Older patients also may still be under the impression that opioids for cancer pain may cause addiction.

- Last, but not least, in a multicultural society like the United States, where a wave of new immigrants has tried to transfer their elderly parents and relatives without any familiarity with spoken English, language barriers may impede the communication of pain.

IMPACT OF PAIN ON FUNCTION AND QUALITY OF LIFE

In older individuals, pain is not just an unpleasant sensation that momentarily lowers a person’s quality of life. Given the limited functional reserve of older individuals, pain may have long-lasting and irreversible consequences that compromise the effects of antineoplastic treatment, the function, and even the survival of the patient [65]. It behooves the practitioner to be highly alert to the possibility of these problems and to intervene promptly to break the vicious circle of pain, dysfunction, disease, and more pain.

Of special concerns are movement limitations and depression. Immobility causes sarcopenia, deep-vein thrombosis and deconditioning and may result in permanent functional dependence in persons who were formerly fully functional [65, 110]. Given the serious implications of immobility in older individuals, the American Geriatrics Society (AGS) [65] and other authorities around the world [11] recommend that even nonmalignant pain be managed with opioids when other interventions fail, because the long-term risks of pain are seen as more dangerous than the long-term drug complications.

Depression is a common complication of both pain and immobility [81–83] and is associated with increased risk of death in older individuals [47–

49]. In the cancer patient, depression may undermine the willingness to live and to take needed treatment [23]. In some situations, the concomitant management of pain and depression may be synergistic in improving both the mood and the pain [81–83].

Age and Pain Assessment

While cognitive decline may be an impediment to proper pain assessment, it is important to underline that reliable pain measurements still may be obtained from individuals who are mildly or moderately cognitively impaired [74, 107–109, 111–113]. It is a common misconception that any degree of dementia may prevent a person from making responsible decisions about his or her life or from being able to verbalize ongoing feelings. It would be a serious disservice to the older person if the inexperienced provider would consult a family member or another caregiver, rather than the patient, about the patient's symptoms under the wrong assumption that patient communication of pain or other symptoms is unreliable just because the patient's memory is failing.

Essentially, the assessment of pain may be performed using three nonmutually exclusive strategies:

1. pain scales,
2. pain interview, and
3. behavioral observation.

PAIN SCALES

The most common pain scales, with their respective advantages and disadvantages, have been summarized by Herr and Garand [74] (Table 2). As a general principle, scales that require a high level of abstract thinking, such as the visual analog scale or MPQ are unsuitable for older individuals, especially for those who are cognitively impaired or have a low educational level, because the abstractive capacity declines with age. The completion rate of these scales by older patients has generally been very low. Of the Numerical Rating Scales, the verticals appear easier to complete by older individuals. Of the visual scales, the thermometer (Fig. 2) is preferred and has the highest completion rate, even among cognitively impaired individuals. The facial expression scales are unreliable in cognitively impaired or emotionally disturbed patients, who may identify the facial expressions with their feelings rather than with their pain.

The verbal descriptor scale probably has the highest completion rate and may be the best to

Table 2

Relative Utility of Pain Scales in the Elderly

PAIN SCALE	CONSIDERATIONS RELATED TO OLDER INDIVIDUALS
Numeric Rating Scale (NRS)	<ul style="list-style-type: none"> • Reliable, but low completion rate • Vertical position of numbers appears more suitable to older individuals
Verbal Descriptor Scale (VDS)	<ul style="list-style-type: none"> • High completion rate • Lack of a numeric measurement
Pictorial Pain Scales	<ul style="list-style-type: none"> • Appear more suitable for adults with limited educations • Pictures involving facial expressions may be unreliable in cognitively impaired or depressed individuals • Thermometer scale is probably the most reliable and is the one proposed by the AGS guidelines
Visual Analog Scale (VAS)	<ul style="list-style-type: none"> • Failure rate increases with age • Generally unsuitable for individuals with low educational levels
McGill Pain Questionnaire (MPQ)	<ul style="list-style-type: none"> • Sensitive to sensory and affective aspects of pain • Not recommended for individuals who are illiterate or cognitively impaired • Length may be a problem, but is available in a shorter version

utilize outside of a research setting. The absence of reference numbers makes this scale unsuitable for research aimed at demonstrating changes in pain and also is inconvenient in following the course of pain in patients undergoing treatment.

