CONSENSUS STATEMENT

Opioids and the Management of Chronic Severe Pain in the Elderly: Consensus Statement of an International Expert Panel with Focus on the Six Clinically Most Often Used World Health Organization step III Opioids (Buprenorphine, Fentanyl, Hydromorphone, Methadone, Morphine, Oxycodone)

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■ **Abstract**
Summary of consensus:

1. The use of opioids in cancer pain: The criteria for selecting analgesics for pain treatment in the elderly include, but are not limited to, overall efficacy, overall side-effect profile, onset of action, drug interactions, abuse potential, and practical issues, such as cost and availability of the drug, as well as the severity and type of pain (nociceptive, acute/chronic, etc.). At any given time, the order of choice in the decision-making process can change.

This consensus is based on evidence-based literature (extended data are not included and chronic, extended-release opioids are not covered). There are various driving factors relating to prescribing medication, including availability of the compound and cost, which may, at times, be the main driving factor.

The transdermal formulation of buprenorphine is available in most European countries, particularly those with high opioid usage, with the exception of France; however, the availability of the sublingual formulation of buprenorphine in Europe is limited, as it is marketed in only a few countries, including Germany and Belgium. The opioid patch is experimental at present in U.S.A. and the sublingual formulation has dispensing restrictions, therefore, its use is limited.

It is evident that the population pyramid is upturned. Globally, there is going to be an older population that needs to be cared for in the future. This older population has expectations in life, in that a retiree is no longer an individual who decreases their lifestyle activities. The "baby-boomers" in their 60s and 70s are "baby zoomers"; they want to have a functional active lifestyle. They are willing to make trade-offs regarding treatment choices and understand that they may experience pain, providing that can have increased quality of life and functionality. Therefore, comorbidities—including cancer and noncancer pain, osteoarthritis, rheumatoid arthritis, and postherpetic neuralgia—and patient functional status need to be taken carefully into account when addressing pain in the elderly.

World Health Organization step III opioids are the mainstay of pain treatment for cancer patients and morphine has been the most commonly used for decades. In general, high level evidence data (Ib or IIb) exist, although many studies have included only few patients. Based on these studies, all opioids are considered effective in cancer pain management (although parts of cancer pain are not or only partially opioid sensitive), but no well-designed specific studies in the elderly cancer patient are available. Of the 2 opioids that are available in transdermal formulation—fentanyl and buprenorphine—fentanyl is the most investigated, but based on the published data both seem to be effective, with low toxicity and good tolerability profiles, especially at low doses.

2. The use of opioids in noncancer-related pain: Evidence is growing that opioids are efficacious in noncancer pain (treatment data mostly level Ib or IIb), but need individual dose titration and consideration of the respective tolerability profiles. Again no specific studies in the elderly have been performed, but it can be concluded that opioids have shown efficacy in noncancer pain, which is often due to diseases typical for an elderly population. When it is not clear which drugs and which regimes are superior in terms of maintaining analgesic efficacy, the appropriate drug should be chosen based on safety and tolerability considerations. Evidence-based medicine, which has been incorporated into best clinical practice guidelines, should serve as a foundation for the decision-making processes in patient care; however, in practice, the art of medicine is realized when we individualize care to the patient. This strikes a balance between the evidence-based medicine and anecdotal experience. Factual recommendations and expert opinion both have a value when applying guidelines in clinical practice.

3. The use of opioids in neuropathic pain: The role of opioids in neuropathic pain has been under debate in the past but is nowadays more and more accepted; however, higher opioid doses are often needed for neuropathic pain than for nociceptive pain. Most of the treatment data are level II or III, and suggest that incorporation of opioids earlier on might be beneficial. Buprenorphine shows a distinct benefit in improving neuropathic pain symptoms, which is considered a result of its specific pharmacological profile.

4. The use of opioids in elderly patients with impaired hepatic and renal function: Functional impairment of excretory organs is common in the elderly, especially with respect to renal function. For all opioids except buprenorphine, half-life of the active drug and metabolites is increased in the elderly and in patients with renal dysfunction. It is, therefore, recommended that—except for buprenorphine—doses be reduced, a longer time interval be used between doses, and creatinine clearance be monitored. Thus, buprenorphine appears to be the top-line choice for opioid treatment in the elderly.

5. Opioids and respiratory depression: Respiratory depression is a significant threat for opioid-treated patients with underlying pulmonary condition or receiving concomitant central nervous system (CNS) drugs associated with hypoventilation. Not all opioids show equal effects on respiratory depression: buprenorphine is the only opioid demonstrating a ceiling for respiratory depression when used without other CNS depressants. The different features of opioids regarding respiratory effects should be considered when treating patients at risk for respiratory problems, therefore careful dosing must be maintained.

6. Opioids and immunosuppression: Age is related to a gradual decline in the immune system: immunosenescence, which is associated with increased morbidity and mortality from infectious diseases, autoimmune diseases, and cancer, and decreased efficacy of immunotherapy, such as vaccination. The clinical relevance of the immunosuppressant effects of opioids in the elderly is not fully understood, and pain itself may also cause immunosuppression.

Providing adequate analgesia can be achieved without significant adverse events, opioids with minimal immunosup-

pressive characteristics should be used in the elderly. The immunosuppressive effects of most opioids are poorly described and this is one of the problems in assessing true effect of the opioid spectrum, but there is some indication that higher doses of opioids correlate with increased immunosuppressant effects. Taking into consideration all the very limited available evidence from preclinical and clinical work, buprenorphine can be recommended, while morphine and fentanyl cannot.

7. Safety and tolerability profile of opioids: The adverse event profile varies greatly between opioids. As the consequences of adverse events in the elderly can be serious, agents should be used that have a good tolerability profile (especially regarding CNS and gastrointestinal effects) and that are as safe as possible in overdose especially regarding effects on respiration. Slow dose titration helps to reduce the incidence of typical initial adverse events such as nausea and vomiting. Sustained release preparations, including transdermal formulations, increase patient compliance. ∎

Key Words: opioids, chronic severe pain, elderly, consensus

INTRODUCTION

Aim of the Consensus Meeting

A multidisciplinary group of experts in the fields of pharmacology, toxicology, pain management, and anesthesia met in Sofia, Bulgaria in May 2005 during the International Forum on Pain Medicine. The aim of the meeting was to review and critically evaluate published evidence for the efficacy and tolerability of the 6 clinically most often used World Health Organization step III opioids in the elderly patient, in order to provide practical recommendations to physicians on the optimal use of these drugs in the target population, ie, elderly patients with chronic severe pain requiring strong opioids. This consensus meeting was supported by Grünenthal GmbH, Aachen, Germany.

Intended users of the recommendations

The intended users of the recommendations are:

- Physicians: primarily general practitioners and family medicine practitioners, but also geriatricians, rheumatologists, orthopaedists, oncologists/palliativists, and pain specialists;
- Nurses, including advanced Practice Nurses;
- Occupational therapists;
- Pharmacists;
- Physician assistants;
- Psychologists and behavioral health clinicians.

Table 1. Opioids Considered in This Review

Compound	Formulations
Morphine	IV, oral, rectal
Oxycodone	Oral
Hydromorphone	IV, oral
Fentanyl	Transdermal, IV, submucosal
Buprenorphine	Transdermal, sublingual, IV
Methadone	IV, oral

Table 2. Rating Scales Used to Assess Strength of Evidence[1–5]

I	Large, randomized, controlled trial. At least 100 patients per group
II	Systematic review
III	Small, randomized controlled trial. Fewer than 100 patients per group
IV	Non-randomized controlled trial or case report
V	Expert opinion

Level of Evidence

Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least 1 randomized controlled trial or SmPC of respective product
IIa	Evidence obtained from at least 1 well-designed controlled study without randomization
IIb	Evidence obtained from at least 1 other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
IV	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

The opioids considered are those of World Health Organization step III that are used most frequently and for which adequate information is available (Table 1).

Evidence rating Scales

There are a number of scales in use for assessing the relative strength of evidence. Despite the different numbering systems, they are very similar, stratifying trials from large randomized studies down to individual opinion (Table 2).

TARGET POPULATION

Demographics of the Elderly Population

The elderly are usually defined as those aged 65 years or more. The proportion of people aged 60 and over is rising throughout Europe (Table 3).[6] Improvements in health care regarding prevention and treatment of diseases have contributed to this, but with the growing life span disease patterns also change and need adequate treatment.

