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03 NOV 2014

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30 October 2014

TO WHOM IT MAY CONCERN

I have enclosed my application to have Buprenorphine sublingual tablets included on the HML for use in hospital. I am a Consultant Anaesthetist at Taranaki Base Hospital. I have a strong interest in acute pain and do regular pain rounds. I also teach nursing staff at our monthly acute pain study days.

I have had extensive experience in using sublingual and transdermal Buprenorphine for the treatment of both acute and chronic pain while working at Sir Charles Gairdner Hospital in Perth last year. I can see that we have an unmet need for improved pain control with opioids for a growing sector in our population; the elderly and infirm. I am concerned with medication safety and am involved in the Health Quality and Safety Commission's collaborative working on reducing harm from opioids.

I have no ties with industry, and this application was my idea, but I have the support of several other practitioners here, including those who work in chronic and acute pain.

Thank you for your consideration,

Dr Joe Taylor
Consultant Anaesthetist

Application for changes to the Pharmaceutical Schedule

A guide to assist clinicians, clinical groups and consumer groups in preparing funding applications to PHARMAC

Foreword

PHARMAC, the Pharmaceutical Management Agency, is primarily responsible for managing the funding of pharmaceuticals for New Zealanders, on behalf of the District Health Boards. PHARMAC's objective is to secure, for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided.

Each year, PHARMAC receives a large number of applications containing proposals to fund new pharmaceuticals or to widen access to pharmaceuticals that are already funded. As we must work within a fixed budget, difficult choices need to be made about which of the proposals should be progressed to a funding decision at any given time. This involves assessing a large amount of often complex information, to identify those proposals that would provide the best health outcomes.

Guidelines for Funding Applications to PHARMAC were issued in 2010. While the information requested in the *Guidelines* is not mandatory, providing it will result in fewer time delays while we undertake our own searches or analysis. We recognise that consumers, clinicians and clinical groups are less able to prepare funding applications to PHARMAC that contain all the information requested by the *Guidelines*, so we have prepared this form to help guide their preparation of applications to PHARMAC. Pharmaceutical suppliers are still expected to follow the *Guidelines*.

Clinician, consumer or clinical group applicants should consider this form to be a guide, and do not have to follow it in detail (or even use the form at all), however we have outlined the general information that we require in assessing a funding application - ensuring that your application addresses these points may reduce follow-up questions to you, and could speed up our consideration of it.

Applications should be sent to us at:

Email: **applications@pharmac.govt.nz**

Post: **PO Box 10-254**
Wellington 6143

You may find it useful to talk to the relevant Therapeutic Group Manager at PHARMAC before making a formal funding application. Please email us as above, and we will get in contact with you.

We will keep you informed as our review of your application progresses. We publish and regularly update a record of all current funding applications via the Application Tracker on our website (**www.pharmac.govt.nz**), which details the current status of applications and relevant PTAC and subcommittee minutes.

Please note:

- Copies of referenced articles should be supplied, wherever possible.
- It is our preference that funding applications relate to medicines that have been registered by Medsafe. While we can consider funding applications for unregistered medicines or unregistered indications, this is determined on a case by case basis.
- We may decide to defer assessment of your application until we receive a full funding application, prepared in accordance with the *Guidelines* from the supplier.

Changes to the Pharmaceutical Schedule

Application Form

Applicant

Name

Dr Joseph Taylor

Department & DHB, practice or organisation

Consultant anaesthetist, Taranaki Base Hospital

Email address

joe.taylor@tdhb.org.nz

Phone or pager

0211821045

Are you making this application on behalf of a wider group *(department, society, special interest group)*? If so, who?

acute pain service, taranaki base hospital

Is there anyone else that we should contact if we have questions about specific parts of this application?

The Funding Application

Chemical

buprenorphine hydrochloride

Presentations and strengths

sublingual tablet 200mcg

Brand name(s)

temgesic

Suppliers (e.g. pharmaceutical companies, wholesalers)

mundipharma, reckitt benckiser

Price

Is it registered by Medsafe?

no

The Funding Application

Describe indication(s)

Acute pain

If this pharmaceutical has been registered by Medsafe, is it licenced for these indications? If not, is it licenced for these indications overseas? Please provide details.

N/A

If this is a new pharmaceutical, are there likely to be other uses for it?

no, it is not intended as substitution therapy in cases of opiate abuse.

Define the patient group(s) ("the population")

C

ncy

New Zealand Government

The Funding Application

Hospital inpatients with acute pain either postsurgical or secondary to their medical problems. Emergency department patients could also benefit.

Are there sub-populations that have a higher health need or higher potential benefit or risks?

There are three scenarios where sublingual buprenorphine would be useful.

The first is in cases where the patient has significant renal impairment. Currently the only oral opiate available that does not have active metabolites which accumulate in renal failure is methadone. Although effective, the pharmacokinetics of methadone are highly variable between people and accurate dosing is difficult. There is a significant risk of accumulation over days as it has a very long half lifel. Buprenorphine is eliminated predominantly via biliary excretion and no dosage adjustment is necessary in renal failure.

The other group of patients are those who have had bowel surgery and spend a prolonged time with an ileus unable to resume oral intake. At present the only options for analgesia for them is to either continue with intravenous analgesia or to have a fentanyl patch. As many of these patients are often elderly and frail and opiate naïve, fentanyl patches tend to be too potent to give to them. The intravenous route demands that they are hooked up to an IV infusion pole and require changes of the IV line every 3-5 days, which adds to their discomfort and reduces the ability to mobilise, clean and shower them. IV fentanyl also promotes fairly rapid tolerance and hyperalgesia, which is reflected by the common observation that patients on fentanyl PCAs for several days tend to escalate their opioid use.

The third group are elderly patients in general who have reduced renal and hepatic function and are taking multiple other medications. Buprenorphine needs no dosage adjustment for renal impairment or hepatic impairment. It is also very unlikely to be affected by pharmacokinetic interactions such as CYP450 enzyme inhibition or induction because it is predominantly excreted unchanged in the faeces. This is very advantageous for the elderly.

What are the treatments that patients with these indications currently receive, if any? (dose, duration of treatment, risks, benefits etc.)

Currently patients with significant renal impairment in acute pain who are coming off IV fentanyl receive oral oxycodone in reduced doses (e.g. 5mg up to 2 hourly) or methadone 2.5 to 5mg tds for 3 days before reducing the dose.

Oxycodone is known to have active metabolites that accumulate in renal failure. It is also a very addictive drug and if the patient is being discharged with a script for it, this increases the chance that it will be diverted in the community to the black market. Anecdotally, clinicians involved in substance abuse clinics in Wellington are being told by their clients that Taranaki is a good source of oxycodone. Unfortunately I do not have hard evidence for this but it does concern me.

As explained above, methadone has a very long and variable half life so the risk is that they will accumulate the drug over 3-5 days and suffer an overdose, particularly if they are being sent home with a prescription for methadone.

Will the pharmaceutical replace or complement these existing treatments? Please explain.

I would anticipate that buprenorphine sublingual tablets would replace oxycodone as a first line alternative to morphine for acute severe pain in patients in this hospital, especially patients with renal impairment or elderly patients. Other than methadone buprenorphine is one of the few long-acting sublingual potent opiates, but is much easier than methadone to dose due to its favorable pharmacolkinetics. The sublingual route of administration makes it advantageous if patients are unable to swallow or suffer from nausea and vomiting.

What is the unmet health need in this population?

As described above.

What is the expected size of this population?

At least 12 patients per month. I got this information by surveying all the general surgical and orthopaedic patients having operations in theatre and identified those with an eGFR <50mL/min who were having significantly painful surgery who would likely receive oral opioids during their admission. This is likely to be an underestimate as it does not include elderly medical patients with pain who would be good candidates for buprenorphine.

What is the expected dosing?

Between 200-600mcg every 2 hours prn

What is the likely duration of treatment, if patients respond to treatment?

Between 2-5 days for uncomplicated procedures and 2-4 weeks for more painful/complex procedures (e.g. amputations).

Is there a particular need for this application to be assessed quickly? If so, what is the basis for this urgency?

no

Describe the setting that this pharmaceutical would be used in. Is the need for this this treatment limited to a hospital setting, or is it also required in the community? If in hospital, is it theatre only, on medical wards, or in outpatient clinics?

Hospital setting only. In theatre as well as on medical and surgical wards. It could potentially be used in the ED too.

Benefits and Risks

Discuss the potential benefits and risks from treatment with the pharmaceutical compared with current treatment options (if any).

Benefits and Risks

Benefits: Buprenorphine needs no dose adjustment for patients with renal failure as no accumulation of active metabolites occurs. This is in comparison to morphine and oxycodone. It can be given sublingually so for patients who cannot resume oral intake this means they can come off IV analgesia earlier. As IV fentanyl promotes rapid tolerance this should result in better pain relief for these patients. It can be safely used in the elderly and frail patients with no increased risk of opiate related side effects compared to other opiates. It has been shown in healthy volunteers to have a ceiling effect on depression of respiration but not on analgesic effect. So long as it is not combined with other CNS depressants drugs, it is less likely than other opiates to depress respiratory drive. It does not cause as much euphoria as oxycodone, hence its addictive potential is less.

Risks: Like any opiate it has side effects such as sedation, respiratory depression, nausea, delayed gastric emptying and constipation. It will interact with other central nervous system depressants to enhance sedation. Naloxone may not be fully effective in reversing the effects of overdose so institution of airway and breathing support may be needed until its effects wear off. Alternatively, higher doses of naloxone may be required (5-12mg). Like other opiates there is a risk that people can get addicted and abuse buprenorphine. The same level of care for prescribing other opiates for discharge would need to apply to buprenorphine.

Please outline the relevant clinical evidence in support of this application (including comparative clinical evidence with the currently funded treatments if available). Copies of referenced articles should be supplied, where possible.

For its use in renal failure, see article in Anaesthesia and Intensive Care 2005 by EJ Murphy.

Buprenorphine can be used in isolation as the sole opiate or in combination with morphine to provide effective postoperative analgesia. There is no evidence to suggest that buprenorphine inhibits the analgesic effects of morphine when the 2 opiates are combined. See the article from Clinical Therapeutics 2009.

For the use of buprenorphine in acute pain in general see the review article in Journal of Pain and Symptom Management 2005. This also outlines its pharmacology and safety in renal failure.

A specific comparison was made between sublingual buprenorphine and intravenous morphine for use in adults with acute fractures to compare the quality of analgesia and incidence of side effects. There were no differences between the groups, except buprenorphine was associated with less side effects (hypotension) than morphine. see the article from Annals of Emergency Medicine 2012. I have included this article to show that buprenorphine use will not lead to inferior pain relief compared to morphine. It is also as effective as IV therapy for acute pain.

The consensus statement on the use of opioids in elderly patients in Pain Practice 2008 outlines the advantages of buprenorphine in elderly patients who have renal impairment and polypharmacy. This article also mentions the reduced risk of confusion and falls in elderly people taking buprenorphine versus morphine, fentanyl and oxycodone.

Would funding the pharmaceutical result in other measurable benefits or risks to the health sector, e.g. changes in number of surgeries, hospitalisations, nursing time, diagnostic tests?

Analgesia is difficult to measure and audit. Reducing the use of oxycodone in hospitals is in the community's best interests as it reduces the supply of this drug to the black market. I envisage that buprenorphine could replace oxycodone in this hospital as an alternative to morphine for use in elderly, frail patients and those with renal impairment. Oxycodone has no benefit over morphine for these patients. We are concurrently planning on severely restricting the use of oxycodone in this hospital in conjunction with the national medication safety campaign.

It appears that buprenorphine also has less central nervous system side effects compared to other opiates. Given that opiates probably contribute to falls and fractures in the elderly, I believe this could contribute to reduced risks in this population.

With regard to nursing time, administration of sublingual buprenorphine is easier and quicker than giving IV fentanyl, so I believe this would make their job easier.

Treatment Initiation

Is treatment with the pharmaceutical started empirically? If so, please describe the symptoms or signs required to initiate therapy.

See earlier.

Are there any specific tests needed to confirm diagnosis? Are these currently routine and funded?

N/A

Should other therapies have been used prior to starting treatment with this pharmaceutical?

N/A

Treatment Continuation

How would treatment success be defined or measured?