PAIN INTERVIEWS

A pain interview includes questions related to the intensity of pain and the variation of pain with movement and the time of the day. Such an interview also contains questions on the number of days pain has interfered with ADLs/IADLs, pleasurable and social activities, exercise, ability to think, appetite, sleep, energy, and mood. Other questions are designed to elicit the number and frequency of pain medications taken during the past week and how the patient rates his or her health [65]. The pain interview should be combined with some objective findings, such as weight loss, a disheveled appearance that may indicate distress or lack of sleep, or slow verbalization [65].

Pain maps are useful complements to the pain interview. They consist of body pictures where the patient is asked to indicate where it hurts [114–115] and are useful in recognizing variations in pain location, especially in cognitively impaired persons. They also may help identify multiple sources of pain.

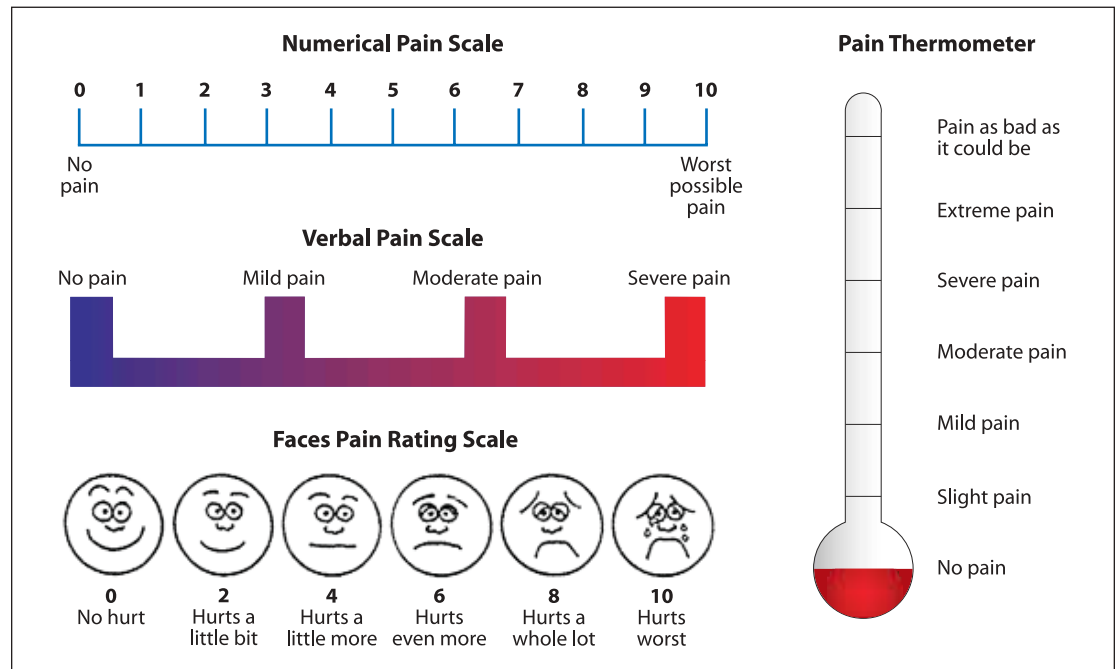


Figure 2 Measuring Pain

The illustration shows examples of visual pain scales for the assessment of pain in the elderly. Of the four scales, the pain thermometer is preferred and has the highest completion rate in the elderly, even among cognitively impaired individuals.

Pain interviews are very helpful but are time consuming and are unsuitable in the research setting due to the lack of measurements. They should be part of the initial evaluation of older patients with pain and may be used for follow up when simpler and more time-efficient forms of evaluation prove unreliable.

BEHAVIORAL OBSERVATIONS

In patients unable to verbalize their symptoms, behavioral observations may be used as indicators of pain [65, 74]. Common pain-related behaviors are described in Table 3.

Pain Management

The general principles of pain management are the same for both younger and older individuals, including the application of the “three-step ladder” proposed by the World Health Organization. It is important to state once more that cognitive impairment does not in any way preclude the use of opioids [111]. In many cases, the effectiveness of treatment may be monitored based on the patient’s responses to specific questions. When the patient is unable to verbalize, the observation of changes in a patient’s behavior is generally a reliable sign of treatment effectiveness [18, 21]. In

the following discussions, some age-related aspects of pain management will be highlighted.