Table 3. Proportion of People Over 60, Actual and Projected[6]

Country	% in 2000	% in 2020
Italy	24	31
Germany	23	29
Spain / France	21	27
Norway	20	26
U.K.	21	26
Switzerland	21	32

Incidence of Pain in the Elderly

Pain is one of the most prevalent symptoms among the elderly.[6] In U.S.A., chronic pain is estimated to affect around 68 million people each year, 25% of whom (17.5 million) will be elderly, while 15% to 20% of the U.S. population suffer acute pain each year.[7,8] Teno et al.[8] report that over 40% of nursing home residents who had pain recorded at their Minimum Data Set assessment had either moderate daily pain or occasional excruciating pain. Persistent pain varied between states from 38% to 50%. Overall, 1 in 7 residents (14%) was in persistent severe pain.

In U.K., pain or discomfort is reported by at least 50% of people aged 65 and over, rising to around 60% in those aged over 75.[9] A large and detailed study of chronic pain in the U.K. suggested that the prevalence of pain in people aged over 60 is even higher than this, at 60%.[10]

Yet, it is known that underreporting of pain is frequent, especially in older people and, as a consequence, physicians tend to undertreat pain in this group, especially pain from nonmalignant causes such as osteoarthritis (OA) and joint pain, but also cancer-related pain.[6]

CHALLENGES IN THE MANAGEMENT OF PAIN IN THE ELDERLY

Perception of Pain

Because of the scarcity of published data relating to opioid use in the elderly, this is the first known attempt by a consensus panel, to assess the information in a comprehensive fashion.

Studies suggest that there are some age-related differences in the perception of, and response to, pain.[11] The response to mild pain is reduced in many individuals, but elderly people may be more sensitive to severe pain. The increase in pain threshold could lead to delays in diagnosis and poor recovery, while the decreased tolerance to severe pain presents management problems. In addition, underprescribing of opioids to the elderly contributes to poor pain management.[12]

The reasons for these age-related changes in pain remain unclear.[13] There are structural, biochemical, and functional changes in the peripheral nervous system with age, with a decrease in the density of myelinated and unmyelinated fibres, together with increased neuronal damage and deterioration. There is also a reduction in the content and turnover of neurotransmitter systems known to be involved with nociception.[14,15] A slowing in peripheral nerve conduction velocity may be the cause of the change in pain sensitivity. Similar changes have also been observed in the central nervous system (CNS).[15]

Studies comparing the efficacy and tolerability of opioids, such as fentanyl patches,[16] morphine,[17] and sublingual buprenorphine[18] in the elderly and other populations have shown that the elderly respond, as well as, or even better, to opioid treatment than younger age groups. Indeed, a recent study by Likar et al. in patients with moderate and severe pain showed that transdermal buprenorphine benefited patients to a comparable or even higher extent in ≥65-year-olds compared with the younger age group,[19] supporting the need to address the problems with underprescribing in this age group.[12]

Cognitive Impairment and Compliance

Many elderly patients suffer cognitive impairment, confusion, and memory loss, either from pathology or medication, and confounded by sight and hearing impairment. This can lead to problems of compliance and also to difficulties in accurately reporting or describing pain and adverse events,[20] with the result that the patient may be overtreated or undertreated, may suffer increased adverse events, or may develop tolerance. The sensory perception of pain is well preserved in the elderly, but the ability to express pain is altered with advancing dementia. Dementia and cognitive failure often lead to atypical behavior and reactions to pain.[21] Senescence results in higher drug concentrations at receptor sites, often exacerbated by delayed elimination, and the elderly often develop bizarre manifestations of drug-induced adverse events.

Sustained release preparations are preferred in patients where compliance may be a problem, as dosing frequency can be reduced. Transdermal analgesics increase patient compliance[22,23] and are suitable for patients with swallowing difficulties or impaired gastrointestinal (GI) function.

Table 4. Effect of Reduced Hepatic Function On Pharmacokinetics of Opioids[28]

Opioid	$T_{1/2}$	Plasma Concentration of Metabolites	Comment	Recommendations	Evidence Level
Morphine	↑	↓	M6G↓	Dosage ↓	IIb
Oxycodone	↑	↑		Dosage ↓	IIb
Hydromorphone	?	?	No data available	Dosage ↓	IV
Fentanyl TD	↑	?		Dosage ↓	III
Buprenorphine TD	↑	↓	Low activity metabolites	Dosage ↓	IIb
Methadone[29]	↑	?	No data available	No dosage change	IIb

$T^{1/2}$, half life; M6G, morphine-6-β-glucuronide (active metabolite of morphine); ?, unknown; TD, transdermal.

Physiological Changes and Altered Pharmacology

There are particular challenges in managing pain in the elderly.[24] Physiological decline in organ function (eg, renal or hepatic) can affect the pharmacology of analgesics and, therefore, the onset of action, the rate of elimination, and the half-life of drugs. Comorbidities and polypharmacy increase the possibility of drug interactions, and adverse events, such as dizziness and respiratory depression, can have serious consequences in a patient that may already be at risk of falls and fractures. The combined effect leads to a narrowing of the therapeutic window and increased difficulty in balancing the risk of adverse events against the need for adequate analgesia.[25]

Volume of Distribution. Increasing age is associated with increased body fat and reduction in total body water, the combined effect of which is to increase the volume of distribution of lipophilic drugs. This delays both the onset of action and the rate of elimination without affecting plasma concentrations. Conversely, there is a decrease in the volume of distribution for hydrophilic drugs, which can increase plasma levels of these drugs. Lower volumes of distribution increase the initial peak plasma levels of morphine, which may affect the response to therapy, particularly the adverse event profile.[26]

Reduced Hepatic Function. Cardiac index tends to decrease at the rate of 1% per year after the age of 50 years, as a result of stiffening vasculature, increasing systolic blood pressure, and reduced myocardial reserve. This reduces renal and hepatic function, resulting in a prolongation of drug circulation, uptake and distribution.

In addition, reduced hepatic mass and blood flow, together with reduced levels of monooxygenases and cytochromes (CYP) (particularly phase 1 reactions metabolized by P450), but with relative preservation of the conjugases, result in a 30% to 40% reduction of elimination of agents metabolized by the liver. Consequently, bioavailability of drugs with high first-pass elimination will be increased.[27] In elderly, patients, with chronic hepatic disease, dosage reductions, or longer dosing intervals, are required to prevent drug accumulation (Table 4).

Reduced Renal Function. Renal function declines steadily with age but may remain undetected by plasma creatinine measurement in elderly patients because of a simultaneous decline in muscle mass. Reduction in glomerular filtration rate can increase the half-life of drugs that are mainly eliminated via the kidneys. Accumulation of drug or active drug metabolites increases the risk of toxicity and the severity of drug-related adverse events.[30] The possible clinical outcomes of administering opioids to patients with impaired renal function are summarized in Table 5.

MANAGING PAIN IN THE ELDERLY

The only international guidelines that are available are from the American Geriatric Society, the most recent being from 2002,[32] which made a number of important recommendations:

- Use the least invasive route for medication;
- Where possible, choose sustained release formulations;
- Introduce 1 agent at a time, at a low dose, followed by slow dose-titration;
- Allow a sufficiently large interval between introducing drugs to allow assessment of the effect;
- Treatment should be constantly monitored and adjusted if required to improve efficacy and limit adverse events;
- It may be necessary to switch opioids[a]

Notes: [a]While pharmacologic tolerance may develop to the opioid in use, tolerance may not be as marked relative to other opioids. This "incomplete cross-

Table 5. Clinical Outcomes of the Use of Opioids in Patients with Impaired Renal Function[31]

Opioid	$T_{1/2}$	$T_{1/2}$ Metabolites	Clinical Outcomes of Decreased Renal Function	Recommendation	Evidence Level
Morphine	↑	↑↑	Increased active metabolites M3G and M6G may lead to long-lasting respiratory depression	Dosage ↓	IIa
Oxycodone	↑	↑	Clearly reduced renal clearance of parent compound and metabolites	Dosage ↓	IIb
Hydromorphone	↑	↑↑	Accumulation of metabolites described	Dosage ↓	IIb
Fentanyl TD	↑	↑	Decreased renal clearance in the elderly	Dosage ↓	IIb
Buprenorphine TD	=	=	No clinically relevant changes	Adjust ±	IIa
Methadone	↑	↑	Not extensively evaluated in patients with renal impairment Use with caution	Dosage ↓	IV

$T_{1/2}$, half life; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide.

tolerance" is likely due to subtle differences in the molecular structure of each opioid or the way each interacts with the patient's opioid receptors. Consequently, when switching opioids, there may be differences between published equianalgesic doses of different opioids and the effective ratio for a given patient. Whether it is necessary to switch opioids because of unremitting opioid-induced sedation or fatigue that limits quality of life, or dose escalation to provide optimum pain control tolerance, start with 50% to 75% of the published equianalgesic dose of the new opioid to compensate for incomplete cross-tolerance and individual variation, particularly if the patient has controlled pain.