N/A

What is the average length of treatment required before determining treatment response?

N/A

What other interventions would be needed in the event of treatment-related adverse events?

stop treatment, supportive care, naloxone use does help but doesn't completely reverse its effects.

Prescribing and Dispensing

Should initiation of this therapy be limited to certain prescriber types? If so, please explain why.

Any doctor who deals with patients in acute pain and can recognize renal impairment on a blood test should be capable.

If so, would it be appropriate for on-going prescribing to be managed by a wider group of prescribers?

N/A

Are there any other issues that PHARMAC should be aware of in relation to the administration of this pharmaceutical, such as infusion time, compounding requirements or safety issues?

no

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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Pain Practice, Volume 8, Issue 4, 2008 287–313

■ **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 transder*mal 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 ↓	Ia
Oxycodone	↑	↑	Clearly reduced renal clearance of parent compound and metabolites	Dosage ↓	Ib
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 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.

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.

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	1pooled 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 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]

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.	—	

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 isoenzmyes 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 effects of enzyme inhibition or induction	IV
	UGT 1A3	(H3G)		
Tramadol[220]	CYP 2D6	M1	carbamazepine: tramadol effect	Ib IIb
			quinidine: tramadol, M1	

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.
Lortab® is a registered trademark of UCB Pharma, Inc.
OPANA® is a registered trademark of Endo Pharmaceuticals.
OxyContin® is a registered trademark of Purdue Pharma L.P.
Percocet® is a registered trademark of Endo Pharmaceuticals.
Ultram® is a registered trademark of Ortho-McNeil Pharmaceuticals.
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]

	Animals		Man	
Agent	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.

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Sublingual Buprenorphine in Acute Pain Management: A Double-Blind Randomized Clinical Trial

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Study objective: We compare the efficacy and safety of sublingual buprenorphine versus intravenous morphine sulfate in emergency department adults with acute bone fracture.

Methods: Enrolled patients received buprenorphine 0.4 mg sublingually or morphine 5 mg intravenously in this double-blind, double-dummy, randomized controlled trial. Patients graded their pain with a standard 11-point numeric rating scale before medication administration and 30 and 60 minutes after, and we recorded adverse reactions.

Results: We analyzed 44 and 45 patients in the buprenorphine and morphine groups, respectively. Mean pain scores were similar at 30 minutes (5.0 versus 5.0; difference 0; 95% confidence interval −0.6 to 0.8) and at 60 minutes (2.2 versus 2.2; difference 0; 95% confidence interval −0.3 to 0.3). Adverse effects observed within 30 minutes were nausea (14% versus 12%), dizziness (14% versus 22%), and hypotension (4% versus 18%).

Conclusion: For adults with acute fractures, buprenorphine 0.4 mg sublingually is as effective and safe as morphine 5 mg intravenously. [Ann Emerg Med. 2012;59:276-280.]

Please see page 277 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Pain is a common complaint in the emergency department (ED) and needs both psychological and pharmacologic interventions, including appropriate analgesics with appropriate dosage. Although timely, effective, and safe pain management is a standard of care in all health care organizations, "oligoanalgesia," or undertreatment of pain, still remains a common problem in many EDs. In one study, for example, the mean waiting time to analgesia was reported to be 1 hour 46 minutes for patients with moderate and severe pain.[1]

Importance

Appropriate pain management relies on selection of the appropriate analgesic and dosage.[2-6] In the hectic environment of the ED, especially in crowded EDs in which only 49% of the patients in severe pain receive analgesics, 59% of patients who receive analgesics experience delays in treatment from their triage, and 20% experience delays from time of room placement,[7,8] easy-to-use drugs are more appealing.

Morphine sulfate is the prototypic analgesic in acute pain management in the ED. It is often used intravenously with a slow rate and under close patient monitoring because of potential adverse effects such as respiratory depression, central nervous system depression, hypotension, and gastrointestinal problems. Several studies have compared morphine with other drugs such as sufentanil and fentanyl or have compared different doses of morphine.[9-12] Other effective modalities and drugs, which can be more conveniently tolerated by patients and administered by nurses, may be a good alternative for morphine sulfate.

Buprenorphine is an agonist-antagonist of opioid receptors, with an analgesic potency 25 to 40 times greater than that of morphine sulfate. It has been successfully used for opioid detoxification, cancer-related pain, and postoperative pain control, with a high clinical safety profile and a more prolonged duration of action. Buprenorphine is well absorbed sublingually and is available as 0.4-, 2-, and 8-mg sublingual tablets in many countries.[13]

Goals of This Investigation

The objective of this double-blind randomized clinical trial is to compare the efficacy and safety of sublingual buprenorphine

Editor's Capsule Summary

What is already known on this topic

In patients with acute fractures, intravenous line initiation delays opioid administration.

What question this study addressed

Is sublingual buprenorphine 0.4 mg as effective and safe as intravenous morphine 5 mg?

What this study adds to our knowledge

In this blinded comparison of 44 adults receiving buprenorphine and 45 receiving morphine, pain scores at 30 and 60 minutes were similar, with confidence intervals that exclude clinically important differences. The adverse effect profile of buprenorphine was similar or better.

How this is relevant to clinical practice

Sublingual buprenorphine appears as effective as intravenous morphine in adults with acute fractures, and is certainly easier to administer.

with that of intravenous morphine sulfate in adult ED patients with acute fracture pain.

MATERIALS AND METHODS

Study Design and Setting

This prospective double-dummy, double-blind, placebo-controlled, randomized clinical trial was conducted in an academic tertiary care adult ED (annual census 50,000) and enrolled a convenience sample of patients during 12 months (February 28, 2010, to March 1, 2011). The study was approved by the ethics committee of Imam Hospital and patients provided informed consent. The trial was registered with clinicaltrials.gov (NCT 01298297).

Selection of Participants

We included patients if they were aged 16 years or older, with acute extremity fracture(s) and a pain numeric rating scale score higher than 3 of 10. We excluded patients unable to understand or communicate because of language barrier or other causes; altered consciousness because of alcohol, sedatives, or other causes; concurrent significant trauma or a life-threatening condition; known opioid allergy; history of chronic respiratory, renal, hepatic, or heart failure; administration of analgesics before ED admission; addiction to narcotics reported by either the patient or the family; pregnancy; or systolic blood pressure lower than 90 mm Hg.

Interventions

Subjects were randomly assigned to receive either 0.4 mg sublingual buprenorphine tablets plus 5 mL of sterile water (as placebo) or 5 mg intravenous morphine sulfate plus 1 sublingual placebo. We used computer-generated randomization blocks of 4 and sealed opaque envelopes to ensure allocation concealment. Patients, physicians, nurses, and research associates all remained blinded to group assignment throughout the entire study.

Methods of Measurement

A research assistant asked subjects to grade their pain as follows: "Tell me on a scale of 0 to 10 what is the level of your pain; 0 is no pain and 10 is the worst possible pain." This 11-point score was assessed at baseline and then 30 and 60 minutes after analgesic administration. The research assistant also recorded adverse effects, including respiratory and central nervous system depression, hypotension, nausea, vomiting, dizziness, and headache.

We monitored patients with continuous pulse oximetry and assessed vital signs at least every 15 minutes. We defined oxygen desaturation as less than 95%, hypotension as a systolic blood pressure decrease of more than 20 mm Hg, and respiratory depression as a rate below 12 breaths/min. Naloxone was immediately available.

Outcome Measures

Our primary study outcome was efficacy, as measured by pain scores 30 and 60 minutes after analgesic administration. Our secondary outcome was adverse events.

Primary Data Analysis

We compared pain scores with the Mann-Whitney test and adverse events with χ^2 or Fisher exact test, with $P<.05$ regarded as significant.

We calculated our sample size according to data of Bounes et al[10] and assuming $\alpha=.05$ and $\beta=.20$ (2-sided), with a result of 46 patients in each group. We enrolled 110 patients to account for possible cases with missing data or withdrawals from the study.

All analyses were performed with SPSS, version 15 (SPSS, Inc., Chicago, IL) or Stata, version 10 (StataCorp, College Station, TX).

RESULTS

Characteristics of Study Subjects

Study subject flow is shown in Figure 1. Baseline characteristics were similar between groups (Table 1).

Main Results

Pain scores were similar between groups 30 and 60 minutes after medication administration (Table 2; Figure 2).

The frequency of nausea and dizziness was similar between groups (Table 3). We observed more hypotension in the morphine group; however, all such patients responded promptly to the administration of intravenous fluids. We did not observe in either group decreased level of consciousness, respiratory

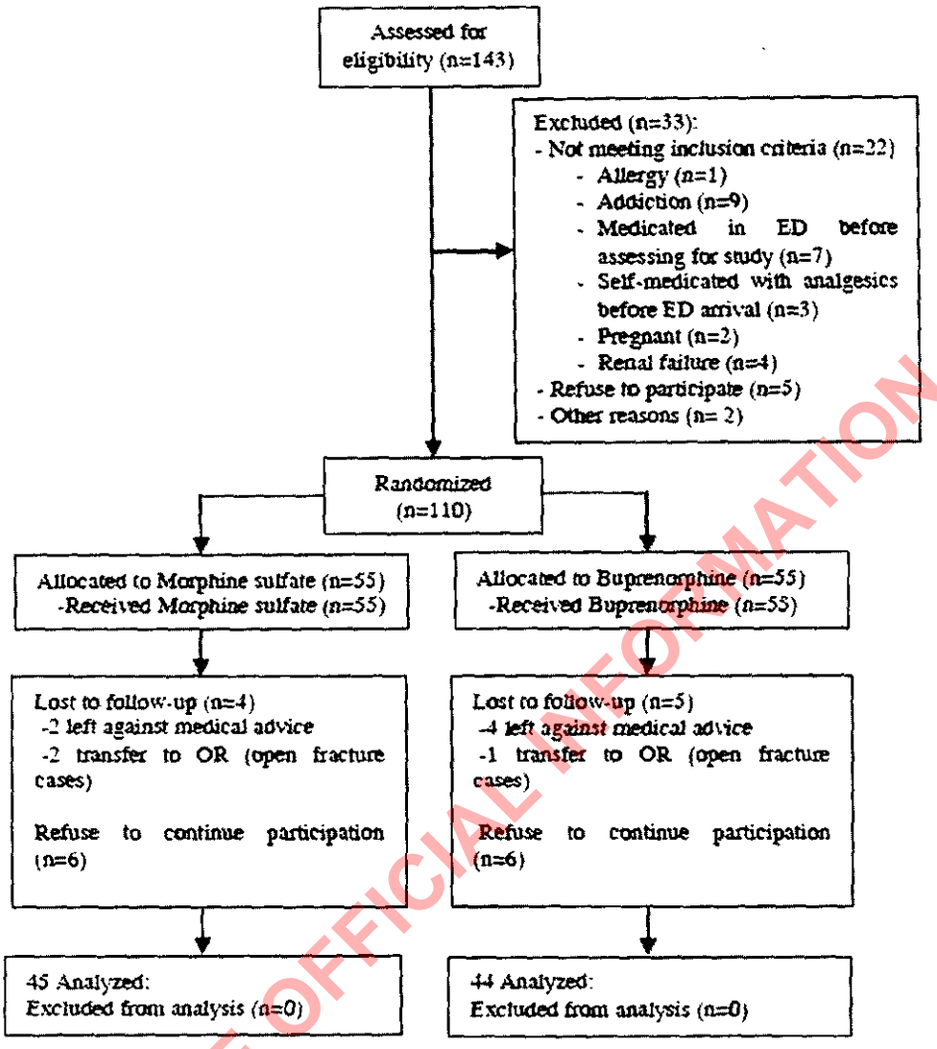

Figure 1. Diagram showing participants flow in study.

Table 1. Baseline data in the morphine sulfate and buprenorphine groups.