NONPHARMACOLOGICAL PAIN TREATMENT STRATEGIES

Despite lack of conclusive evidence, older individuals often like to adopt alternative strategies for pain management [21]. They include traditional home remedies, such as massages and heating pads, or informal cognitive strategies, such as visiting friends, social gathering, prayer, and humor [116]. Whereas the reports related to transcutaneous electrical nerve stimulation (TENS) are mainly anecdotal [117], a recent randomized controlled trial demonstrated the effectiveness of percutaneous electrical nerve stimulation (PENS) in the management of low-back pain [118]. Other methods often quoted include hypnosis, meditation, relaxation, guided imagery, biofeedback, prayer, and music therapy. The practitioner should be aware of these approaches and support their application in individual cases where they seem to be effective.

TREATMENT OF UNDERLYING CONDITIONS

It is stating the obvious to say that the most definitive treatment of cancer-related pain is the

treatment of cancer. In addition to that, however, a number of low-toxicity options are now available, from bisphosphonates and radioisotopes, in the case of bone metastases, to low-dose chemotherapy. Low-dose chemotherapy can include capecitabine (Xeloda), weekly taxane therapy, vinorelbine (Navelbine), gemcitabine (Gemzar), and liposomal doxorubicin (Doxil), and appears to be well tolerated, even by frail patients [60].

As previously stated, depression may portend and aggravate the complaints of pain. Management of depression often is a very helpful adjuvant treatment to pain [81–83].

ANALGESIC DRUGS

Acetaminophen is the analgesic of choice in most circumstances [21, 65]. This drug works in the central nervous system but has no anti-inflammatory effects. For this reason, it may be less effective than nonsteroidal anti-inflammatory drugs (NSAIDs) [21]. It is inactivated by glucuronidation in the liver, and its elimination does not appear to be compromised by age.

NSAIDs are particularly beneficial in the presence of inflammatory pain, such as bone metastases. Some principles of management that can help make these agents safe and cost-effective:

- Gastrointestinal bleeding. The risk of gastrointestinal bleeding and other bleeding complications is higher for COX-1 than for COX-2 inhibitors. The use of COX-1 inhibitors should be proscribed in patients at increased risk of these complications, including a recent history of gastrointestinal bleeding, *H pylori* gastritis, or bleeding diatheses (thrombocytopenia, anticoagulation) [119]. In older patients without risk factors, the increased risk of bleeding does not seem to justify the increase in cost of the COX-2 inhibitors. The COX-1 inhibitors that should be avoided in older individuals due to enhanced risk of bleeding include indomethacin (Indocin), ketorolac (Toradol), piroxicam (Feldene), and mefenamic acid (Ponstel) [120].

- Renal toxicity. COX-1 and COX-2 inhibitors have similar renal toxicity [119]. Precautions that may minimize renal toxicity include monitoring of electrolytes and creatinine at the start of treatment and 1–4 weeks later, low initial dosage with slow titration, and use of medication on an “as needed” basis.

- Drug interactions. Of the COX-2 inhibitors, rofecoxib (Vioxx) is less dependent on the CYP450

Table 3

Common Pain Behaviors in Cognitively Impaired Elderly Persons^a

Facial expressions
<ul style="list-style-type: none"> • Slight frown; sad, frightened face • Grimacing, wrinkled forehead, closed or tightened eyes • Any distorted expression • Rapid blinking
Verbalizations, vocalizations
Sighing, moaning, groaning
Grunting, chanting, calling out
<ul style="list-style-type: none"> • Noisy breathing • Asking for help • Verbally abusive
Body movements
<ul style="list-style-type: none"> • Rigid, tense body posture, guarding • Fidgeting • Increased pacing, rocking • Restricted movement • Gait or mobility changes
Changes in interpersonal interactions
<ul style="list-style-type: none"> • Aggressive, combative, resisting care • Decreased social interactions • Socially inappropriate, disruptive • Withdrawn
Changes in activity patterns or routines
<ul style="list-style-type: none"> • Refusing food, appetite change • Increase in rest periods • Sleep, rest pattern changes • Sudden cessation of common routines • Increased wandering
Mental status changes
<ul style="list-style-type: none"> • Crying or tears • Increased confusion • Irritability or distress

^a Adapted from American Geriatrics Society Panel on Persistent Pain in Older Persons,⁶⁵ with permission.

enzyme system for metabolism than is celecoxib (Celebrex) [121]; hence, the risk of drug interactions is lower for rofecoxib.