Unfortunately, not all currently favored World Health Organization step III opioids are considered here.

There are no European guidelines on the use of long-acting analgesics in the treatment of chronic pain in elderly, although some recent reviews propose the use of long-acting analgesics and opioids as the mainstay for the treatment of chronic pain for reasons of stable pharmacokinetic and pharmacodynamic features, as well as for reasons of therapy compliance;[33–36] however, there is no real scientific proof to support the use of long-acting analgesics over short-acting analgesics. Patients should also be prescribed short-acting analgesics for the treatment of breakthrough pain.

The role of Opioid Analgesics in Pain Control

Opioid analgesic drugs are an important component in the control of moderate to severe pain; the criteria for selecting analgesics for pain treatment in the elderly are dependent on a number of factors explained previously.

The readiness to prescribe opioids in this group varies between countries, and they are possibly under-used, particularly in chronic conditions, such as arthritis. The paucity of guidelines for opioid use in the elderly reflects

Table 6. Evidence for General Principles of Opioid Use in Cancer Pain[37,38]

STRONG (randomized controlled trials) evidence exists for the following statements:
- Immediate release (IR) morphine for titration
- Controlled-release opioids should be used for long-term therapy
- Spinal opioids are effective
- Transdermal fentanyl is effective in stable pain

MEDIUM (case study) evidence exists for the following statements:
- Provide continuous analgesia around the clock
- The World Health Organization analgesic ladder should be followed
- Strong opioids are useful for moderate to severe pain
- Transdermal formulations are an effective alternative in stable pain
- Opioids should be switched when the side effects are intolerable
- Addiction is unlikely

WEAK (expert opinion) exists for the following statements:
- Oral route is preferable
- Start with IR morphine
- Rescue doses are needed for breakthrough pain
- Dose reduction, hydration and drugs for opioid central nervous system toxicity [??]
- 1:2 or 1:3 ratio for oral:parenteral morphine

?, unknown.

the lack of studies of these drugs on the old. Hence, it seemed timely to review the evidence, ie, available and to attempt to formulate some recommendations for the use of opioids in the elderly population.

REVIEW OF OPIOID EFFICACY IN PAIN MANAGEMENT IN THE ELDERLY

Cancer-Related Pain: Assessment of Therapeutic Options

There is little high-grade data on opioid use specifically in the elderly cancer patient; most recommendations and clinical practice are based on expert opinion. From the available studies that have been carried out in the cancer pain area (mostly level Ib or IIb) (Tables 6 and 7), we can draw a number of conclusions, with varying degrees of certainty, about the efficacy of opioids in treating cancer pain, and extrapolate these to the elderly.

Table 7. Published Data on the Use of Opioids in the Management of Cancer Pain

Substance	Studies in Cancer Pain	Evidence Level	Reference
Morphine	42 randomized controlled trials (RCTs)	Ib	39–42,43–80
	6 open-label studies	IIb	81,82–86
	4 retrospective analyses	III	87–90
Oxycodone	8 RCTs	Ib	39,42,81,91,92,93–95
Hydromorphone	7 RCTs	Ib	40,96–101
	2 open-label studies	IIb	101,102
	3 retrospective studies	III	103–105
Fentanyl	1 pooled analysis	Ib	14
	1 RCT	III	106
	4 open-label pilots	IIb	107–110
	11 open-label prospective	II/III	108,111–120
	2 follow-up	III	121,122
	1 quality of life study.	III	123
Buprenorphine	4 RCTs	Ib	124–127
	1 open-label extension	IIb	128
	1 retrospective study	III	129
	1 large postmarketing surveillance (incl. 28 % cancer patients)	III	130
Methadone	9 RCTs	Ib	41,54,74,131–136
	6 open-label studies	IIb	82,137–141
	1 retrospective study	III	89

Morphine. Morphine has been used to treat cancer pain for many years and is undoubtedly effective as shown in numerous clinical studies, comparing it against oxycodone,[39] hydromorphone,[40] fentanyl,[142] or methadone.[41] However, many of the studies comprised a rather low number of patients; thus, the reliability of the data is relatively low. No studies have been performed to evaluate the efficacy in elderly cancer patients. Moreover, newer medications are now available with improved tolerability profiles, and in formulations, that may provide smoother and more extended analgesic cover.

Morphine is metabolized (>90%), mainly in the liver, to morphine-3-glucuronide (M3G) and to smaller amounts of morphine-6-glucuronide (M6G) and normorphine. All 3 metabolites are active. M6G is thought to contribute somewhat to morphine's analgesic effect, but M3G has neuroexcitatory properties (seizuregenic). Although normorphine is generally present in only small amounts following parenteral administration, large amounts of this neurotoxic metabolite form following oral administration.

Enterohepatic recirculation of M3G and M6G results in the continued presence of metabolites in the feces and urine days after the last dose, even in healthy individuals. The elimination of morphine metabolites is significantly altered in patients with renal failure, such that, patients with renal failure may have toxic reactions because of accumulated levels of the metabolites. In the elderly, M6G may accumulate because of age-related reduction in renal function or because of relative dehydration; this is especially true if morphine is taken on a regular basis.

Oxycodone. A number of randomized double-blind studies, comparing oxycodone vs. morphine[39,42,81] or comparing different release forms of oxycodone,[91,92] have demonstrated that the drug is equally effective to morphine and in general well tolerated in the treatment of cancer pain. No data are available for the elderly.

Hydromorphone. For hydromorphone, 5 randomized double-blind studies have been performed in cancer patients, some comparing different application forms of hydromorphone,[96,97] others showing similar efficacy compared with morphine[40,98] or other opioid comparators[99] but, again, no specific data for the elderly exist.

Fentanyl. Fentanyl has been frequently investigated but mostly in open-label studies where it has proven to be effective and well tolerated. There is only 1 randomized, double-blind, placebo-controlled study, which demonstrated the efficacy of transdermal fentanyl at 50 to 75 μg/hour vs. placebo in 95 patients with chronic cancer pain.[106] Transdermal fentanyl provided effective analgesia and was well tolerated, with a low incidence of constipation, somnolence, or nausea; although, because of an unexpected high placebo response in this

group of cancer patients with high interindividual variability, transdermal fentanyl was not statistically superior to placebo.

One open multicenter study from China[143] investigated the management of moderate to severe cancer pain in 1664 elderly patients aged 65 to 90 years with transdermal fentanyl 25 to 150 µg/hour initially to 25 to 200 µg/hour at days 15 and 30. Transdermal fentanyl was effective in reducing pain in >97% of patients and improving quality of life rate from 25% to >71%.

Buprenorphine. Four randomized controlled trials vs. placebo are available,[124–127] the latter dedicated to cancer pain, the other 3 with mixed indications. The first study was in 151 patients with severe to very severe chronic cancer/noncancer pain who maintained "at least satisfactory pain relief" with sublingual buprenorphine 0.8 to 1.2 mg/day during an open-label 5-day run-in phase.[124] Patients were randomly allocated to transdermal buprenorphine at 35 µg/hour, 52.5 µg/hour, or 70 µg/hour, or placebo, receiving 2 patches consecutively, each applied for 72 hours. Patients treated with transdermal buprenorphine benefited substantially in terms of reduced pain intensity, improved pain relief, and duration of sleep, compared with placebo recipients.