Baseline Characteristics	Morphine Sulfate, n=55	Buprenorphine, n=55
Age, mean (standard deviation), y	35 (13)	35 (13)
Sex, No. (%)		
Male	45 (82)	44 (80)
Female	10 (18)	11 (20)
Mechanism of injury, No. (%)		
Motor vehicle crash	12 (22)	17 (31)
Falling	22 (40)	17 (31)
Auto-pedestrian accident	19 (34)	16 (20)
Assault	1 (2)	3 (5)
Direct injury	1 (2)	2 (4)
Site of fracture, No. (%)		
Forearm	15 (27)	15 (27)
Wrist	7 (13)	4 (7)
Hand	8 (14)	7 (13)
Leg	4 (7)	9 (16)
Foot	8 (14)	5 (9)
Other sites	13 (24)	15 (27)

depression, oxygen desaturation, seizure, or vomiting, and no naloxone was administered.

LIMITATIONS

Our study has several limitations. First, it was conducted only with patients who could participate actively in their pain scoring, and we lost intoxicated patients, patients with other distracting injuries, and patients who had an accompanying trauma or were under investigation for other reasons. Second, for practical reasons, we used fixed doses of medications in all patients, although it may be preferable to use the body weight–adjusted doses. Third, we selected 1 group of patients with pain, ie, only those with pain resulting from bone fracture. Future studies should be conducted to evaluate this medication in other settings such as in patients with abdominal pain, headache, or renal colic; in special populations such as children and elderly patients; and with higher buprenorphine doses such as 2 mg. Excluding patients with chronic respiratory or heart failure may

Table 2. Pain numeric rating scale scores before medication administration and 30 and 60 minutes after.

Time	Regimen	Median (95% CI)	Mean	SD	SEM	*P* Value*	Mean Difference (95% CI)
Score 0	Bup	8 (7 to 9)	8.0	1.7	0.2	.2	0.3 (−0.3 to 1.0)
	MS	8 (7 to 8)	7.7	1.7	0.2		
Score 30	Bup	5 (4 to 6)	5.0	1.8	0.3	1.0	0.0 (−0.6 to 0.8)
	MS	5 (4 to 6)	5.0	1.7	0.2		
Score 60	Bup	2 (2 to 3)	2.2	0.7	0.1	.9	0.0 (−0.3 to 0.3)
	MS	2 (2 to 3)	2.2	0.7	0.1		

CI, Confidence interval; *SD*, standard deviation; *SEM*, standard error of mean; *Bup*, buprenorphine group; *MS*, morphine sulfate group.
*Mann-Whitney test.

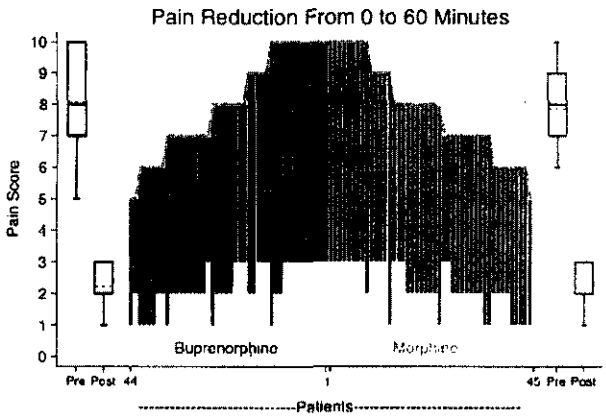

Figure 2. Graphic depiction of pain score reduction. The vertical bars represent patients (sorted by initial pain score), with the initial pain score at the top (grey line) and the 60-minute score at the bottom.

mean that one should be careful when generalizing the results to older populations. Last, a noninferiority design would be more suitable for proving (or disproving) that buprenorphine is as effective as morphine sulfate in pain management.

DISCUSSION

Our study showed that sublingual buprenorphine can decrease acute fracture pain in ED patients as effectively as intravenous morphine, and with a similar safety profile. Considering that the range in differences (confidence intervals) between the pain scores of the 2 groups at each point does not include values that are clinically important, effective equivalence between the 2 regimens can be concluded. We observed no serious or persistent adverse effects with either drug.

Our findings about buprenorphine are compatible with those in the study conducted by Risbo et al,[14] in which the effect of sublingual buprenorphine in postoperative pain management was evaluated in 50 patients who had elective knee joint surgery. This study showed that buprenorphine was as effective as morphine in pain relief and had a superior safety profile. In another study, 80 patients undergoing abdominal surgery exhibited consistently lower pain scores with buprenorphine sublingually than did those receiving morphine intramuscularly.[15]

Abid et al[16] compared the efficacy and safety of sublingual buprenorphine with subcutaneous morphine in 50 patients with cesarean section and showed that the pain relief was similar in 2 groups, whereas more morphine patients experienced pruritus. In this study, nurses considered buprenorphine to be more efficient, easier to use, and safer than subcutaneous morphine.[16]

Buprenorphine use has also resulted in greater patient satisfaction than placebo in patients with hip/knee osteoarthritis and chronic low back pain.[17,18] In a large surveillance study, buprenorphine was administered to 13,179 patients by different physicians in different doses to control moderate and severe cancer-related and noncancer-related pain. About 80% of patients reported their pain relief as good or very good, and less than 5% of patients discontinued their drug because of unsatisfactory results.[19] But buprenorphine is not routinely used in EDs and has not been evaluated for acute pain management in ED patients.

In summary, we found that sublingual buprenorphine is as effective as intravenous morphine for pain relief in adult patients presenting with fractures. Because sublingual dosing

Table 3. Frequency of occurrence of adverse events in sublingual buprenorphine and intravenous morphine sulfate groups.

Adverse Events, No. (%)	Buprenorphine		Morphine		*P* Value	
	30 min (n=49)	60 min (n=44)	30 min (n=50)	60 min (n=45)	30 min*	60 min†
Nausea	7 (14)	0	6 (12)	1 (2)	.73	1.00
Dizziness	7 (14)	0	11 (22)	2 (4)	.32	.49
Hypotension	2 (4)	0	9 (18)	1 (2)	.02	1.00

*χ^2 Test.
†Fisher-exact test.

allows for easier and quicker administration, buprenorphine appears to be a promising alternative to intravenous morphine for acute pain management.

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Review Article

Buprenorphine: Considerations for Pain Management

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Abstract
New effective analgesics are needed for the treatment of pain. Buprenorphine, a partial mu-opioid agonist which has been in clinical use for over 25 years, has been found to be amenable to new formulation technology based on its physiochemical and pharmacological profile. Buprenorphine is marketed as parenteral, sublingual, and transdermal formulations. Unlike full mu-opioid agonists, at higher doses, buprenorphine's physiological and subjective effects, including euphoria, reach a plateau. This ceiling may limit the abuse potential and may result in a wider safety margin. Buprenorphine has been used for the treatment of acute and chronic pain, as a supplement to anesthesia, and for behavioral and psychiatric disorders including treatment for opioid addiction. Prolonged use of buprenorphine can result in physical dependence. However, withdrawal symptoms appear to be mild to moderate in intensity compared with those of full mu agonists. Overdoses have primarily involved buprenorphine taken in combination with other central nervous system depressants. J Pain Symptom Manage 2005;29:297–326. © *2005 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Buprenorphine, pharmacology, pharmacodynamics, pharmacokinetics, pain management, partial agonists, formulations, opioids

Introduction

Buprenorphine has been available worldwide as a parenteral and sublingual analgesic since the 1970s. Parenteral buprenorphine has been approved for commercial marketing in the United States since December 1981. It is one of

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a number of opioid partial agonists and mixed agonist-antagonists currently approved as analgesics by the Food and Drug Administration (Table 1).[1]

Buprenorphine (Figure 1) is a derivative of the morphine alkaloid thebaine[2,3] and is a member of the 6,14-endo-ethanotetrahydrooripavine class of compounds that includes other potent analgesics such as diprenorphine and etorphine.[4,5] Although buprenorphine has been shown to interact *in vivo* and *in vitro* with multiple opioid receptors, its primary activity in man is that of a partial agonist at the mu-opioid receptor and antagonist at the kappa receptor.[6–10] The effects of binding at mu-opioid receptors include supraspinal analgesia, respiratory depression, and miosis. Buprenorphine, being a partial mu-opioid agonist, may have a wider safety profile compared to full mu agonists, especially with regard to respiratory depression. Further, the slow dissociation of buprenorphine from the receptor may result in fewer signs and symptoms of opioid withdrawal upon termination of buprenorphine therapy than those which occur with full mu-opioid agonists, such as morphine, heroin, and methadone. Buprenorphine's antagonist effects at the kappa receptor are associated with limited spinal analgesia, and dysphoria and psychotomimetic effects.[11]

Several delivery formulations of buprenorphine have been investigated. Oral bioavailability of buprenorphine is low because of extensive first-pass hepatic metabolism.[12,13] However, buprenorphine has certain physiochemical properties (discussed later) that can allow for other drug delivery technologies to be utilized. The administration of buprenorphine by the sublingual route allows for bypassing of the first-pass hepatic metabolism. Transdermal administration

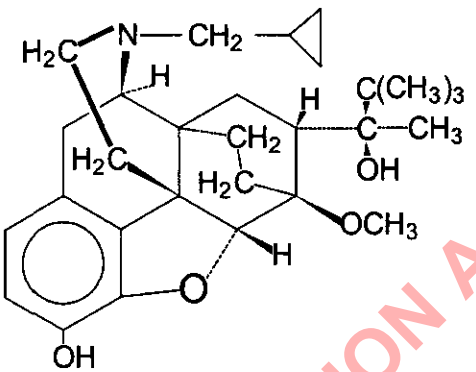

Fig. 1. Chemical structure of buprenorphine. The chemical name of buprenorphine is 6,14-ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α-(1, 1-dimethylethyl)-4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy-α-methyl-, [5α, 7α, (S)]. The structural formula is described in Reference 2.

has proven clinical utility for numerous medications and provides clinicians the opportunity to treat patients who cannot take oral medications, such as those with head, neck, mouth or bowel lesions, or persistent nausea and vomiting. Both the sublingual and transdermal analgesic dosage forms of buprenorphine are approved for use outside of the United States. In the United States, the sublingual formulation has been recently approved for the treatment of opioid addiction (but not as an analgesic)[14] and a transdermal formulation is under development. Both are discussed in this review.

The purpose of this review is to provide clinicians and researchers with information regarding the appropriate therapeutic use of buprenorphine for pain management, and an understanding of the mechanisms underlying its pharmacodynamic actions. Buprenorphine is approved for use as an analgesic for various

Table 1
Opioid Partial Agonist and Agonist/Antagonists Analgesics Commercially Available for Analgesia in the United States

Medication	Activity at Mu-opioid Receptor	Activity at Kappa-opioid Receptor	Dosage Forms Available	Usual Single Analgesic Dose (mg)	Controlled Substances Act Schedule
Buprenorphine	partial agonist	antagonist	parenteral	0.3	III
Pentazocine	partial agonist or weak antagonist	agonist	parenteral	30	IV
			oral	50	
Butorphanol	partial agonist	strong agonist	parenteral	1–2	IV
			nasal	1–2	
Nalbuphine	antagonist	agonist	parenteral	10	Unscheduled

Adapted from Gutstein and Akil.[1]

types of pain (e.g., acute, chronic, and neuropathic pain). It has also been used for treating various behavioral and psychiatric disorders (e.g., depression and opioid dependence).