Opioids are the mainstay for treatment of cancer pain, even in older individuals [65]. Special considerations related to specific agents include:

- Weak opioids such as codeine and tramadol [Ultram] have limited efficacy. They are pro-drugs requiring metabolic activation by CYP2D6 enzymes. Their efficacy is variable, as it depends on the individual CYP phenotype [18, 119]

- Meperidine (Demerol) is best avoided in older individuals because the metabolite normeperidine is excreted from the kidneys, accumulates in the circulation in the presence of renal insufficiency and may cause seizures [21, 119]. The concentration of normeperidine is increased by antiepileptic

agents that stimulate the synthesis of CYP3A4. Another important drug interaction is with hydroxyzine, as meperidine enhances sedation and orthostatism of this drug.

- Morphine is probably the most often used opioid in older individuals [21]. It is glucuronated in the liver to morphine 6-glucuronide and morphine

3-glucuronide, both of which are eliminated by the kidneys [24]. The metabolites accumulate in the circulation in the presence of a reduced glomerular filtration rate. The 6-glucuronide is 10- to 60-fold more active than the parent compound [122], whereas the 3-glucuronide is not effective as an analgesic but may cause neurotoxicity. Delayed

PEER VIEWPOINT

Commentary by Joanne Mortimer, MD and Matthew Loscalzo, MSW

With aging, an individual's chronological and functional age may differ because the rate of decline in organ reserve varies. The abilities to objectively assess the functional age, understand the impact of comorbid conditions, and titrate the associated polypharmacy are skills of geriatricians. We have much to learn from these subspecialists, as demonstrated in Dr. Balducci's superb review of pain management in the elderly. Pain management in this population requires knowledge of the biology of aging, a unique clinical skill set (probably not taught to most practicing oncologists in medical school or residency), time, and patience.

Despite effective medications, patients with cancer experience significant pain, which is far too often inadequately treated even by cancer specialists. Minority populations, women, and the elderly are most likely to be undermedicated [1,2]. Dr. Balducci does not chastise the oncology community for this. Rather, he points out the consequences of inadequate pain control—functional decline with inactivity and resultant venous thromboemboli, poor nutrition, and depression.

LISTEN TO THE PATIENT

Dr. Balducci did not point out that non-geriatricians tend to infantilize this population, but he could have. Due to the real time constraints of clinical practice, we do not always get an adequate history from the patient but instead, all too often, defer to a family member or caregiver to tell us about the patient. The author drives home the importance of making the patient central to the pain assessment and reinforces the notion that the best assessment of pain comes from patients themselves and not a family member or caregiver. He provides data that support his position that the most accurate assessment of pain comes from the patient, even the demented patient.

The use of "maps" of the body to help in identifying sites of pain and scales to determine severity has proven to be helpful. Dr. Balducci favors the use of the "thermometer scale" to determine pain severity. However, direct comparisons of visual analog, numeric, and "smiley face" scales have not been subjected to head-to-head comparisons. Scales that ask patients of any age to give an average are questionable at best. Because changes in function provide important information about the impact of pain on the patient, Dr. Balducci stresses the importance of the functional assessment. Here, the family and caregiver may indeed provide valid information to the physician. While most practicing oncologists have not been trained to perform a comprehensive geriatric assessment, some determination of the patient's mental and physical functioning may provide important additional information about the severity and impact of pain.

THE SINGLE MOST IMPORTANT PREDICTOR OF LONGEVITY

Due to the comprehensive nature of this review, the author did not offer a simplified functional assessment. However, it has been shown that as simple a thing as observing the patient walking from the waiting room to the exam room may provide important information, as the rapidity of gait is the single most important predictor of longevity in this population and may provide signs of the impact of pain on the patient's functioning [3].

This paper reminds us to be attentive to non-verbal communication of discomfort, such as facial expressions and body movements, and alterations in the patient's function. All are considered to be essential components of the pain assessment.

Dr. Balducci reviews how the biology of aging and declining organ reserve should help guide us in the selection of analgesic medications. To preserve renal function, acetaminophen or rofecoxib (Vioxx) is preferred over nonsteroidal

excretion of these metabolites may be responsible for increased sensitivity to morphine in the elderly. The availability of oral, rectal, and sublingual preparations of morphine and of sustained-release forms makes this agent particularly convenient for older individuals. In addition, topical morphine [123], which has minimal systemic absorption, is

particularly suitable for painful skin lesions.