The second study was carried out in 30 centers in 6 countries (France, Belgium, Netherlands, Austria, Croatia, and Poland):[125] Two hundred and eighty-nine patients with severe cancer pain were treated successfully with transdermal buprenorphine at 70 µg/hour during the 14-day run-in period, then 188 patients were randomized to either transdermal buprenorphine at 70 µg/hour or placebo, applied for 72 hours for 14 days. The analgesic activity of transdermal buprenorphine at 70 µg/hour was statistically significantly more effective than placebo, with reduced pain intensity and rescue medication (sublingual tablet consumption), and had a comparably good side-effect rate.

The third study was a randomized, double-blind, placebo-controlled, multicenter study, in 154 patients with chronic, severe pain related to cancer or other diseases and inadequately controlled with weak opioids.[126] Patients were randomized to receive transdermal buprenorphine at 35 µg/hour, 52.5 µg/hour, or 70 µg/hour, or placebo patch, applied for 72 hours, for up to 15 days. Transdermal buprenorphine was shown to be an effective analgesic against chronic, severe pain in this study population, and showed improved duration of sleep and reduced need for additional oral analgesics.

The fourth multicentre, double-blind, placebo-controlled, parallel-group study was of 137 patients with either cancer or noncancer-related pain (NCP).[127] Following a 6-day open-label, run-in phase with sublingual buprenorphine 0.8 to 1.6 mg/day as needed, patients were randomized to receive 3 sequential patches of either buprenorphine at 35 µg/hour or placebo, applied for 72 hours. In this study, transdermal buprenorphine provided adequate pain relief and improvements in pain intensity and duration of pain-free sleep.

All have shown buprenorphine to be effective and well tolerated, but again no specific studies in the elderly were performed; however, a postmarketing surveillance study of 13,179 patients (mean and median age 68 years),[130] one-third of whom suffered from cancer pain, showed that transdermal buprenorphine provides effective, sustained, and dose-dependent analgesia, irrespective of age.

Methadone. For methadone 9 randomized controlled trials could be identified (Table 7) in cancer pain, comparing methadone mainly with morphine, but with no specific data in the elderly.

Recommendation for the Use of Opioids in Cancer Pain. World Health Organization step III opioids are the mainstay of pain treatment for cancer patients and morphine has been the most commonly used for decades. In general, high level evidence data (Ib or IIb) exist, although many studies have included only few patients. Based on these studies, all opioids are considered effective in cancer pain management, but no well-designed specific studies in the elderly cancer patient are available. Of the 2 opioids that are available in transdermal formulation—fentanyl and buprenorphine—fentanyl is the most investigated, but based on the published data both seem to be effective, with low toxicity and good tolerability profiles especially at low doses.

Noncancer-Related Pain

Common etiologies for NCP include OA, rheumatoid arthritis and herpes zoster. In U.S.A., more than 1 million new cases of herpes zoster arise each year,[144] with approximately 10% to 15% of these cases developing postherpetic neuralgia (PHN). The age distribution of its victims, however, includes a disproportionate number of the elderly: nearly half of older patients,

greater than 60 years old, with herpes zoster that will have enduring neuropathic pain.[144–146] PHN is usually refractory to simple analgesic therapies, and treatment is most often pharmacologic, including a wide variety of drugs and routes of delivery.[147,148] The most commonly used agents are oral medications. Currently, the standard treatment for PHN is with various tricyclic antidepressants (amitriptyline, desipramine, and clomipramine) either as monotherapy or in combination with other medications, such as carbamazepine or opioids.

Unfortunately, only 50% of patients treated with tricyclic antidepressants for PHN in clinical trials experience pain relief in the absence of intolerable adverse effects. Different therapeutic options do exist for these patients, but usually side-effects play a major role in the criteria for analgesic selection, especially with regard to relative toxicities of the agents and their particular relationship to the elderly, eg, nonsteroidal anti-inflammatory drugs (NSAIDs) and GI toxicity, or COX-2 inhibitors, NSAIDs, and cardiovascular toxicity. Because of these toxicities, the medications from the more traditional stepladder approach are commonly undertaken. The utilization of low-dose opioids as first-line therapy in these types of situations becomes more rational.[149–151]

Moderate to severe NCP arises from musculoskeletal disease (MSD), such as osteoporosis, collapsed vertebrae, polymyalgia, and Paget's Disease; peripheral vascular disease, such as leg ulcers, coronary artery disease, and other conditions, such as diabetes, stroke and back pain. As curative treatment is often impossible, the management goal is usually palliative.

There is still no consensus as to the pain mechanisms in MSD but microfractures around osteoarthritic joints could produce a rise in prostaglandins, giving rise to an inflammatory component. Significant hyperalgesia can develop, producing painful allodynia on walking. Morning stiffness is also a typical pattern with arthritis; therefore, analgesia needs either to have a rapid onset, or to be in place from overnight application.

Besides some studies of evidence level Ib or IIb, the literature on opioid therapy for NCP consists of "surveys" or uncontrolled case series (Table 8). Despite this, the available data suggest that patients with NCP can achieve satisfactory analgesia by using a constant dose of an opioid, most conveniently delivered via an oral slow release preparation or a transdermal patch.[162] Opioids are effective, but need careful individual dose titration, because side-effects are common. The use of opioids is limited by patients' fears and the possible

Table 8. Published Data on Management of Non-cancer-Related Pain with Opioids

Study	Evidence Level	Reference
Morphine sustained release (SR), non-cancer-related pain	IIa	152
Oxycodone in back pain: instant vs. SR	Ib	153
Oxycodone in osteoarthritis (OA): SR at 2 doses vs. placebo	Ib	166
Hydromorphone SR: mixed chronic pain. No studies in OA, osteoporosis	IIb	102
Transdermal fentanyl (TDF) vs. oxycodone + acetaminophen, low back pain	IIb	155
TDF, back pain from osteoporosis	III	156
TDF vs. morphine SR: cancer and non-cancer pain	Ia/IIb	157
TDF vs. oxycodone SR: non-cancer-related chronic pain	III	158
TDF vs. oxycodone + acetaminophen: low back pain, neuropsychological effects of long-term opioid use	IIb	159
TDF vs. morphine SR: non-cancer-related chronic pain	Ib	160
TDF vs. oxycodone + acetaminophen: low back pain, sleep and somnolence changes	IIb	161
TDF vs. morphine SR: mixed pain, pooled data analysis	Ib	14
Transdermal buprenorphine (TDB): chronic non-cancer-related pain	Ib	124
TDB: mixed pain	Ib	126
TDB: mixed pain	Ib	127
Methadone. No studies.	—	

negative effects on balance and motor function. A high percentage of emergency room visits by elderly patients are for falls, so analgesia should ideally not contribute to unsteadiness or dizziness.[163]

The options for NCP are increasing and there are now a number of oral sustained releases or patch preparations. The desired advantage of sustained release or steady-state administration vs. intermittent dosing of an opioid (or any drug) is maintenance of the drug's plasma level within its therapeutic range without the peaks and troughs characteristic of intermittent dosing that might lead to either inadequate pain relief or excess adverse effects. If adequate compliance can be achieved with intermittent dosing, equivalent therapeutic outcome would be expected, and is reported. However, poor compliance, particularly with opioids, is not uncommon with the elderly, for a variety of reasons. A concern that steady-state exposure of opioid receptors to agonist might lead to greater tolerance and dependence is not borne out in studies of transdermal patches.[157]

Morphine. Treatment for up to 6 years with a moderate dose of up to 195 mg/day morphine or its equivalent

has been reported[164] and even up to 360 mg and 2 g/day.[165] Cognitive function is relatively unaffected in patients taking stable, moderate doses but it may be impaired for up to 7 days after a dose increase.[166] The most important effect of age is reduction in renal clearance. Many aged patients thus excrete drugs slowly and are highly susceptible to nephrotoxic agents. Acute illness may lead to rapid reduction in renal clearance, especially if accompanied by dehydration. Dosage should be generally substantially lower than for younger patients and it is common to start therapy with about 50% of the adult dose. Simple treatment regimes should be implemented and only drugs with a clear indication should be prescribed and, whenever possible, given once or twice daily. Complicated regimes should be avoided.

Instructions concerning prescription and use should be given clearly: the patient being asked not only if they understand them, but also asked to repeat them to the prescriber. Written instructions should also be clear and readable by someone with imperfect eyesight.