Preclinical Pharmacology

Receptor Binding/Interactions Studies

In vitro studies have shown that buprenorphine binds with high affinity to mu- and kappa-opioid receptors and relatively lower affinity to delta-opioid receptors.[15,16] Although most *in vitro* studies have shown buprenorphine to be relatively non-selective for these receptors, others have shown a selective potency of the (-) enantiomer of buprenorphine for $kappa_1$ = mu > delta > $kappa_{2a}$ > $kappa_{2b}$,[17] with a slow dissociation from all receptors.[18]

In vivo studies have shown that buprenorphine binds at the mu-opioid receptor,[19] where it is believed that analgesic and other effects (e.g., supraspinal analgesia, respiratory depression, miosis, decreased gastrointestinal motility, and euphoria) are mediated. Buprenorphine is an antagonist at the kappa-opioid receptor; agonist activity at the kappa-opioid receptor is thought to be associated with spinal analgesia, sedation, miosis, and psychotomimetic (i.e., dysphoric) effects. Although buprenorphine binds with high affinity to the delta opioid receptor (but still lower than to the mu or $kappa_1$ receptor), the functional significance of this interaction has not been fully elucidated.[1] More recently, it has been proposed that partial agonist activity at the opioid-receptor-like 1 (ORL-1) receptor, with its endogenous ligand nociceptin or orphanin FQ (N/OFQ), may contribute to the analgesic effect of buprenorphine.[20]

Buprenorphine Effects in Pain Models

Buprenorphine has been shown to increase the nociceptive threshold to electrical stimulation in the tooth pulp assay in dogs.[21,22] The antinociceptive potency of buprenorphine in the rat and guinea pig paw pressure tests was noted to be greater than morphine,[23] and buprenorphine was shown to be 10 times more potent than morphine in the formalin test (a model of post-injury pain).[24]

In addition to the biphasic dose-response curve observed for buprenorphine with regards to effects on respiration in mice and intestinal motility in rats,[25] a bell-shaped dose-response curve for the antinociceptive action of buprenorphine has been observed in certain preclinical pain models (e.g., mouse and rat hot plate, rat and monkey tail dip, and rat electrical stimulation of the tail and formalin-induced flinching),[26–31] whereas a linear dose-response relationship has been observed in others (e.g., rodent writhing and tail pressure).[26] A curvilinear dose response for antinociceptive effects was first observed by Cowan and coworkers in the rodent tail dip/flick test,[26] and later by Dum and Herz[27] in *in vivo* binding studies in the rat. Explanations for this bell-shaped curve include a 2-receptor model and noncompetitive autoinhibition.[7,17,19,26] The peak of the dose-response curve occurred at a dose of approximately 1 mg/kg. The entire curve shifted to the right following pretreatment with the opioid antagonists naloxone[32] or naltrexone.[27] Although readily demonstrated in preclinical analgesic studies, the bell-shaped dose-response curve has not been observed in clinical analgesic trials that have utilized much lower doses of buprenorphine. A study (not an analgesic trial) designed to find the peak of this dose-response curve in human subjects used a maximum single dose of 32 mg administered as a sublingual solution.[33] A plateau of subjective and respiratory depressive effects was observed, consistent with the partial agonist classification of buprenorphine (Figure 2); however, the effects were not biphasic even in this dose range.

Distinguishing (Discriminative) Stimulus Properties and Self-Administration

In studies where animals were trained to distinguish between an opioid (e.g., morphine) and no drug (e.g., saline), buprenorphine generalized to medications such as morphine and fentanyl.[34,35] These results indicated that the internal drug cues produced by buprenorphine are similar to those of the other opioids. Animals that have previously been made dependent on morphine will acquire drug-taking behavior (i.e., self-administration by pressing a lever that activates administration) when exposed to morphine-like drugs. Albeit sometimes weakly, buprenorphine has been shown to support intravenous self-administration in animals under various conditions of reinforcement.[36–40] Both drug-naive and drug-experienced

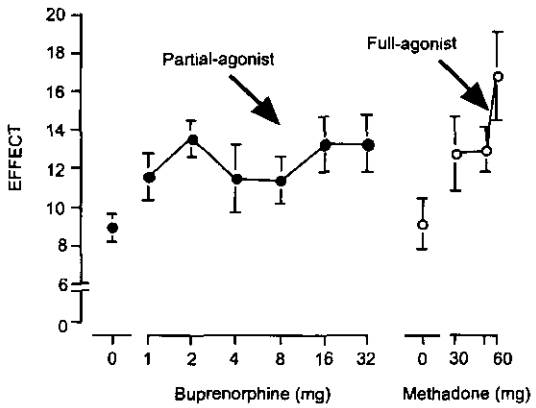

Fig. 2. The effects of the partial-agonist buprenorphine (closed circle) and the full-agonist methadone (open circle) on an opioid agonist scale. The scale contains 16 adjectives descriptive of opioid-like agonist effects rated on a 0–4 ordinal scale (maximum score = 64). Each vertical bar represents ± 1 SEM. Reprinted from Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clinical Pharmacology and Therapeutics, 1994. 55: 569–580,[33] with permission from the American Society for Clinical Pharmacology and Therapeutics.

animals have been shown to self-administer buprenorphine.[37,38]

Physical Dependence Liability

Three primary preclinical experimental procedures have been used to evaluate the morphine-like physical dependence potential of buprenorphine in animals. The first procedure is the substitution of buprenorphine for morphine in morphine-withdrawn animals. The second is the precipitation of an opioid abstinence syndrome by buprenorphine in morphine-dependent animals. The third is the substitution of placebo (i.e., saline) to assess the presence of spontaneous withdrawal in buprenorphine-maintained animals.

In studies of the above-described procedures, buprenorphine has been shown to produce either no, or a protracted but mild, opioid-like withdrawal syndrome in rats, dogs, and non-human primates.[6,26,27,37,41,42] For example, Martin and coworkers showed that in dogs maintained on 125 mg/day morphine, at low doses, buprenorphine substituted for morphine (i.e., suppressed spontaneous withdrawal) and at higher doses, precipitated an abstinence syndrome.[6] Buprenorphine was also reported to precipitate an abstinence syndrome in rhesus monkeys maintained on morphine.[43] In another study, no signs of opioid withdrawal were observed when saline was substituted for chronically-administered buprenorphine in rhesus monkeys, and there were no signs of disruptions in other behaviors such as food intake.[37] Taken together, the ability of buprenorphine to generalize to morphine-like drugs along with its production of only relatively mild physical dependence indicates that buprenorphine's potential for abuse is limited compared to many other opioids.

Tolerance to the behavioral effects of buprenorphine has been reported in the rhesus monkey.[38,44] Cross-tolerance of buprenorphine to morphine has been shown in the mouse[25] and rat.[41]

Safety

The LD_{50} values for buprenorphine, assessed in a number of animal species by various routes of administration, are shown in Table 2.[45] Table 3 shows the comparison of the ratio of the acute toxic doses to the antinociceptive doses yielding the therapeutic index for morphine and buprenorphine in rats. These data are consistent with a wide safety margin for buprenorphine.

Studies in mice and rats have shown that buprenorphine is not a carcinogen at doses 1600 times greater than the analgesic dose. From genetic toxicity studies, including the Ames test, the chromosomal aberration assay, and the mouse lymphoma forward mutation assay, it has been concluded that buprenorphine is not a mutagen and presents no genetic danger to man.

Table 2
Acute Toxicity (LD_{50}) of Buprenorphine

Species	Route of Administration	LD_{50} (mg/kg) Base	HCl salt
Mouse	oral	260	800
Mouse	intravenous	24	72
Mouse	intramuscular	–	>600
Mouse	intraperitoneal	90	–
Mouse	subcutaneous	–	>1000
Rat	oral	–	>1000
Rat	intravenous	31	62
Rat	intramuscular	–	>600
Rat	intraperitoneal	197	–
Rat	subcutaneous	–	>1000
Dog	intravenous	–	79

– -Data not available. Reference 45.

Table 3
Therapeutic Indices for Morphine and Buprenorphine

Opioid	LD_{50}, Acute (mg/kg)	ED_{50}, Tail Pressure (mg/kg)	Therapeutic Index LD_{50}/ED_{50}
Morphine	306 [237, 395]	0.66 [0.26, 1.6]	464
Buprenorphine	197 [145, 277]	0.016 [0.011, 0.024]	12,313

References [25,26]
Numbers in brackets are 95% confidence limits.

Although buprenorphine has been reported to be without teratogenic effects in rodents,[46] significant increases in skeletal abnormalities were noted in rats after subcutaneous administration of 1 mg/kg/day and greater, but not at oral doses up to 160 mg/kg/day.[14] Increases in skeletal abnormalities in rabbits after intramuscular administration of 5 mg/kg/day, or 1 mg/kg/day or more given orally were not statistically significant. Buprenorphine produced statistically significant pre-implantation (oral doses of 1 mg/kg/day or more) and post-implantation (intravenous doses of 0.2 mg/kg/day) losses in rabbits.[14]

Unlike effects observed from some other opioids, prenatal exposure in rats to buprenorphine does not appear to affect activity, cycles of rest-activity, or developmental milestones.[46–52] The oral administration of buprenorphine to rats during gestation and lactation, at doses several hundred times greater than the analgesic dose, has been associated with delayed postnatal development of the righting reflex and startle response.[14,53] It has been reported that buprenorphine reduces striatal nerve growth factor[54] and produces toxic effects similar to methadone.[52] Mixed effects of buprenorphine on maternal water intake, postnatal growth, maternal weight gain, frequency of resorption, or pup birth weights, number of stillbirths, and offspring mortality have also been reported.[14,52,55–57] Physical dependence and tolerance to the antinociceptive effects of morphine in pups exposed perinatally to buprenorphine and methadone have been demonstrated; generalized neuromuscular development does not appear to be delayed by perinatal exposure to buprenorphine.[57]

Pharmacokinetics

General Observations

Buprenorphine is an extremely lipophilic compound[58] that dissociates very slowly from the mu-opioid receptor.[18,58–60] This slow receptor dissociation has generally been regarded as the property responsible for buprenorphine's relatively long duration of action as an analgesic. Buprenorphine also has a high affinity for the mu-opioid receptor, and is not displaced easily by antagonists, such as naloxone, which have a lower receptor affinity.[61]

The elimination half-life of buprenorphine in humans has been described as either biphasic[62] or triphasic.[63,64] Buprenorphine is highly bound (96%) to plasma proteins, primarily to α- and β-globulin fractions.[65] Studies utilizing human liver microsomal preparations indicated that buprenorphine is demethylated to form norbuprenorphine, and is also metabolized to other compounds by cytochrome P-450 3A4.[66,67] Both buprenorphine and norbuprenorphine form conjugates with glucuronic acid.[68,69] Studies in rats utilizing intraventricular administration of norbuprenorphine and buprenorphine indicated that the intrinsic analgesic activity of norbuprenorphine was 25% that of buprenorphine.[70]

The oral bioavailability of buprenorphine is approximately 10%, secondary to extensive first-pass hepatic metabolism.[12,71] Preclinical studies in rats indicate that buprenorphine distributes rapidly to the brain following intravenous administration.[70] Brain to plasma concentration ratios of buprenorphine in rats following a single intravenous dose ranged from 3.0 at 15 minutes to 10.5 at 6 hours post-drug administration.[72] The more polar metabolite norbuprenorphine has an n-octanol:water partition coefficient about 10% that of buprenorphine[70] and penetrates into the central nervous system to a much lesser degree than the parent compound.[73] In the rat, dog, monkey, and human, approximately 70% or more of an intravenous dose is recovered in the feces;[74] enterohepatic recycling is likely.[75] A much lesser percentage of buprenorphine (10–30%) is found in the urine following administration by various other routes.[65,75] Concentrations found in human red blood cells are comparable to those in the plasma.[63]

Parenterally Administered Buprenorphine

In the United States, buprenorphine, used as an analgesic, is only approved for parenteral administration, typically by the intramuscular

or intravenous route. Peak plasma concentrations following intramuscular administration occurred, in general, 5 minutes after dosing, and in some patients, by 2 minutes.[63] Mean plasma concentrations of buprenorphine in that study differed little after 5 minutes postdrug administration by either the intravenous or intramuscular routes; intramuscular bioavailability ranged from 40% to greater than 90%. The volume of distribution at steady state has usually been found to be between 200 and 400 liters.[76]

Following the administration of 0.3 mg of intravenous buprenorphine given intraoperatively, the initial half-life was found to be about 2 minutes,[63] with a mean terminal half-life of 5 hours.[77] A study by Mendelson and coworkers[78] indicated that the mean terminal half-life of intravenously given buprenorphine (1 mg infused over 30 minutes) was about 6 hours. Kuhlman and colleagues[79] reported a mean terminal half-life of 3.2 hours following single doses of 1.2 mg given intravenously.