- Hydromorphone undergoes metabolic changes similar to those of morphine. In addition to the formation of an active 6-glucuronide and a neurotoxic 3-glucuronide, hydromorphone metabolizes to an active hydromorphiquinone by hepatic reduction [124]. As in the case of morphine, the

anti-inflammatory drugs) or celecoxib (Celebrex). Of the opioid analgesics, morphine, oxycodone, and methadone should be used instead of prodrugs, such as codeine and tramadol, which require metabolic activation. The flexibility of morphine preparations is stressed, and slow escalation of dose is recommended. He reminds us that elderly patients are highly sensitive to the analgesic effects of opioids and that they experience side effects much more readily than younger patients.

AN IMPORTANT DISTINCTION

Dr. Balducci emphasizes the importance of distinguishing delirium from dementia. He also describes how depression is common in both aging and cancer and how uncontrolled pain may worsen depression. Agents such as selective serotonin reuptake inhibitors may not only be effective in treating the depression but may also provide adjunctive pain relief.

The need for geriatric expertise in oncology is now being recognized and will be even more important in the upcoming years, for "by the year 2030 more than 70% of all cancers will be diagnosed among those who are 65 and older." Evidence-based data are needed to determine how best to care for this population. Despite the prevalence of cancer in the elderly, older patients are consistently underrepresented in clinical trials.

Geriatricians and oncologists share much of the same terrain. The biologic changes of telomere shortening and defective DNA repair are common to both cancer and aging. Geriatricians and oncologists care for patients with multiple and complex medical problems that require constant monitoring. The goal of intervention is to improve quality of life rather than effect a cure. Other high-risk commonalities include home caregivers of similar age who also may have medical conditions requiring careful monitoring and barriers to compliance and comfort in the home.

Geriatric patients and cancer patients experience similar chronic physical symptoms and social isolation, as the extended family is increasingly unavailable in our culture. Financial concerns and limited health-insurance coverage may compromise continuity of care. Within the context of any serious illness is a family who has the need to put this experience into an evolving history and who wishes to infuse some meaning to the event. The physician has the challenge and opportunity to create a therapeutic environment in which the end of life can bring a sense of caring, purpose, and closure that is unique to the physician-patient experience.

The importance of incorporating geriatrics training into oncology and other medical subspecialties has been appreciated by philanthropic organizations such as the Hartford and Atlantic Foundations, which are funding joint training programs. We need more physicians with Dr. Balducci's expertise and skills to meet the needs of our aging society.

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effectiveness and toxicity of this compound are increased in the presence of a reduced glomerular filtration rate. Like morphine, hydromorphone is available in oral, rectal, and sustained-release forms and is suitable for intrathecal and epidural administration.

- Fentanyl. Unlike morphine and hydromorphone, fentanyl is lipophilic and suitable for transdermal administration. It is metabolized by CYP3A4 to norfentanyl, which is inactive. With chronic administration or hepatic failure, it may accumulate in the circulation due to saturation of storage sites. In the presence of hypoalbuminemia, both the effectiveness and toxicity of fentanyl may be increased, as the drug is highly protein-bound [125]. However, compared with morphine, fentanyl is less likely to cause side effects, including

pruritus, nausea, and constipation [21]. In addition to sublingual (Actiq) and transdermal (Duragesic) administration, fentanyl is suitable for epidural and intrathecal administration.

- Oxycodone is another popular opioid that is eliminated by hepatic metabolism via CYP2D6. In reality, oxymorphone is more active than the parent compound, but it is a minor metabolite, accounting for only 10% of the activity of the drug. The fact that its pharmacokinetics are largely independent of age, renal function, and serum albumin concentration makes this compound attractive for the elderly [126], but it is important to remember that the elimination of the drug is delayed in women. Oxycodone also is available in a sustained-release form.

- Methadone is enjoying renewed popularity as an analgesic, one reason being its low cost [21].

PEER VIEWPOINT

Commentary by Roberto Bernabei, MD

This very informative paper by Prof. Balducci highlights the issue of management of cancer pain in elderly patients.