Morphine is administered as tablets (normal release), tablets (modified release), solution, suspension, or capsules. Because the pharmacokinetic profiles of modified release compounds differ, it is best to keep individual patients on the same brand. Most are administered twice daily, and some daily.[167–169]

The time to reach peak plasma concentration is significantly shorter using an aqueous solution of morphine than with an oral tablet (0.5 hours : 1.5 hours), suggesting that morphine solutions are a better option than tablets for pro re nata (as needed) use.

The starting dose of morphine should be calculated to give a greater analgesic effect than any previously used medication. If the patient is frail and/or elderly, a low dose, eg, 5 mg 4-hourly, will help to reduce the likelihood of drowsiness, confusion, or unsteadiness. If the patient was previously receiving a weak opioid regularly, 10 mg 4-hourly is a reasonable commencing dose, alternatively 20 to 30 mg modified release 12-hourly. Thereafter, providing adverse effects which do not intervene, the dose should be increased stepwise until adequate analgesia is achieved. "Adequate" should be what the patient deems satisfactory, as total analgesia is not always the ultimate goal.

Step increases are generally 33% to 50%, with 65% of patients never needing more than 30 mg 4-hourly (100 mg 12-hourly for modified release preparations). The remainder will need up to 200 mg 4-hourly (600 mg 12-hourly for modified release) or, on occasions, in excess of this. Should the total daily dose reach 3 g daily without adequate analgesia, opioid-resistant pain should be suspected, and additional analgesics of other types introduced or interventional techniques considered. If a patient presents with severe, uncontrolled pain, intravenous (IV) titration is the mode of choice. There is no place for the use of the intramuscular route of administration in this or other situations.

Oxycodone. The 2 short oxycodone studies with doses up to 40 mg/day demonstrated effective analgesia with typical opioid adverse events. The second study[154] had a 6-month extension period (with optional treatment for an additional 12 months), which found no evidence of tolerance.

Hydromorphone. The single hydromorphone study[102] provided a lower level of evidence but showed adequate efficacy and tolerability in a mixed group of cancer and noncancer patients.

Fentanyl. A larger body of evidence is seen with transdermal fentanyl[14,156–161] but the studies in NCP pain are fewer than in cancer pain. In a randomized open-label 2-way crossover study,[161] both groups reported benefit from treatment. Patients switching to fentanyl from oxycodone/acetaminophen at the 3 month crossover point, however, experienced better pain relief, while those switching from fentanyl did not. The results of 8 studies in cancer and noncancer pain were pooled[14] and demonstrated that pain scores were significantly reduced with fentanyl but adverse events were high in active and placebo groups. Many of these were not necessarily related to treatment, and discontinuations were lower in the fentanyl group than with morphine. In an analysis of patients over 65 in the California Medicare database,[158] oxycodone was associated with a sevenfold higher constipation rate than fentanyl, while Jamison et al. investigated the psychomotor effects of long-term oxycodone with acetaminophen or transdermal fentanyl use in 144 patients with low back pain.[159] All subjects were administered 2 neuropsychological tests (Digit Symbol and Trail Making Test-B) before being prescribed the opioids for pain, and at 90 and 180 day intervals. The neuropsychological test scores significantly improved, which suggests that long-term use of oxycodone with acetaminophen or transdermal fentanyl does not significantly impair cognitive ability or psychomotor function.

Similar improvements have also been reported from a 6-month, open-label, randomized, multicenter, 2-way

crossover study with transdermal fentanyl or oxycodone.[161] The study compared health-related quality of life, measured by the Treatment Outcomes in Pain Survey (including a short-form-36 component and a pain-specific component), in 229 patients with chronic low back pain. Patients receiving transdermal fentanyl showed a significant improvement in the SF-36 mental health summary scale, pain, perceived disability, and total pain summary scales during the 3- to 6-month trial period.

Buprenorphine. Three double blind placebo-controlled studies with transdermal buprenorphine have investigated the efficacy and safety in patients with pain of different origin, among which there was a large proportion of noncancer pain indications.[124,126,127] These studies provide a good level of evidence, demonstrating good dose progression and responsiveness, and the ability to control adverse events with careful titration (see also previous section on cancer-related pain).

Methadone. No adequate clinical studies of methadone in NCP were found.

Recommendations for the Use of Opioids in NCP. Evidence is growing that opioids are highly efficacious in noncancer pain (increasing treatment data of level Ib or IIb), but need individual dose titration and consideration of the respective tolerability profiles. Again, no specific studies in the elderly have been performed, but it can be concluded that opioids have shown efficacy in noncancer pain, which is often due to diseases typical for an elderly population. The appropriate drug should be chosen based safety and tolerability considerations.

Neuropathic Pain

Our knowledge base of neuropathic pain (damage/injury or central-mediated pain) is increasing, in that we are more cognizant that other pain syndromes also contain a neuropathic component, such as long-standing OA, which has a mixed pain syndrome, including neuropathic pain. Various modalities, eg, one example in the elderly—PHN—can use monotherapy or combination therapy with opioids,[170–172] anticonvulsants.[173] Postmeeting information on first-line medications for neuropathic pain was recently published by Dworkin et al.[9] Various types of delivery systems, including topical application of lidoderm plaster, are used, with the combination with opioids having proven efficacy also in elderly patients.[174] When opioids are used, however, very high doses may be required.[175] The published data for the use of opioids in neuropathic pain are summarized in Table 9.

Morphine. There is very little information on the use of morphine in elderly patients with neuropathic pain. In a study investigating IV morphine in patients with multiple sclerosis,[176] 4 out of 14 patients responded. In poststroke and spinal cord-injury-related pain,[177] the intensity of brush-induced allodynia was reduced in all 15 patients but the age of the patients was not recorded. In a study on diabetic neuropathy ($n = 35$) and PHN

Table 9. Published Data for the Use of Opioids in Neuropathic Pain

Agent	Study	Evidence Level	Reference
Morphine	IV in multiple sclerosis	IIb	176
	IV in central pain	Ib	177
	Oral with gabapentin in PHN, PDN	Ib	178
Oxycodone	Oral—PHN	Ib	179
	Controlled release—PDN	Ib	180
	Controlled release—PDN	Ib	181
Hydromorphone	No studies		
Fentanyl	IV v diazepam	Ib	182
	Transdermal v placebo	IIa	157
	Transdermal v placebo	III	183
Buprenorphine	Intrathecal—phantom pain	III	84
	IV post thoracotomy (i)	IIb	85
	IV post thoracotomy (ii)	Ib	86
	Transdermal—neuropathic & nociceptive pain	III	87
	Transdermal—mixed neuropathic pain	III	23
	Transdermal—mixed neuropathic pain	Ib	124
	Transdermal—mixed neuropathic pain	Ib	126
Methadone	Oral—low dose	Ib	188
	Oral methadone/morphine ratio study	III	189

PHN, post-herpetic neuralgia; PDN, Painful diabetic neuropathy.

(*n* = 22), a combination of oral morphine with gabapentin produced better analgesia than the single agents or placebo but adverse events were common.[178]

Oxycodone. Studies with oxycodone have focused on painful diabetic neuropathy (PDN) and PHN. In a randomized, double-blind, cross-over study in 50 elderly PHN patients, oxycodone effectively reduced allodynic symptoms and spontaneous pain, and was preferred to placebo.[179] In a similar study in 36 elderly PDN patients, oral slow-release oxycodone significantly reduced mean daily pain and general disability compared with placebo.[190] A further randomized, double-blind, cross-over study in 159 PDN patients found a significant decrease in the daily pain score with controlled-release oxycodone compared with placebo, but 96% of patients reported opioid-related adverse effects.[181]

Hydromorphone. There are no studies on hydromorphone in neuropathic pain.

Fentanyl. Fentanyl in transdermal and IV preparations is moderately effective[157,182,183] but the response is variable even at high transdermal doses of 100 μg/hour or IV infusion 5 μg/kg/hour for neuropathic pain. Adverse events, particularly nausea, were commonly encountered. In these studies, analgesic efficacy was independent of the type of neuropathic pain and there were a marked number of nonresponders. All 3 studies included elderly patients. The findings were the same for both IV and transdermal form.