Buprenorphine clearance following intravenous administration has typically been reported to be between 70 and 80 liters/hour when doses in the analgesic range have been used.[63,79] The clearance of buprenorphine in anesthetized patients was found to be lower than in the same individuals not under anesthesia secondary to reduced hepatic blood flow from the anesthetic.[63]

Buprenorphine Sublingual Liquid/Buccal Strip

The absorption of buprenorphine liquid from the sublingual mucosa is rapid, occurring within 5 minutes.[80] In a study utilizing healthy volunteers,[80,81] the bioavailability of buprenorphine in a 30% ethanol solution administered sublingually was approximately 30%. Kuhlman and colleagues[79] studied the pharmacokinetics of buprenorphine by various routes of administration using a crossover design in healthy, non-dependent men who had a history of heroin abuse. Buprenorphine bioavailability by the sublingual and buccal routes was approximately 51% and 28%, respectively, with much interindividual variability. The mean terminal half-lives were 28 hours following sublingual administration and 19 hours following buccal administration, compared with 3.2 hours following the intravenous route, perhaps related to the sequestering of buprenorphine in the oral mucosa. Average clearances for the 3 routes of administration were 210, 712, and 77 liters/hour, respectively. In a study that evaluated sublingual dosages of buprenorphine up to 32 mg,[33] peak plasma concentrations of buprenorphine were observed at 60 minutes following doses of 2 and 4 mg, and at 30 minutes for doses of 8, 16, and 32 mg. Plasma concentrations after administration of the 32 mg dose were significantly elevated for up to 60 hours following medication administration. As noted previously, the oral bioavailability of buprenorphine is very low (approximately 10%). Thus, the swallowing of buprenorphine that is not absorbed buccally or sublingually would contribute little to overall absorption.

Buprenorphine Sublingual Tablets

Following the sublingual administration of 0.4 or 0.8 mg doses, there was no significant rise in buprenorphine plasma concentrations for 20 minutes; the time to maximum concentration was variable, ranging from 90 to 360 minutes.[76,77] The average systemic bioavailability was 55%, with large intersubject variability.

A number of studies have assessed the pharmacokinetic profile of a buprenorphine tablet formulation. Bioavailability of the tablet was reported to be approximately 50–65% that of the sublingual solution, based on 48- and 24-hour AUC measurements, respectively.[82,83] Results were generally comparable regardless of whether buprenorphine was administered as a single dose, or administered once daily over multiple days. When buprenorphine tablets were given over multiple days, average concentrations peaked 2 hours after medication administration, in contrast to 1 hour as has been found for the solution.

Buprenorphine for Intranasal Administration

The bioavailability of intranasal buprenorphine has been assessed in humans[84] and sheep[85] using a polyethylene glycol 300 (PEG) and a 5% dextrose vehicle. The buprenorphine formulation in humans was found to be approximately 50% bioavailable, with a time to maximum concentration of 30 minutes. In sheep, the bioavailability of buprenorphine in PEG and dextrose was 70% and 89%, respectively; time to maximum concentration was 10 minutes. From these data, it appears that an intranasal formulation of buprenorphine would

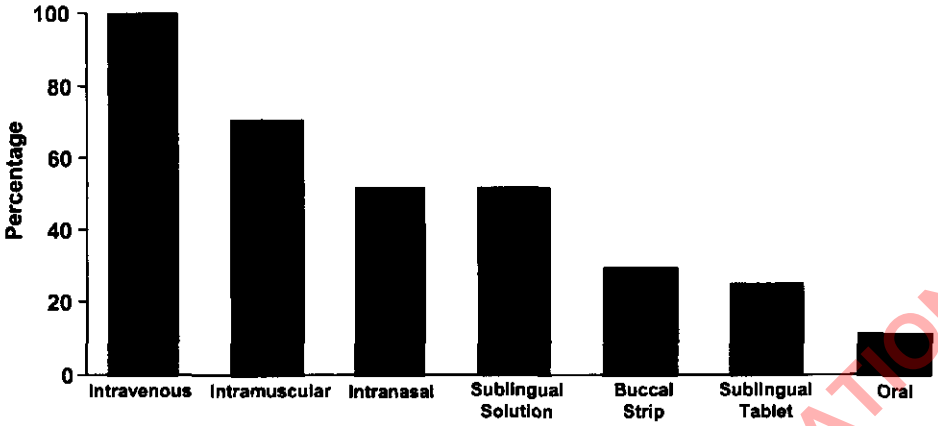

Fig. 3. Approximate bioavailability of buprenorphine by route of administration. Reprinted from Methadone Treatment for Opioid Dependence [Figure 13.2 (c)]. Strain, Eric C., M.D., and Maxine L. Stitzer, Ph.D., eds. The Johns Hopkins University Press. Baltimore, Maryland: The Johns Hopkins University Press, 1999: 300. Reprinted with permission from The Johns Hopkins University Press.

provide a rapid onset of analgesic effect. The approximate bioavailability of buprenorphine by various routes of administration is shown in Figure 3.

Buprenorphine for Transdermal Administration

The ideal medication for transdermal administration should be highly lipophilic and of low molecular weight (less than approximately 1000) for ease of crossing the skin barrier.[86] It should also be highly potent so that adequate doses could be delivered through the skin. Buprenorphine meets these requirements. It has an octanol-to-water partition coefficient of 1217 (i.e., high lipophilicity),[87] a molecular weight of 468, and is 25 to 50 times more potent as an analgesic, per mg, than morphine. Further, with a transdermal formulation, a therapeutic blood level could be maintained over an extended period of time, thus improving compliance and effectiveness of the medication.

Recently, a transdermal buprenorphine product has been approved and marketed in a number of European countries.[88,89] This transdermal system is designed to continuously release buprenorphine at one of three defined rates: 35, 52.5, or 70 µg/hr, corresponding to daily doses of 0.84, 1.26, and 1.68 mg/24 hr, respectively. Effective plasma levels are reached within 12 to 24 hours and are kept at a constant level for 72 hours. The buprenorphine is incorporated into a polymer adhesive matrix.

Three dosage strengths of a seven-day buprenorphine transdermal system are being developed in the United States, which deliver 5, 10, or 20 µg/hr buprenorphine, respectively.[90] The highest strength patch (20 µg/hr) will result in a dosage of 0.48 mg/day. Compared to the higher-strength European product described above, these three dosage strengths may be more useful for milder pain syndromes. The buprenorphine is dissolved in a polymer matrix and the rate of drug release is controlled by the diffusion of the buprenorphine in the adhesive matrix through the stratum corneum of the epidermis. The concentration of buprenorphine mixed in the adhesive matrix is the same for each strength. After application of the transdermal system with release rates of 5, 10, and 20 µg/hr to healthy subjects, mean (±SEM) peak buprenorphine plasma concentrations (C_{max}) were 176 ± 34, 191 ± 19, and 471 ± 77 pg/mL, respectively.[90] The concentration of buprenorphine released from each system per hour is proportional to the surface area of the system. The time to reach steady-state plasma concentrations was approximately 24 to 48 hours and the percentage of the total dose delivered in 7 days was 15%.[90] Following system removal, concentrations decreased to about one-half in 12 hours, then declined more gradually with an apparent terminal half-life of 26 hours.[90,91]

Special Considerations

Buprenorphine in Renal Failure. The disposition of buprenorphine in patients with renal failure

was examined in studies utilizing both single- and multiple-dosing.[92] In the single-dose study using balanced anesthesia, buprenorphine was given intravenously at a dose of 0.3 mg. In the multiple-dose study, a variable-rate infusion was utilized with controlled ventilation to provide analgesia in the intensive care unit (median infusion rate of 161 µg/hr for a median of 30 hours). In the first study, there were no differences in buprenorphine kinetics between healthy patients and those with renal failure (all dialysis-dependent with creatinine clearances less than 5 mL/min). Buprenorphine clearances and dose-corrected plasma concentrations were similar in the 2 groups of patients. However, in patients with renal failure (plasma creatinine concentration greater than 140 µmol/liter), plasma concentrations of norbuprenorphine were increased by a median of 4 times, and buprenorphine-3-glucuronide by a median of 15 times.

Another study, which measured only buprenorphine (not metabolites) over a 3-hour sampling period, reported that the disposition of buprenorphine was similar in patients with end-stage renal failure compared to healthy controls.[93] The renal failure patients did not show clinical evidence of sedation or respiratory depression.

Buprenorphine in Hepatic Failure. Few data are available with regard to the use of buprenorphine in patients with hepatic failure. A recent study evaluated the pharmacokinetic profile of buprenorphine (0.3 mg given intravenously) in subjects with mild to moderate chronic hepatic impairment and in healthy controls matched for age, weight, and sex.[94] No differences between the groups were observed for most pharmacokinetic parameters (e.g., steady-state volume of distribution, total clearance). However, the maximum plasma concentrations of buprenorphine and norbuprenorphine were 50% and 30% lower, respectively, in individuals with hepatic impairment. These subjects also had less nausea and vomiting than the controls. The results did not indicate the need for a buprenorphine dosage adjustment in individuals with mild to moderate chronic hepatic impairment.

Buprenorphine in Children and Infants. When buprenorphine (3 µg/kg) was given intravenously as premedication to children aged 4 to 7 years, mean clearance was 3.6 liters/hr/kg and steady state volume of distribution varied from 1.2 to 8.3 liters/kg.[95] None of the kinetic parameters correlated with age, body weight, or body surface area. Because buprenorphine plasma concentrations declined rapidly, terminal elimination half-life could not be estimated reliably. In a study of the pharmacokinetics of a buprenorphine infusion in premature neonates,[96] the clearance of buprenorphine was lower than values previously reported for adults and children, probably related to immaturity of the glucuronidation metabolic pathway.

Clinical Pharmacology

Analgesia and Anesthesia

Pain Assessment and Treatment. Pain may be described as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. It is typically categorized broadly as being either acute or chronic. Whereas acute pain is often associated with a particular injury or procedure, chronic pain is pain that has been present for more than three months, and which may be persistent or intermittent. In addition, chronic pain may persist after the disease itself has been effectively treated.[97]

As noted by Bonica,[98] few basic and clinical scientists had devoted their efforts to pain research prior to the 1960s. Differences between acute and chronic pain were not appreciated, and animal models, particularly for chronic pain, were not being developed. More recently, preclinical and clinical research studies have elucidated multiple mechanisms and sites associated with the production of pain.[99] Pain itself is subject to much inter-individual variability with regard to threshold and tolerance, and has expectational and emotional components.[100] Thus, all clinical practice guidelines emphasize the need to use patient self-report as the gold standard for assessing pain rather than observers' reports because pain is such a personal experience.

Numerous opioids and opioid-like medications have been used to treat both acute and chronic pain. Chronic pain may involve pain related to cancer, as well as noncancer pain due

to osteoarthritis, chronic back pain, and neuralgia. Although morphine is the prototypical agent, numerous other drugs such as hydrocodone, oxycodone, methadone, and others have been utilized effectively. The use of opioid analgesics for the treatment of chronic noncancer pain, however, still elicits controversy, much of it related to concerns regarding adverse effects and possible addiction.[101] It is especially important to differentiate between addiction to opioids and the appropriate use of opioids for analgesia and between addiction and physical dependence. Although patients using opioids for chronic pain may become physically dependent, they usually do not exhibit evidence of behaviors indicative of addiction.[102] Although the treatment of pain in patients with a current or past diagnosis of addiction presents its own unique challenges,[103] opioids have generally been shown to be safe and effective for the treatment of chronic pain.[104,105]

Buprenorphine has undergone clinical evaluation for the treatment of acute and chronic pain, analgesic anesthesia, and to a much lesser extent, neuropathic pain. Buprenorphine is indicated for the treatment of moderate to severe pain. Doses of 0.3 mg of buprenorphine are typically considered to produce analgesia approximately equivalent to 10 mg of morphine when both medications are given parenterally.[106–108] As a parenteral analgesic, buprenorphine has been administered by the epidural, intra-articular, intramuscular, intravenous, and subarachnoid routes. It has also been given through the use of subcutaneous implanted micropumps and by continuous subcutaneous infusion.[3,11,109] The sublingual and transdermal routes of administration have also been utilized. There are no published data indicating an analgesic ceiling dose in humans.