This was once a hidden problem that is now gradually emerging following shocking reports, such as the one we published in the *Journal of the American Medical Association* in 1998 [1], which showed that up to 40% of elderly residents of US nursing homes with daily pain from cancer didn't receive any treatment, not even aspirin. These findings went on to become front-page stories in *The New York Times* and *The Washington Post*, as well as the topic of a *Doonisbury* cartoon. Thus, lay people are now informed about—and consequently much more interested in—what can be done if pain arises, especially in a disease like cancer, where pain can be the leading and most troubling symptom. And lay people are, of course, very worried about being inadequately treated when it is known that pain can be adequately controlled in the vast majority of patients by utilizing the principles of the World Health Organization's three-step ladder.

The clear message from Balducci's paper is the necessity for health professionals to properly assess both pain and the patient's overall problems, using the comprehensive geriatric assessment (CGA). I would like to reflect on these issues because they are at the core of the

underreporting and undertreatment of pain. If you don't diagnose pain and all the pain-related problems (ie, malfunctioning), you will never provide careful planning that will address the need for a specific analgesic, as well as the overall treatment of a cancer patient with pain.

THE NEED FOR STANDARDIZED ASSESSMENT

With respect to the assessment of pain, the strategies presented by Balducci—pain scales, pain interviews, and behavioral observation—are generally accepted as the pathway for the clinician to follow, tailoring one or more of them to the specific patient's problem or type of pain. With respect to the CGA, Balducci describes its benefits in the light of conditions that may alter the clinical picture of pain and of the clinical consequences of pain or the risks associated with pharmacologic management. What is missing in his approach is the need for a *standardized* CGA. A standardized CGA, with uniform assessment instruments, would provide homogeneous information and would help us escape from the present "tower of Babel" state of assessment.

At present, everyone makes his/her own assessment, thus preventing the collection of large numbers of cases and the creation of large, high-quality databases [2]. Such databases would advance our knowledge and understanding of the prevalence and incidence of

Other advantages of the drug include the fact that it is not excreted by the kidneys, and it has a lower risk of visual hallucinations, myoclonus, and constipation than that of morphine [21]. However, this agent can be problematic because of its unpredictable pharmacokinetics. The commercial preparation consists of an analgesic *l*-isomer and a *d*-isomer that inhibits monoamino-oxidase reuptake inhibitor. The plasma clearance is dependent on the patient's phenotype of CYP isoenzymes. Drug accumulation may occur after several days, while methadone induces its own metabolism that may shorten its half-life with long-term administration.

Local anesthetics include transdermal lidocaine, which relieves dermatomal pain in the area where it is placed [21]. It is particularly suitable in the

management of neuropathic pain in older individuals, given the minimal systemic absorption, similar to the morphine gel already described [123].

Neuropathic Pain

The management of neuropathic pain is just as difficult in older individuals with cancer as it is in younger patients [127]. Indeed, older individuals may be more susceptible than younger ones to the neuropathic complications of cancer treatment, especially radiation therapy and chemotherapy [128], and consequently the issue of neuropathic pain may be more common among the aged. The mainstay treatments include antiepileptic drugs and tricyclic antidepressants [127].

Gabapentin (Neurontin) is probably the agent of choice [129], given its safety profile over a

pain, as well as all of the correlates of pain [3]. They would also allow us to address unanswered questions, such as the identification of patients who need to be treated according to precise parameters; track outcomes of treatment; and develop optimal monitoring procedures to record toxicity and quality of care as treatment proceeds. Moreover, we also need to incorporate into such a CGA a variety of items, including laboratory parameters such as various cytokines, tumor necrosis factor- α , C-reactive protein, estrogens, androgens, brain natriuretic peptide, dehydroepiandrosterone, growth hormone, erythropoietin, and amyloid precursor protein, and the presence of such conditions as sarcopenia or anemia that may not be cancer related but help to describe the "aging" or "frailty" status of the patient.

Finally, recognizing that almost all health-care professionals in this era are so driven by cost analysis, Balducci reminds us of the complexity and time consumption of completing a CGA in the face of a shortage of healthcare resources. Therefore, he proposes alternative forms of geriatric assessment, such as a screening questionnaire and tests of physical activity. Granted, this approach would probably reduce costs. But what puzzles me is that use of the CGA has achieved the important goals of reducing morbidity and mortality [4], whereas screening questionnaires or physical performance tests only predict incident dis-

ability [5]. Such prediction is important, but far less so than reducing mortality.... Nobody questions the cost in time and money of doing nuclear magnetic resonance (NMR) imaging, which, as we all know, costs much more than a CT scan or more traditional radiology. The question I ask is: Why should we accept the cost of an NMR but not of a CGA?