Buprenorphine. Buprenorphine has demonstrated efficacy in neuropathic pain, but information on elderly patients is limited: Two elderly patients with phantom limb pain were successfully treated with intrathecal buprenorphine.[184] IV buprenorphine was used to treat postoperative and incipient neuropathic pain in a series of 42 patients undergoing thoracotomy for lung resection.[185] A double-blind randomized controlled trial in 21 postsurgical patients found that buprenorphine was able to control pain, but at higher doses, than is needed for nociceptive pain.[186] Transdermal buprenorphine was used in a retrospective multicenter study of 237 patients with nerve injury-related pain[23] and was effective in relieving neuropathic pain. Similar results were obtained from case studies[187] and in 3 early studies where, among others, neuropathic pain indications were also included.[124,126,187]

Methadone. Methadone has been investigated in 2 studies. One was a randomized, double-blind, placebo-controlled study on 18 patients of variable ages, including some elderly.[183] Lower doses of methadone had no effect on the neuropathic pain, but higher doses produced statistically significant improvements in reported pain scores. However, withdrawals were high, with 7 patients discontinuing because of adverse events. A retrospective analysis of 34 patient records of patients of mixed ages with neuropathic and non-neuropathic pain found that methadone was effective in both neuropathic and nonneuropathic pain.[190]

Recommendation for the Use of Opioids in Neuropathic Pain. The role of opioids in neuropathic pain has been under debate in the past, but is nowadays more and more accepted. Most of the treatment data are level II or III, and suggest that incorporation of opioids earlier on might be beneficial, at least in a number of patients. Buprenorphine shows a distinct benefit in improving neuropathic pain symptoms, which is considered a result of its specific pharmacological profile.

SAFETY AND TOLERABILITY
Adverse Drug Reactions and Adverse Events

The tolerability profile of opioids is very important in elderly patients, as adverse events, which have minimal consequences in younger patients, such as drowsiness, dizziness, and motor imbalance, can have serious consequences in fragile patients who are already more prone to falls. Common adverse reactions with opioids use include:

- constipation, nausea and vomiting;
- sedation;
- impaired judgement;
- impaired psychomotor function;
- respiratory depression.

With all opioids, these can be limited by using lower starting doses, longer dose intervals, and slow titration; however, constipation, nausea, and vomiting often require prophylaxis or therapy.

Gastrointestinal System. Elderly patients often have increased gastric pH, reduced gastric and intestinal motility, decreased enzyme activity and absorption. These changes manifest themselves as prolonged colon transit times, frequent constipation, and GI distress. Constipation is a well-known and frequent adverse

event of opioid analgesics, which is exacerbated in patients with reduced GI function. It is apparent that, in the elderly population, constipation or obstipation is something that patients are acutely aware of, and treatments that can potentially result in this are not favored. Although constipation can be managed with laxatives and other bowel treatment regimens,[191] it may on occasion be such a problem that the patient may need to switch opioids. Buprenorphine and potentially transdermal fentanyl produces less constipation than morphine and oxymorphone, and may be preferable to other opioids where constipation cannot be easily managed.[87,128]

Central nervous system Effects. Opioid neurotoxicity is a significant issue in the elderly, presenting as hallucinations, confusion, and loss of cognition. Most opioids are associated with this when given long-term at high doses, particularly in dehydrated, severely ill patients with renal impairment. This is particularly harmful for elderly patients, for whom the risk of falling with subsequent skeletal fractures may be increased.

Central nervous system effects have been demonstrated for all opioids except buprenorphine, although more data on the use of buprenorphine in this patient group are needed. A Danish nationwide register-based study has shown that the use of morphine and other opioids, including fentanyl and oxycodone, increased the risk of fractures. It is speculated that this may be related to the risk of falls because of CNS effects or accidents resulting from an altered state of consciousness. Increased fracture risk was lowest in those patients taking buprenorphine.[192]

Addiction. The under-treatment of pain may lead cancer patients to complain and request opioids; such drug-seeking behavior mimics addictive behavior, and

these patients may be incorrectly perceived as addicts by health professionals. In fact, this is an iatrogenic condition that has been termed "pseudoaddiction", and can be avoided by listening to the patient, conducting a careful pain assessment, and treating the pain.[193]

The risk of addiction or aberrant opioid use can be monitored by recognition of published characteristics, such as failure of a drug to work or frequently demands by the patient for increasing doses that can assist the physician in making decisions to prescribe opioids,[194] and by adequate follow-up and observation. Portnoy suggested 3 types of aberrant phenomena that characterize addiction: loss of control over drug use, compulsive drug use, and continued use despite harm.[195]

A review of 24 papers by Fishbain et al., however, showed that addictive behavior was not common in the general chronic pain population (3.2% to 18.9%),[196] and examples from postoperative pain studies indicate that addiction is almost nonexistent.[197–199] In addition, McQuay and Evans both reported that medical use of opioids does not create "street addicts".[194,200]

In summary, many clinical studies have shown that long-term opioid therapy can be maintained without escalation of dose or tolerance to effect presenting. Such confidence in opioid therapy should be purveyed to both nonspecialist professionals and the general public.

Drug interactions. The average nursing home patient is taking 7 prescription medicines and the average elderly person takes 2 to 4 prescription drugs per day. The probability of drug interactions increases nearly exponentially with the number of drugs being prescribed[201] and the potential for drug–drug interactions, and exacerbation of adverse events is therefore high. Hence, analgesics with the lowest level of drug interactions are preferred (Table 10).

Table 10. Pharmacokinetic Interactions of Opioids

Opioid	Mainly Metabolized By	Drug-Drug Interactions	Evidence Level
Morphine	UGT 2B7	Ranitidine, rifampicin, valspodar	IIb
	UGT 1A3		IIb
Oxycodone	C60 2D6	Unlikely to cause effects	IV
Hydromorphone	UGT WB7	Very little data on potential effects	IV
	UGT 1A3		
Fentanyl TD	CYP 3A4	Ritonavir: ↑fentanyl	Ib
Buprenorphine TD	CYP 3A4	Only minor effects described	IV
Methadone	CYP 3A4	Inducers and inhibitors of the respective CYP enzymes	IV
	CYP 2B6		
	CYP 2C19		

A number of drug interactions have to be taken into account for morphine, fentanyl, and tramadol, based on their metabolism by liver enzymes which may be affected by other drugs. Also, some opioids are metabolized by CYP P450 isoenzymes for which genetic polymorphisms have been reported in the population, which may account for high rates of side-effects or minor efficacy in affected patients. This holds true for oxycodone and tramadol, which are metabolized by CYP2D6. Buprenorphine is metabolized by CYP3A4; however,[202] this pathway appears to play only a minor role in buprenorphine metabolism. Nonetheless, an interaction has been reported for protease inhibitors like indinavir and for azole antimycotics with buprenorphine *in vitro*.[203] Whether this will result in clinically relevant changes in plasma levels during therapy is unknown. Buprenorphine binds to alpha and beta globulins, unlike the majority of drugs, which bind to albumin. As a result, the likelihood of drug–drug interactions related to protein binding for this drug is small.[204,205]

The importance of the CP450 system plays an important role when administering polypharmacy to special patient populations, such as the elderly. CYP450 is one of the principal pathways of drug metabolism for 60% to 70% of all drugs, including statins, selective serotonin reuptake inhibitors, NSAIDs, proton pump inhibitors, sedative hypnotics, and beta-blockers. Sixty-seven per cent of patients on opioids are taking at least one other prescription drug.[206] Forty per cent of people over 65 years of age take 5 or more different drugs per week with 12% taking 10 or more. The majority of patients are on polypharmacy, including over-the-counter medication, psychiatric, psychoactive medications, CNS drugs, and/or other drugs for other medical conditions.[207] Adverse drug reactions are linked to polypharmacy—in excess of $1 million annually in U.S.A. As many as 28% of events are avoidable and occur most commonly with cardiovascular drugs, diuretics, opioid analgesics, antidiabetic agents, and anticoagulants.[208] Buprenorphine binds to alpha and beta globulins[209] unlike the majority of drugs, which bind to albumin and therefore theoretically the drug–drug interaction is limited (Tables 11–13).