Acute Pain. Most studies of acute pain have used 1 or 2 doses of the medication, typically in postoperative patients. One of the earliest assessments of buprenorphine when given parenterally for postoperative pain found that it generally provided good or adequate pain relief with an incidence of less than 1% of drug-associated respiratory depression.[110] Various other studies have shown buprenorphine to be as or more effective than morphine as a postoperative analgesic,[111–116] and more effective than meperidine, often with a longer duration of activity.[112,117–119] Patients undergoing various types of surgical procedures, including abdominal, gynecological, and cardiac, were evaluated. Nausea/vomiting and dizziness were sometimes more common following buprenorphine administration, but other effects (e.g., decreased respiratory rate, drowsiness) were often observed no more frequently than with the comparison opioid. Further, doubling the intravenous dose of buprenorphine from 0.3 to 0.6 mg has been reported to produce a dose-dependent increase in analgesia without a parallel increase in respiratory depression.[64] Doses as high as 7 mg given intravenously for postoperative analgesia have been reported to be without associated respiratory depression.[120] Although, as noted previously, the dosage at which the peak of the analgesic dose-response curve occurs has been estimated in animal models, there are insufficient data to determine that dosage in humans. Thus, whereas at typical analgesic dosages buprenorphine is approximately 25 to 50 times more potent than morphine, determining potency equivalency at very high doses (such as the 7 mg dose mentioned above) is problematic.

Wallenstein and coworkers found relative potencies of intramuscular to sublingual buprenorphine of about 2:1 in postoperative cancer patients.[121] The sublingual buprenorphine (tablet formulation) was approximately 15 times more potent than intramuscular morphine. Additionally, the sublingual, but not the intramuscular, formulation was found to be longer acting than morphine.

For the treatment of postoperative pain by the intramuscular route, buprenorphine is about 30 times more potent than morphine.[106–108] In contrast, buprenorphine administered epidurally has been shown to be only about 8 to 12 times more potent than morphine.[122,123] However, doses of buprenorphine were typically less by the epidural (e.g., 0.06 to 0.15 μg) than by the intramuscular (0.3 mg) route.[123,124] Although higher epidural buprenorphine doses (0.3 to 0.9 mg) have also been used successfully with a low occurrence of side effects, little additional benefit (as far as duration of action or quality of analgesia) from doses greater than 0.3 mg has been observed.[125] Pain relief for 12 to 24 hours has typically been observed when buprenorphine is administered epidurally.[126] Intrathecal buprenorphine, 0.03 or 0.045 mg, with bupivacaine has also been

shown to produce effective, long-lasting analgesia, with nausea and vomiting as the predominant side effects.[127]

With regard to comparisons to other analgesics, buprenorphine has been found to compare favorably to the agonist-antagonist nalbuphine when the medications were given intravenously for pain after abdominal surgery.[128] Buprenorphine (0.15 mg/mL) or nalbuphine (10 mg/mL) were administered as a continuous infusion at the rate of 0.2 mL/kg per 24 hours. Patients who received buprenorphine had significantly greater pain relief and requested less additional analgesic than those who were given nalbuphine. Compared to pentazocine (30 and 60 mg) in men undergoing orthopedic procedures, buprenorphine (0.3 and 0.6 mg) was associated with less nausea, vomiting, and euphoria, but more sedation, when both medications were given intramuscularly.[129] Buprenorphine, although more potent, was found to provide equivalent analgesia and a similar side effect profile as pentazocine when both were given intravenously on demand post cholecystectomy.[130]

Sublingually administered buprenorphine has also been shown to be an effective postoperative analgesic.[76,131–134] Benefits associated with buprenorphine treatment included decreased need for additional analgesics and a long duration of activity. One trial showed that buprenorphine given sublingually (0.4 mg) was associated with less depression of consciousness than when administered intramuscularly (0.3 mg) following major abdominal surgery.[135] Although lack of salivation was problematic with regard to sublingual administration, instillation of normal saline sublingually was used to overcome this limitation.

A recent study evaluated the efficacy of intra-articular buprenorphine and bupivacaine after knee arthroscopy.[136] Both buprenorphine (0.1 mg) and bupivacaine (50 mg) were associated with good postoperative pain control and reduced need for analgesia after surgery. Although systemic effects of buprenorphine contributing to its effectiveness could not be ruled out, the low dose of buprenorphine used compared to the therapeutic response observed would seem to argue against this.

Girotra and coworkers found that caudal buprenorphine (4 μg /kg) provided prolonged analgesia with less nausea and vomiting in children undergoing orthopedic surgery compared to buprenorphine administered intramuscularly at the same dose.[137] Results from other studies have also supported the efficacy of caudal buprenorphine in children.[138,139]

Patient-controlled analgesia (PCA) utilizing opioids, including buprenorphine, is widely used for the management of postoperative pain. One study of buprenorphine given as sublingual tablets (up to two 0.2 mg tablets every 3 hrs; maximum of 8 tablets in 24 hrs) following cholecystectomy observed that an acceptable level of pain relief was attained in about 80% of the patients.[140] Another study showed that sublingual buprenorphine compared favorably to intramuscular meperidine with respect to pain relief following gynecological surgery.[141] Other studies have also shown the utility of PCA with buprenorphine using various routes of administration, including intravenous and intramuscular.[142–145] The amounts of buprenorphine administered varied based on a number of factors, including the route of buprenorphine administration, type of surgical procedure, and other medications used.

Buprenorphine/naloxone combinations have been evaluated as an analgesic combination to reduce potential abuse, including use in patient-controlled analgesia paradigms.[146] In one study, patients undergoing abdominal or orthopedic surgery were evaluated.[147] They were randomly assigned to receive either buprenorphine or a mixture of buprenorphine and naloxone, with the amount of naloxone equal to 60% that of buprenorphine on a mg basis. Although the admixture decreased both the analgesic and respiratory depressant effects of buprenorphine, it nonetheless provided an adequate analgesic response. In another investigation, single intramuscular injections of either buprenorphine (0.3 mg) or buprenorphine (0.3 mg) with naloxone (0.2 mg) were compared in individuals following abdominal surgery.[148] Patients in both groups had a good analgesic response that lasted for approximately 12 hours, with no significant differences between the groups observed for efficacy. A trial comparing buprenorphine and buprenorphine/naloxone at the same dosages in patients following orthopedic or gynecological surgery produced similar results.[149]

Chronic Cancer and Noncancer Pain. Buprenorphine has also been studied for the treatment of chronic cancer pain. One of the earliest studies evaluated sublingual buprenorphine in the dosage range of 0.15 to 0.8 mg per dose for an average duration of 12 weeks of treatment.[150] Ninety-four of 141 cancer patients on the initially offered dosage range of 0.15 to 0.4 mg discontinued participation in the study within 1 week of initiation. Of those who discontinued, approximately one-half (50 patients) discontinued secondary to side effects that included, in order of frequency, dizziness, nausea, vomiting, drowsiness, and lightheadedness. However, no constipation was reported. Another study[151] utilizing a range of daily buprenorphine doses between 0.4 and 3.2 mg (median of 1.6 mg for individuals with pain of malignant origin compared to 1.0 mg for those with nonmalignant pain) found similar results, with most patients withdrawing secondary to adverse effects or inadequate analgesic response. As in the first study, the early dropout rate was severe, with 26 of the 70 patients discontinuing treatment within one week. No correlation between buprenorphine plasma levels and analgesic response was found.

When single doses of intramuscularly administered buprenorphine (0.3 mg) and morphine (10 mg) were compared, buprenorphine was found to have a longer duration of action.[152] When compared to pentazocine (50 mg given orally), sublingual buprenorphine (0.2 mg) was found to be superior with respect to analgesia, quality of life, and study terminations secondary to side effects when 1 to 2 tablets were administered every 6 to 8 hours.[153]

In a long-term evaluation (representing 9,716 days of treatment) of 139 patients with cancer whose pain was not previously controlled using conventional analgesic approaches, epidural morphine or buprenorphine provided pain relief in 87% of patients.[154] Mean, daily doses of morphine and buprenorphine were 15.6 (range: 2 to 290) and 0.86 mg (range: 0.15 to 7.2), respectively. The mean duration of treatment was 72 days (range: 2 to 700).

Results from a study of 12 opioid-naïve individuals with cancers of various types, and who did not previously respond to nonsteroidal anti-inflammatory agents, indicated similar analgesic efficacy for buprenorphine (0.3 mg) and morphine (3 mg) when both were administered by the epidural route.[155] Changes in respiratory function indices associated with buprenorphine in this study were judged to be clinically irrelevant.

A continuous subcutaneous infusion of buprenorphine at a rate of 4 μg/kg per day, following the intramuscular administration of 0.004 μg/kg, provided adequate pain relief with few side effects in 10 patients with pain secondary to cancer.[156] Buprenorphine, administered through the use of an external subarachnoid catheter connected to a micropump, has also been used to treat pain associated with various types of cancers.[157] Subarachnoid buprenorphine, 0.06 to 0.15 mg per day titrated to individual response, provided effective analgesia in all 23 patients studied. No respiratory depression was observed, even in one individual who received 0.52 mg in 24 hours secondary to a dosing error.

Fewer studies have been conducted evaluating the use of buprenorphine for chronic noncancer pain than those assessing its utility for cancer pain, and some include a heterogeneous patient population including individuals suffering from both cancer and noncancer pain. In an evaluation of the use of sublingual buprenorphine in individuals over 65 years of age with chronic pain of various etiologies (including osteoarthritis and malignancy), buprenorphine was well tolerated over the 14-day treatment period.[158] Individuals were given 0.1 mg buprenorphine 3 to 4 times daily as required. Patients in the over-80 years age group had a better analgesic response than those aged 65 to 80 years; the incidence of side effects was low.

The analgesic effectiveness of buprenorphine in the treatment of chronic cancer and noncancer pain was assessed in a number of studies using transdermal administration. With regards to the evaluation of the transdermal product already available in Europe (described previously), three randomized, controlled, double-blind trials have been performed. In one, 157 patients with chronic severe pain related to cancer or other disorders and inadequately controlled with so-called "weak" opioids were randomized to receive buprenorphine or placebo patch for up to 15 days. Patients were switched directly from their previous analgesics on day one of the study and rescue medication (sublingual buprenorphine) was available to all participants.[159] Buprenorphine dosages of 35

and 52.5 μg/hr were associated with significantly higher response rates than placebo. Interestingly, the response to the highest buprenorphine dosage tested, 70 μg/hr, did not reach statistical significance, perhaps secondary (as the authors suggested) to fewer patients assigned to this group and the presence of several refractory patients. Only summary data are available for the two other double-blind studies.[160,161] In the first, patients who had been inadequately treated with weak opioids or 30 mg morphine were randomized directly to one of the three doses of transdermal buprenorphine or placebo. The double-blind phase lasted for 15 days, and no problems were encountered by patients switching from one of the other opioids to buprenorphine. In the second, patients were treated in an open, run-in phase with buprenorphine sublingual tablets. Individuals who obtained at least satisfactory pain relief were then randomized to either 35 μg/hr buprenorphine transdermal or placebo for 9 days. When the daily dose (0.84 mg) delivered by the patch was added to the additional sublingual buprenorphine required, the total dose in the double-blind phase was comparable to the sublingual dose during the run-in phase. The efficacy of this product was also demonstrated in an open-label follow-up study conducted following the completion of the double-blind studies[160] and from a survey of 3,255 patients with chronic pain.[162]

Clinical studies have been conducted with the 7-day buprenorphine transdermal delivery system that is being developed in the United States. Patients with chronic back pain were treated up to 84 days with the buprenorphine transdermal system (5 to 20 μg/hr).[163] Pain intensity was significantly reduced after treatment with the buprenorphine transdermal system compared to placebo. Another study in patients with pain from osteoarthritis showed higher odds ratio of successful treatment with the buprenorphine transdermal system for up to 28 days compared with placebo.[164] Studies showed similar pain control after treatment with the buprenorphine transdermal system compared with active controls, such as hydrocodone/acetaminophen or oxycodone/acetaminophen.[163,165] Additionally, the buprenorphine transdermal system was shown to be well-tolerated over long-term study periods, up to 18 months.[163–166]

Even in consideration of the above data, the use of buprenorphine for the treatment of advanced cancer pain cannot be generally recommended because treatment typically requires high doses of opioids and a rightward shifting of the analgesic dose-response curve may occur. Most of the above-cited studies represent small or uncontrolled trials. Further, data supporting the use of buprenorphine for the treatment of cancer-related pain is very limited compared to the data available for many other opioids (e.g., morphine, fentanyl, and oxycodone). Thus, additional large-scale, controlled trials of buprenorphine will be required before the true utility of buprenorphine in this area can be determined.