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wide dose range and its demonstrated superiority over amitriptyline in a randomized, prospective study of the management of diabetic neuropathy [130]. It should be noted, however, that the pharmacokinetics of gabapentin are unpredictable, and in older patients the half-life of the drug may be prolonged beyond 24 hours [21]. Also, gabapentin has the potential for drug interactions; it particularly enhances the analgesic effect of morphine [21].

Lamotrigine (Lamictal) has proved to be very effective in diabetic neuropathy, but experience with this agent in neuropathic pain of cancer and in the elderly is very limited [21].

For peripheral painful neuropathy, transdermal lidocaine should be the front-line treatment [21].

Conclusions and a Summary of the AGS Recommendations

With the aging of the population, cancer in older people and the management of cancer-related pain in these patients are becoming increasingly common problems. Aging may present some unique challenges to the clinician, including recognition of the atypical manifestations of pain; utilization of individualized forms of pain assessment capable of embracing a wide array of different cognitive, emotional, and functional statuses; and selecting the treatment that best fits the complexity of the individual case.

Recognizing these unique challenges, the AGS annually convenes a panel of experts to discuss the management of pain in the elderly. The panel's recommendations are published each year in a supplement to the Society's journal [65]. The principles enounced in this article are in substantial agreement with those of the latest AGS panel and include the following:

- Pain in older individuals is common and undertreated due to a number of barriers, including atypical manifestations of pain in the elderly and the inability and unwillingness of older persons to verbalize pain complaints. It behooves the practitioner in charge of the older person to elicit an appropriate pain history, to recognize atypical pain, and to provide adequate pain relief.

- Effective treatment of pain in the older person is compelling, because pain may compromise the general health and even shorten the survival of the older person. By causing disability, depression, and/or poor nutrition, pain may compromise the

management of other conditions, including cancer.

- The assessment of pain in older patients may require a more comprehensive assessment than in younger patients; the assessment needs to include conditions that may be exacerbated by or may exacerbate or in some way modulate the perception of pain, such as depression, disability, and comorbidities. Simultaneous management of these conditions may enhance the effectiveness of pain management. Other conditions, such as functional dependence, may be followed to monitor the effectiveness of pain treatment.

- Self-report of pain by older individuals is reliable, even in the presence of moderate dementia. Vertical visual scales, such as pain thermometers, and numerical or verbal descriptor scales are the most suitable for older individuals with cognitive impairment and/or a low educational level. Observation of pain behavior is useful and reliable in assessing pain in individuals unable to verbalize their complaints.

- Nonpharmacological treatment may be helpful in selected individuals. Special attention should be paid to whether the pain is constant or enhanced by certain movements. In the latter case, the administration of analgesics could be timed or limited to the time of pain-producing activities.

- In the absence of risk of gastrointestinal bleeding (recent bleeding, history of *H pylori* gastritis, thrombocytopenia, or anticoagulation), COX-1 inhibitors are more cost-effective than COX-2 inhibitors, as long as indomethacin, piroxicam, mefenamic acid, and ketorolac are avoided. Of the COX-2 inhibitors, rofecoxib has a lesser risk of drug interactions.

- Older individuals may have an increased sensitivity to opioids, due to decreased hepatic metabolism and decreased renal excretion, as well as a reduced number of opioid receptors due to brain atrophy. Morphine, hydromorphone, oxycodone, and fentanyl are the opioids most commonly used. In general, one should initiate treatment with lower doses and longer dose intervals than would be used in younger patients. Dose escalations should be guided by individual pain relief, just as they are for younger subjects.

Research Perspectives

New insights into the biology of aging and new knowledge about pain management have opened a number of research perspectives in the management of pain in the older patient. Of special interest

would be studies such as the following:

- Early institution of intrathecal opioids [60], which might be associated with a reduced risk of adverse drug effects and better maintenance of function and nutrition.
- Effects of pain management on functional

decline and on the concentration of catabolic cytokines in the circulation.

- Management of pain with low-dose anti-neoplastic chemotherapy in frail patients.
- Qualitative research in the construct and consequences of cancer pain in the elderly.

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