Recommendation for Selecting Opioids with Regard to Tolerability Profile. The adverse event profile varies greatly between opioids. As the consequences of adverse events in the elderly can be serious, agents should be used that have a good tolerability profile (especially regarding CNS and GI effects) and that are as safe as

possible in overdose. Slow dose titration helps to reduce the incidence of adverse events. Sustained release preparations, including transdermal formulations, increase patient compliance.[22,23]

Specific Safety Aspects

Impaired Hepatic and Renal Function. Existing opioids differ in terms of their pharmacokinetics in hepatic and renal impairment (Tables 4 and 5).

Morphine is metabolized in the liver mostly into the analgesically inactive metabolite morphine-3-glucoronide (M3G), and morphine-6-glucoronide (M6G), which is a potent analgesic.[26] Both metabolites are completely eliminated by the kidneys and secreted through the urine. The elimination of metabolites is reduced in case of renal impairment, where, in this situation, both metabolites accumulate. The accumulation causes increased plasma concentrations of M3G and M6G, and the increase in M6G levels in particular, but also M3G levels, can result in intoxication.

Oxycodone has multiple active metabolites that may accumulate in renal dysfunction. Hydromorphone has only one glucouronide, but this is neuroexcitatory and could accumulate in renal dysfunction.

Fentanyl is metabolized by the liver, mostly into the inactive norfentanyl and several other unspecified inactive metabolites. Nearly 10% of the active substance is not metabolized, with less than 10% of the inactive metabolite, norfentanyl, eliminated by the biliary system, and excreted in the feces. The vast majority of the metabolites—around 75%—are eliminated in the urine. In cases of renal impairment, the clearance of fentanyl is reduced and the terminal half-life of the drug is prolonged. The kinetics of fentanyl in geriatric patients has not been extensively studied. Patients with renal impairment or elderly patients taking fentanyl as analgesic therapy need to be monitored very closely. Insufficient information exists to make recommendations regarding fentanyl in patients with impaired renal or hepatic function. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

For buprenorphine, approximately, two-thirds of the drug is not metabolized at all, and the rest is metabolized by the liver: the 3 major metabolites are norbuprenorphine, buprenorphine-3-glucuronide, and norbuprenorphine glucuronide. Approximately, two-thirds of the parent drug is eliminated by the biliary system via the feces. The metabolites are eliminated via the biliary system and the kidneys. The kidneys' overall exposure to

Table 11. Pharmacokinetic Interactions

Opioid	Pharmacokinetic interactions
Buprenorphine[205,210]	Up to 30% of buprenorphine metabolism is mediated by cytochrome (CYP) 3A4. New studies indicate buprenorphine and norbuprenorphine are not predicted to cause clinically important drug interactions with other drugs metabolized by hepatic P450s. Inhibitors or inducers of CYP 3A4 are not expected to cause significant alteration of buprenorphine metabolism or effects. Buprenorphine is not expected to cause significant alteration of other drugs' metabolism because of the low plasma concentrations reached after transdermal application.
Morphine[211,212]	Although a small fraction (less than 5%) of morphine is demethylated, for all practical purposes, virtually all morphine is converted to glucuronide metabolites; among these, morphine-3-glucuronide is present in the highest plasma concentration following oral administration. UGT 2B7 and UGT 1A3 are the enzymes responsible for glucuronidation of morphine; M6G is an active metabolite that contributes significantly to morphine's analgesic effects, whereas M3G is inactive as an analgesic, but may cause paradoxical central neuroexcitatory effects.
Fentanyl[213]	The concomitant use of fentanyl with potent CYP P450 3A4 inhibitors (ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving fentanyl and potent CYP3A4 inhibitors should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted.
Methadone[214]	Methadone is primarily metabolized by N-demethylation to an inactive metabolite, 2-ethylidene-1,5-dimethyl-3, 3-diphenylpyrrolidene (EDDP). CYP P450 enzymes, primarily CYP3A4 and to a lesser extent CYP2D6 are responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in urine.
Oxycodone[215]	Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known. The formation of oxymorphone, but not noroxycodone is mediated by CYP P450 2D6 and, as such, its formation can, in theory, be affected by other drugs.
Hydromorphone[216]	Hydromorphone metabolites have been found in plasma, urine, and in human hepatocyte test systems However, it is not known whether hydromorphone is metabolized by the CYP P450 enzyme system Hydromorphone is a poor inhibitor of human recombinant CYP isoforms, including CYP1A2, 2A6, 2C8, 2D6 and 3A4 with an IC50 > 50 μM. Therefore, hydromorphone is not expected to inhibit the metabolism of other drugs metabolized by these CYP isoforms.

UGT, glucuronosyltransferase; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide.

Table 12. Pathways of Opioid Metabolism: Relevance to Drug–Drug Interactions

Opioid	Mainly Metabolized By . . .	Active Metabolites?	Drug–Drug Interactions Proven With . . .	Evidence Level
Morphine[217,218]	UGT 2B7	(M3G)	ranitidine, rifampin	IIb
	UGT 1A3	M6G	Pgp: valspodar	IIb
Buprenorphine TD[202]	CYP 3A4	-	none described nor expected	IV
Fentanyl TD[219]	CYP 3A4	-	ritonavir: fentanyl	Ib
Oxycodone[215]	CYP 2D6	Oxymorphone	unlikely to cause any effects	IV
Hydromorphone[216]	UGT 2B7	H6G	very little data on potential	IV
	UGT 1A3	(H3G)	effects of enzyme inhibition or Induction	
Tramadol[220]	CYP 2D6	M1	carbamazepine: tramadol effect	Ib
			quinidine: tramadol, M1	IIb

TD, transdermal; UGT, glucuronosyltransferase; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide; CYP, cytochrome.

buprenorphine metabolites is very small. In case of hepatic impairment, the half-life of the drug is prolonged, but because of the low activity of the metabolites, this is of low clinical relevance. Nevertheless, careful monitoring of patients with hepatic impairment is recommended. In cases of renal impairment, no clinically important accumulation of metabolites has been observed; therefore, a dose reduction is not necessary.

Table 13. Overview of Common Pain Therapies

Compound	Active Components	Dosing	Metabolism (CYP450)
OPANA® ER	Oxymorphone[221]	Q 12 hours[221]	No CYP450 drug/drug interactions at clinically relevant doses[221]
OxyContin®	Oxycodone[222]	Q 12 hours[222]	2D6, 3A4[222]
Vicodin®Lortab®	Hydrocodone + acetaminophen[223,224]	Q 4–6 hours pro re nata[223,224]	2D6*[225]
Ultram®	Tramadol[220]	Q 4–6 hours[220]	2D6[220]
Percocet®	Oxycodone + acetaminophen[226]	Q 6 hours[226]	2D6, 3A4[222,226]
Codeine	Codeine[227]	Q 4 hours pro re nata[227]	2D6†[228]
Avinza®	Morphine[229]	Q 24 hours[229]	Conjugated in the liver[227]
Kadian®	Morphine[230]	Q12–24 hours[230]	Conjugated in the liver[229]

Notes: Avinza® is a registered trademark of King Pharmaceuticals.
Kadian® is a registered trademark of Alpharma Pharmaceuticals LLC.
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Vicodin® is a registered trademark of Abbott Laboratories.

In elderly patients with impaired hepatic and renal function, it is important to be cognizant of the accumulation of metabolites from certain opioids, such as morphine. In practice, it is preferred to avoid such accumulation, by using compounds such as hydromorphone and buprenorphine.

Recommendation for the Use of Opioids in Elderly Patients with Impaired Renal and Hepatic Function. Functional impairment of excretory organs is common in the elderly, especially with respect to renal function. For all opioids except buprenorphine, half-life of the active drug and metabolites is increased in the elderly and in patients with renal dysfunction. It is, therefore, recommended that doses should be reduced, a longer time interval be used between doses, and creatinine clearance be monitored. Oxycodone, hydromorphone, and buprenorphine appear to be a safe choice for opioid treatment in the elderly.[25]

Respiratory Depression. Respiratory depression is mediated via the μ-opioid receptor and, with full agonists such as morphine and fentanyl, there is a clear dose-dependent effect which, at high doses or combined with other CNS system depressants, progresses to apnoea.[231,232]

Respiratory depression is rare in opioid-naïve patients if low starting doses and proper titration are used. However, it is of particular concern in very elderly and debilitated patients, and those with underlying pulmonary conditions such as chronic bronchitis, multiple sclerosis, chronic obstructive pulmonary disease, etc. or who receive other CNS drugs that affect ventilation.