Neuropathic Pain. The treatment of neuropathic pain with opioid analgesics is controversial. Neuropathic pain is generally thought to be relatively less responsive to opioids; however, analgesia may be obtained when adequate medication doses are administered.[167,168] It was reported that 85% of approximately 850 patients with noncancer pain benefited from treatment (of up to 14 years' duration) with opioids. Additionally, 67–80% of individuals treated with patient-controlled opioid analgesia for neuropathic pain were responsive to treatment.[169] Buprenorphine injected near the upper cervical or stellate ganglion has been used effectively for sympathetically-maintained pain.[170,171] Although the buprenorphine literature is limited in this regard, there is evidence that buprenorphine may be effective for treating some types of neuropathic pain.

Preclinical efficacy was assessed in a rodent model that utilized intrathecal administration of pertussis toxin to produce effects similar to symptoms reported by patients suffering from neuropathic pain. Buprenorphine-induced antinociception, unlike the effects of other opioids, was not inhibited.[172,173] The clinical effectiveness of buprenorphine in combination with bupivacaine has been reported in a 77-year-old woman who developed refractory nociceptive-neuropathic pain after a total hip arthroplasty. Mean daily doses of 37 mg bupivacaine and 0.114 mg buprenorphine administered intrathecally (for over 6 years) provided the patient with 85–100% pain relief.[174] In another evaluation, 21 patients were studied immediately after (nociceptive pain) and at 1 month (neuropathic pain) following thoracic surgery.

The analgesic dose of buprenorphine needed to reduce pain by 50% (the AD50) for postoperative nociceptive pain was compared to the AD50 for neuropathic pain. Neuropathic pain could be adequately controlled by buprenorphine; however, the AD50 for it was significantly higher than for nociceptive pain. Further, when the AD50 for nociceptive pain was low (e.g., 0.16 mg), the AD50 for neuropathic pain was 3 times higher (e.g., 0.5 mg). However, when the former was high (e.g., 0.6 mg), the latter was only slightly increased (e.g., 0.66 mg), showing that a large part of the difference seen in neuropathic pain was due to a pre-existing painful condition.[169] The authors concluded that postoperative neuropathic pain is treatable with opioids, treatment is dose responsive, and that dose responsiveness may be more reflective of individual differences and not of the neuropathic pain, per se.

Analgesic Supplemented Anesthesia. Buprenorphine has been used successfully as a supplement to anesthesia in dosages typically ranging from 5 to 40 µg/kg.[175–177] In one of the trials,[177] one-half of the patients undergoing biliary surgery who received buprenorphine in dosages of 30 to 40 µg/kg requested an analgesic within 5 minutes of extubation. Surprisingly, none of the patients receiving 10 to 20 µg/kg needed an analgesic within 1 hour of the operation, although some required supplemental analgesics intraoperatively. Although a precise explanation for this phenomenon is lacking, and analgesic requests could have been related to sedation, nausea, or vomiting, all patients reportedly were awake or woke up when spoken to. The influence of nausea and vomiting during the first postoperative hour was apparently negligible. In a study of single-dose, buprenorphine-supplemented anesthesia in patients undergoing cholecystectomy, multiple regression techniques indicated that the duration of analgesia was dependent on the age of the patient, but not on the weight-adjusted dose of buprenorphine, nor the sex, or body weight of the patient.[178]

In a comparison of intraoperative buprenorphine (0.6 mg) to methadone (20 mg) in women undergoing laparohysterectomy, those who received buprenorphine required fewer doses of supplemental analgesic and had a longer duration of analgesia.[179] Buprenorphine (2 and 5 µg/kg) has also been compared to meperidine (0.8 mg/kg) for intraoperative use in balanced anesthesia.[180] Twenty percent of the patients in the buprenorphine group required analgesic supplementation compared to 40% in the meperidine group, although recovery was quicker in the meperidine group.

Drug Discrimination, Abuse Liability, and Physical Dependence

Drug Discrimination. Drug discrimination studies are often used to determine if the properties of a test drug are similar to those of a known (control) drug. In these types of investigations, an individual is trained to discriminate the control drug and is subsequently exposed to varying doses of the test drug to determine its generalization of effects compared to the control. The greater the generalization to the control drug of abuse, the greater the likelihood for abuse.

A 2- or 3-choice procedure has been utilized in clinical laboratory studies to assess an individual's ability to discriminate buprenorphine from no drug (saline placebo), a mu-opioid agonist (e.g., hydromorphone), or a mu-opioid mixed agonist-antagonist (e.g., butorphanol, pentazocine, nalbuphine). In the 2-choice procedure, the subject is trained to recognize 2 drugs, or 1 drug versus placebo (saline), whereas in the 3-choice procedure, the subject is trained to recognize 3 drugs, or 2 drugs versus placebo.

Using the 2-choice procedure, 3 opioid agonist-antagonists (pentazocine, butorphanol, nalbuphine) and the partial agonist buprenorphine were discriminated as hydromorphone-like.[181] When varying doses of pentazocine and placebo were compared to varying doses of buprenorphine in a 3-choice procedure, buprenorphine was identified half the time as hydromorphone and half as pentazocine. No dose of buprenorphine generalized completely to pentazocine or hydromorphone.[182] These studies demonstrated that, although buprenorphine may be discriminated as hydromorphone when the only choice is between hydromorphone and saline, it must also share some discriminative stimulus properties of pentazocine because buprenorphine has also been identified as that drug.

In a 3-choice procedure, buprenorphine produced a subjective effects profile similar to hydromorphone, whereas nalbuphine produced

a profile more similar to, and was identified as, butorphanol.[183] Pentazocine was not found to be similar to either butorphanol or hydromorphone. In a variation of the 3-choice procedure where individuals were trained to discriminate between high- and low-doses of hydromorphone, nalbuphine generalized to low-dose hydromorphone, whereas buprenorphine produced 75% responding (partial generalization) to low-dose and 25% responding (slight generalization) to high-dose hydromorphone.[184]

The authors of the above two studies concluded that the effects observed with buprenorphine were consistent with a mu-opioid partial agonist because buprenorphine was discriminated as hydromorphone-like in both the 2- and 3-choice procedures. The observation that it was discriminated as both hydromorphone and pentazocine under a 3-choice procedure in which individuals were trained to discriminate pentazocine, hydromorphone, and saline can be explained by the fact that pentazocine has some mu-opioid-like activity. It can, therefore, be concluded from these studies that buprenorphine has a unique pharmacological profile that differs from mixed agonist-antagonists and that this profile is consistent with a mu-opioid partial agonist.

Abuse Liability. FDA Research Guidelines describe "abuse liability" as the "likelihood that a drug with psychoactive or central nervous system effects will sustain patterns of nonmedical self-administration that result in disruptive or undesirable consequences."[185] Psychoactive medications that produce elevations in the feeling of pleasure, euphoria, or mood may have potential for abuse. Individuals trained to recognize a mu agonist will identify buprenorphine as a mu agonist when it is the only choice they have. However, when these same individuals are exposed to a mixed agonist-antagonist, buprenorphine may be identified as a mixed agonist-antagonist and less often as a pure mu agonist. Taken together, these results indicate that buprenorphine likely has an abuse potential similar to the mixed agonist-antagonists. Buprenorphine appears to produce a maximal effect of euphoria similar to that of 20 mg of morphine/70 kg.[186] As the dose is increased, buprenorphine is associated with a plateau with regard to subjective and physiologic effects,[33,187,188] unlike full mu-opioid agonists. This ceiling effect may limit the abuse potential of buprenorphine.

Between 1994 and 2001, there have been 26 mentions of buprenorphine in the Drug Abuse Warning Network (DAWN) "Table of Estimates of Drug-Related Emergency Department Visits and Mentions."[189] There are a number of reports of buprenorphine abuse in the international literature; generally this abuse has been associated with ease of availability, lack of regulatory controls, and/or a decrease in availability of strong opioids. In the United States, buprenorphine is currently classified as a Schedule III substance under the Controlled Substance Act of 1970 and will be subject to regulatory controls appropriate to its abuse liability.

Physical Dependence. Buprenorphine has the capacity to produce physical dependence as assessed from behavioral and physiologic changes that occur following the withdrawal of the medication after prolonged administration of high (i.e., supra-analgesic) doses. The withdrawal syndrome has been associated mainly with reports of subjective discomfort but not autonomic signs. It has generally been reported to be mild to moderate in intensity (25% of the maximum possible withdrawal-scale score), and has appeared to follow the time course of short- as compared to long-acting opioids; namely, onset of 1 to 3 days, peak of 3 to 5 days, and duration of 8 to 10 days.[190,191] Although the slow receptor dissociation of buprenorphine would suggest that its withdrawal syndrome would be more similar to long-acting opioids, other factors, such as elimination half-life and intrinsic activity, also influence the observed time course.

Further evidence of buprenorphine's capacity to produce physical dependence has been demonstrated using a naloxone or naltrexone challenge test.[61,192] Qualitatively, the withdrawal syndrome observed in individuals maintained on high doses of buprenorphine is indistinguishable from that observed with a full mu-opioid agonist. However, quantitatively, the dose of naloxone or naltrexone needed to induce the withdrawal syndrome is 15 to 50 times greater than that required to precipitate withdrawal effects at a comparable dose of a full mu-opioid agonist. Results from these tests are consistent with buprenorphine being a partial agonist at the mu-opioid receptor with high affinity and low intrinsic activity.

Role of Buprenorphine in the Treatment of Depression, Schizophrenia, and Other Mental Disorders

The use of opioids for the treatment of depression and other psychiatric and behavioral disorders may date back to the earliest recognition of opium's therapeutic properties. However, concerns regarding the abuse potential and liability of dependence have limited therapeutic opioid use primarily to the areas of analgesia and opioid dependence. Studies have shown that buprenorphine may be effective for the treatment of depression[193–196] in patients who are nonresponsive to conventional therapy.[197,198] It is estimated that 10–30% of patients with major depressive symptoms are non-responsive to conventional therapy.[199] The antipsychotic effects of buprenorphine in the treatment of schizophrenia have also been evaluated and potential benefits have been observed.[200,201]

The prevalence of major depression in chronic pain patients may exceed 20%[202] and the occurrence of depression in patients referred for pain symptoms has been reported to be as high as 80%.[203] Buprenorphine could be a medication with potential utility in patients with a comorbid diagnosis of depression and pain; however, studies in this group of patients have not been reported.

Safety

Buprenorphine Alone

Buprenorphine is safe and well-tolerated when used as recommended for both analgesia (as demonstrated in over two decades of use) and for the treatment of opioid dependence; the current number of patients receiving treatment for opioid dependence is approaching 200,000 worldwide (personal communication; Chris Chapleo, PhD, Reckitt Benckiser, March 3, 2004). Preliminary data from a survey of 3,255 patients with chronic pain who had used a transdermal buprenorphine product available in Europe indicated that, although adverse events were similar to those observed with other opioids, the incidence was relatively low compared to these opioids.[162] Long-term use of buprenorphine administered as a transdermal system (mean exposure time 234 days, range 1–609 days) in approximately 400 patients with chronic pain in a clinical trial showed no unexpected safety concerns.[169]

Adverse events associated with buprenorphine, when used for either analgesia or addiction treatment, have been typical of opioids in general. These include constipation, headache, nausea, vomiting, sweating and dizziness, as well as respiratory depression, and changes in blood pressure and heart rate.[186,204–206] Buprenorphine, when given alone, can produce a dose-related increase in respiratory depression and sedation[207–210] to a maximal effect that is generally clinically nonsignificant. For example, although Gal and coworkers, utilizing a carbon dioxide rebreathing method, observed marked drowsiness and a 40–50% decrease in the slope of the carbon dioxide response following the administration of buprenorphine (0.3 mg/70 kg IV) to healthy volunteers, the authors did not report that any subjects were terminated from the trial for safety reasons, but did note (with reference to buprenorphine-induced sedation) that quiet sleep alone was previously reported to produce a 20% decrease in the slope of the carbon dioxide response.[208] Additionally, Walsh and colleagues reported that buprenorphine (given at a maximum dose of 32 mg sublingually to volunteers who were opioid-experienced but not physically dependent on opioids) maximally reduced respiratory rate by about 4 breaths per minute and reduced oxygen saturation by about 3% from the placebo condition of 98%; respiratory depression did not require medical intervention.[33]

One of the most recently reported investigations was a dose-ranging study involving 6 experienced opioid users without opioid dependence.[211] The study was conducted single-blind, double-dummy, with buprenorphine administered by both the intravenous (0 to 16 mg) and sublingual (0 and 12 mg) routes. The main adverse effects reported were sedation, mild irritability, nausea, and itching; 1 subject was discontinued from the study after the 12 mg IV dose secondary to severe nausea. The authors concluded that there was a ceiling for cardiac and respiratory effects and that buprenorphine had a high safety margin when administered by the intravenous route in the absence of other drugs.