Morphine, oxycodone, hydromorphone, fentanyl, and methadone all cause a dose-dependent decrease in respiration, with apnoea at high doses.

Buprenorphine has a well-defined ceiling effect for respiratory depression and respiratory rate rarely drops below 10 breaths per minute (50% of baseline).[233] The reason for this favorable effect is not clear. It may be that the intrinsic activity at a receptor to produce analgesia is less than that required to produce respiratory depression. Respiratory depression with buprenorphine can be reversed with opioid antagonists, such as naloxone, but this must be given by continuous infusion for at least 90 minutes or longer, and not only until respiration is normalized.[234]

Central nervous system depressants, such as benzodiazepines, barbiturates, antidepressants, phenothiazine derivatives, and alcohol, increase the risk of respiratory depression if taken with any opioid analgesic;[235,236] this may progress to total apnoea.

Recommendation for Interpreting Data on Opioids and Respiratory Depression. Respiratory depression is a significant threat for opioid treated patients with, eg, underlying pulmonary condition or receiving concomitant CNS drugs associated with hypoventilation. Not all opioids show equal effects on respiratory depression: buprenorphine is the only opioid demonstrating a ceiling for respiratory depression. The different features of opioids regarding respiratory effects should be considered when treating patients at risk for respiratory problems.

Immunosuppression. There is a gradual decline with age in responsiveness of the immune system (immunose-

Table 14. Opioid Immunosuppression in Animals and Man[243–245,249–251]

Agent	Animals		Man	
	Immunosuppression	Evidence level	Immunosuppression	Evidence level
Morphine	++++	Ia	++++	Ib
Oxycodone	–	IIa	ND	
Hydromorphone	–	IIa	ND	
Fentanyl	++++	Ib	++++	Ib
Buprenorphine	–	Ib	ND	
Methadone	?	IIb	ND	

++++, high degree of immunosuppression; –, not immunosuppressive; ?, data inconclusive; ND, not determined.

nescence), leading to increased susceptibility to infectious diseases,[237] cancer, and reduced ability to fight such illnesses. T-lymphocyte production is reduced and B-cell production in the bone marrow is diminished. Neutrophils and granulocytes are decreased, producing fewer reactive oxygen species. Macrophage production of reactive oxygen species and cytokines is also reduced,[238] while prostaglandin production is increased, leading to a proinflammatory environment. Natural killer cells increase in number but are functionally less active.[239] This general decline in immune responses makes the elderly particularly at risk when further immunosuppression is achieved, such as during surgery or in the presence of immunomodulating drugs. Moreover, it is well known that pain itself is an exquisite stressor as it has both psychological and physiological components. The linked responses of the CNS and the hypothalamic-pituitary-adrenal axis to a perceived stress involve a complex network of signals, including catecholamines, peptides—such as endorphins, and corticosteroids—such as cortisol. All of these factors can lead to immunosuppression. Pain relief is obviously beneficial for the immune function; however, several opioids possess intrinsic immunosuppressive activities.

Morphine is the most immunosuppressive of the opioids, acting via the μ-opioid receptor.[240] These receptors are on all immune cells and are activated directly by morphine. There are also indirect effects via the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, the former generating release of glucocorticoids, and the latter, norepinephrine, which binds to leukocytes, modulating the immune function.[241] The immunopharmacological profile of the potent opioid, fentanyl, does not seem to differ from that of morphine. When administered to experimental animals, fentanyl induced a clear dose-related immunosuppression.[242,243] The immunosuppressive properties of fentanyl have been replicated in the human, as it has been

shown to affect cellular immune responses in humans, and immune modulation seems to be dose related: the few studies conducted in human, however, deal only with acute fentanyl treatment.[244,245]

It is not clear why other opioids, which also bind to the μ-receptor, do not depress the immune system; buprenorphine, hydromorphone, and oxycodone have been reported to be less immunosuppressive than morphine.[243,246] In particular, analysis of the literature existing on the immune effects of buprenorphine points to a different profile of this molecule in comparison with morphine or fentanyl.[243,247,248]

It is speculated that nonimmunosuppressive opioids —buprenorphine, hydromorphone, oxycodone—have little or no neuroendocrine effect, or that κ-opioid receptor antagonism may be involved.[249] Either way, there is little evidence available to gauge the immunosuppressive effects of other opioids and even less evidence in the elderly (Table 14).

Although the long-term clinical impact of opioid-induced immunomodulation is not yet clear, and further studies are needed, it is evident that the possibility to reach adequate and equivalent pain control choosing either immunosuppressive drugs or drugs without effect on immune responses could represent a further point to be considered in opioid therapy.

Recommendation for Interpreting Data on Opioids and Immunosuppression. Providing adequate analgesia can be achieved without significant adverse events; opioids with minimal immunosuppressive characteristics should be used in the elderly. The immunosuppressive effects of most opioids are poorly described and this is one of the problems in assessing the true effect of the opioid spectrum. Taking into account all the available evidence from acute opioid administration in the general population and chronic administration in dependent subjects, buprenorphine can be recommended, while

Table 15. Overview of Opioid Metabolism

Opioid	Metabolism
Buprenorphine[205,210]	• Plasma protein binding of about 96%, but not to the albumin fraction like most drugs but only to the α- and β-globulin fractions; the very low plasma levels of buprenorphine are far below (by approximately a factor of 100) the molar concentrations of plasma globulins. Hence, any relevant interaction based on competition of globulin binding sites is highly unlikely • Primarily metabolized to norbuprenorphine and N-dealkylbuprenorphine • 2/3 of metabolites are excreted via the faeces, only 1/3 is renally excreted • Evidence of enterohepatic recirculation in non-human studies • Low plasma levels of buprenorphine during transdermal analgesic therapy
Morphine[211,212]	• Large presystemic elimination (in gut wall and liver) • Only about 40% of dose reaches central compartment
Fentanyl[213]	• Primarily oxidized to norfentanyl • 75% excreted within 72 hours mostly as metabolites, 10% excreted unchanged Information from a pilot study of the pharmacokinetics of IV fentanyl in geriatric patients indicates that the clearance of fentanyl may be greatly decreased in the population above the age of 60
Methadone[214]	• Converted to 2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidene and 2-ethyl-5-methyl-3, 3-diphenylpyraline
Oxycodone[215]	• Oxycodone hydrochloride is extensively metabolized to active noroxycodone, oxymorphone, and their glucuronides • Oxycodone and its metabolites are excreted primarily via the kidney • In general: the plasma concentrations of oxycodone are 15% greater in the elderly, with large interindividual variation
Hydromorphone[216]	• Metabolized to hydromorphone-3-glucoronide, hydromorphone-3-glucoside, and dihydroisomorphine-6-glucoside

morphine and fentanyl cannot; only few data are available at present for oxycodone and hydromorphone, and their reported minimal immunosuppression needs to be confirmed.

OVERALL CONCLUSIONS

In light of the International Association for the Study of Pain motto for 2006 to 2007, "Pain in Older Persons", the topic of this consensus statement is highly relevant. Opioids are the mainstay of treatment for chronic, severe pain, and morphine is an effective analgesic—certainly better than nothing in areas where other opioids may not be available or affordable. Significant data are available for the use of the 6 reviewed opioids in general, but not specifically in the elderly. Efficacy of the 6 opioids is comparable for chronic, severe pain, although there seem to be some differences with respect to efficacy against neuropathic pain.

The level of clinical evidence is high (mostly Ib or IIb) in general for cancer pain and chronic, noncancer pain; the level of evidence for neuropathic pain is at present less strong.

In order to choose the best treatment option in the elderly pain patient, the important pharmacological and pharmacokinetic differences between the 6 reviewed opioids should influence treatment decisions (Table 15). In this respect, evidence from data submitted to authorities upon registration of the opioids reveals that dosage adjustments need to be considered for all opioids in subjects with impaired liver function; however,

accumulation of the drugs or their active metabolites in renal failure has been reported for all opioids except buprenorphine. Renal dysfunction and polymedication are 2 very common traits of the elderly patient; therefore, opioids with robust pharmacokinetics in renal dysfunction and with little drug interaction potential should be used with preference in his age group.

ACKNOWLEDGEMENTS

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