If an overdose of buprenorphine is suspected and significant respiratory depression is observed, standard intravenous doses of an opioid

antagonist (e.g., naloxone or nalmefene) will not be effective in reversing the respiratory depression. In fact, doses of naloxone hydrochloride as high as 10–35 mg/70 kg may be required.[61,192] Buprenorphine is longer acting and binds more tightly to opioid receptors than naloxone or nalmefene. Thus, in cases of suspected buprenorphine overdose, the patient should be closely monitored and maintained with life support measures (e.g., artificial respiration), including multiple administrations of high-dose naloxone or nalmefene as needed to maintain respiration.

Dysphoric and psychotomimetic effects appear to be minimal, possibly because of the kappa antagonist properties of buprenorphine. It is possible for buprenorphine to precipitate an opioid abstinence syndrome in individuals heavily dependent on opioids. Therefore, buprenorphine should be given with caution to patients who are physically dependent on other opioids, and taking greater than or equal to the equivalent of 30 mg of oral methadone or 120 mg of parenteral morphine. The most serious adverse events, including death, have been reported when buprenorphine has been administered in combination with other CNS depressants, especially the benzodiazepines (see Buprenorphine Overdosage section, below). A number of studies have assessed subjective effects of buprenorphine in drug-nonabusing volunteers.[210,212,213] Analgesic doses of buprenorphine were associated with significant psychomotor impairment and subjective changes compared with pre-buprenorphine baseline.[212,213] Additionally, when administered intravenously, 0.3 mg of buprenorphine was associated with a greater magnitude of subjective and psychomotor impairing effects than an equianalgesic (10 mg) dose of morphine.[210] Compared to individuals maintained on a full agonist (e.g., methadone), individuals chronically maintained on buprenorphine appear to have less cognitive-motor impairment as measured by psychomotor performance and driving ability.[214] Increases in aminotransferase (AST and ALT) levels have been reported in clinical trials assessing buprenorphine for addiction treatment.[204,215] Further, hepatoxicity has been reported in large overdoses and individuals misusing buprenorphine parenterally[216,217] and 53 cases of buprenorphine-associated cytolytic hepatitis have been reported in France since buprenorphine was introduced as a treatment for opioid dependence in 1996.[218] However, adverse hepatic effects have not been reported for individuals receiving buprenorphine in analgesic dose ranges.

Buprenorphine Overdosage

Most reports of buprenorphine overdosage have involved the inappropriate use (e.g., crushing and injection of sublingual preparations) of high-dose buprenorphine for the treatment of opioid dependence, and have occurred in combination with other central nervous system depressants (e.g., benzodiazepines). Reports from the United States have been limited primarily to those from clinical investigations. Effects have included respiratory depression (with a ceiling) at doses between 8 and 16 mg of the sublingual solution,[33] and severe nausea and vomiting following rapid intravenous buprenorphine infusion of 0.3 mg/70 kg.[219]

There have been only a few case reports of buprenorphine (alone) overdoses outside the United States, and only 2 of these were fatal. The cause of death in these cases was ascribed to Mendelson's Syndrome (acute aspiration of gastric contents), with reported blood buprenorphine concentrations of 0.8 ng/mL and 3.1 ng/mL.[220] Other reports included cases of cutaneous complications following injection of crushed tablets,[221] myocardial infarction following insufflation,[222] and respiratory depression[211,223] in which individuals made a full recovery.

In France, buprenorphine is the predominant medication used to treat opioid dependence, with approximately 100,000 patients in treatment (personal communication: Chris Chapleo, PhD, Reckitt Benckiser, March 3, 2004). Primary care physicians prescribe buprenorphine with minimal regulatory restrictions. This wide availability and limited regulatory control has provided an opportunity to assess the overall safety of buprenorphine. There have been a number of reports of fatal overdoses associated with buprenorphine since its introduction in France for use in the treatment of opioid dependence.[220,224,225] The report by Tracqui and coworkers[225] totaled 20 fatalities. Another report described 117 buprenorphine-associated fatal overdoses between January 1996 and May 2000.[220] All of these 137 reported cases associated with buprenorphine

recently have been reviewed.[226] Most of these fatal overdoses were associated with the concomitant use of psychotropics or CNS depressants, especially benzodiazepines. The majority of these deaths occurred when buprenorphine tablets were crushed and injected intravenously along with another drug. An additional report compared the number of deaths associated with buprenorphine ($n = 27$) and methadone ($n = 19$) between 1994 and 1998.[224] The low number of deaths reported by Auriacombe and colleagues probably reflects fewer patients in treatment for opioid dependence between 1994 to 1998 compared to 1996 to 2000.

Reversal of Buprenorphine Effects with Naloxone, Nalmefene, or Naltrexone

Currently, there are 2 (naloxone and nalmefene) opioid antagonists approved by the FDA for the treatment of acute opioid overdose. Naloxone was the first approved and is a short-acting antagonist with high affinity for the mu-opioid receptor. Naloxone reverses multiple actions of opioids, including respiratory depression. It is essentially without intrinsic activity, including respiratory or cardiovascular effects.[227] When naloxone is administered to an opioid dependent person, it will precipitate an acute opioid withdrawal syndrome and will reverse signs and symptoms of acute opioid overdose, including respiratory depression, sedation, and hypotension. At doses of 0.4 to 0.8 mg given parenterally, it begins to reverse the manifestations of opioid overdosage within 2 minutes. Because naloxone competes with the opioid agonist for receptor binding sites, the dose required to treat overdosage depends on the opioid taken and the severity of intoxication. Larger doses may be necessary in certain circumstances (see Buprenorphine Alone section, above). The duration of naloxone action is between 1 and 4 hours depending on dose and route of administration. The difference in onset and duration of naloxone's actions on the respiratory depressant effect of buprenorphine compared to a mu-agonist (e.g., morphine) is striking. Studies have shown that naloxone doses ranging from 5 to 12 mg are required to reverse the respiratory depressant effects of buprenorphine in the analgesic therapeutic dose range.[208,228,229] The effects of naloxone were delayed for 30 to 60 minutes and extended for up to 3 to 6 hours. Naloxone may need to be given in repeated doses when treating an overdose induced by a long-acting opioid such as buprenorphine. Further, because of the short duration of naloxone effect, patients should be observed even after apparent recovery. No adverse effects of naloxone have been observed in cases of acute opioid intoxication, and parenteral doses of 24 mg/70 kg and oral doses as high as 3000 mg have been given without incident.[230] However, in some cases, naloxone may not be effective in reversing the respiratory depression produced by buprenorphine. Thus, the primary management of overdose should be the reestablishment of adequate ventilation with mechanical assistance of respiration, if required.[2,231]

Nalmefene is also approved to treat opioid overdose and for reversal of postoperative opioid effects. After intravenous administration, the onset of action is within 2 minutes and peak effect occurs in 5 minutes. Nalmefene and naloxone are equipotent, but nalmefene has a longer duration of action.[232] However, multiple doses may still be necessary.

Naltrexone is another mu-opioid antagonist. It is approved in the United States as an oral medication for the treatment of opioid and alcohol dependence. It is not approved for the treatment of opioid overdose, although there are reports of its utility for methadone overdose treatment.[233,234] When compared to parenteral naloxone, oral naltrexone produced equivalent dose-dependent opioid-withdrawal effects in buprenorphine-maintained individuals.[61]

Buprenorphine with Medications Used Therapeutically

Increased respiratory and central nervous system depression may occur when buprenorphine, like other opioids, is combined with other CNS depressant medications. These medications may include other opioid analgesics, general anesthetics, various sedatives and hypnotics (including benzodiazepines), antihistamines, and other drugs.[235–239] For example, in a study of 12 patients undergoing cholecystectomy, buprenorphine was administered preoperatively at a dose of either 30 or 40 µg/kg intravenously.[240] Pre- and intra-operative medications included diazepam, thiopentone, pancuronium, suxamethonium, and nitrous oxide. The respiratory rate fell below 8 breaths per minute in one-half of the patients 15 minutes

following buprenorphine administration. A significant decrease in arterial pH and increase in $PaCO_2$ were observed postoperatively in the 40 compared to 30 μg/kg group.

Clinically, buprenorphine functions as a potent mu-opioid agonist analgesic at low doses, but at high doses has been shown to have a maximal opioid effect that is less than would be expected of a full mu-opioid agonist. As a result, buprenorphine may precipitate a withdrawal syndrome in individuals who are highly tolerant to, and dependent on, other opioids. It is unlikely, however, that buprenorphine will antagonize or reverse the agonist effects of chronically administered opioids at dosages equivalent to less than 120 mg/day of parenteral morphine, or 30 mg/day of oral methadone. In opioid-dependent individuals stabilized on 60 mg/day of intramuscularly given morphine, buprenorphine 2 mg (administered intravenously) failed to reverse morphine effects with regard to various physiologic, subjective, and observer-rated measures.[241,242] Further, buprenorphine 6 mg (given intramuscularly) failed to antagonize morphine-associated effects in individuals treated chronically with intramuscular morphine in dosages of up to 120 mg/day.[243] Similar studies have been conducted in individuals maintained on 30 and 60 mg of methadone daily[209,244,245] and challenged with buprenorphine in the dose range of 0.5 to 8 mg (given intramuscularly) or 2 to 8 mg (given sublingually). At the 30 mg methadone dose level, buprenorphine was associated with opioid-withdrawal effects when administered 2 hours after the methadone dose but not when administered 20 hours after methadone dosing. At the 60 mg methadone dose level, buprenorphine was associated with opioid-withdrawal effects when administered 40 hours after the methadone dose. Thus, although buprenorphine may antagonize some of the effects of morphine or other opioid agonists, this potential effect is dependent on at least 3 factors: dose of buprenorphine, dose of the other opioid, and the time interval between the administration of the 2 medications.

It is important to note the possibility of a drug interaction between buprenorphine and certain HIV-1 protease inhibitors, especially because buprenorphine may be used in the management of AIDS-associated pain (and the treatment of opioid addiction) in individuals receiving these inhibitors. As discussed earlier, buprenorphine is metabolized by cytochrome P-450 3A4. A study utilizing human liver microsomes indicated that ritonavir, indinavir, and saquinavir competitively inhibited the metabolism of buprenorphine;[246] the most potent inhibitor was ritonavir. A recent investigation also gave a preliminary indication that the use of buprenorphine (at higher than analgesic doses) in HIV-infected drug users had no major, short-term influence on HIV viral load in individuals receiving highly active antiretroviral therapy.[247]

Although data are limited, there may also be a potential for a buprenorphine interaction with other drugs and compounds that induce or inhibit the cytochrome P-450 3A4 system. There are many agents in this category and they include erythromycin, zileuton, and grapefruit juice (inhibitors), as well as carbamazepine, phenobarbital, phenytoin, and rifampin (inducers). In an *in vitro* study of the effects of the selective serotonin reuptake inhibitors fluoxetine and fluvoxamine, the demethylated metabolite of fluoxetine (norfluoxetine) and fluvoxamine, but not fluoxetine, were both shown to inhibit buprenorphine dealkylation.[248]

Buprenorphine with Abused Drugs

Some of the therapeutic drugs that have the potential to interact with buprenorphine may also be used as drugs of abuse (e.g., opioids, benzodiazepines). When abused, these drugs are often used in larger amounts and for longer periods of time then when used therapeutically. The abuse or therapeutic use of buprenorphine in combination with drugs that are more often abused than used therapeutically, such as cocaine, could also raise concerns regarding a potential for increased toxic effects secondary to the combined use of both drugs. Interestingly, a preclinical study revealed that buprenorphine (0.3 to 3.0 mg/kg intraperitoneally) protected against the lethal effects of cocaine-induced convulsions in mice.[249] Cocaine (75 mg intraperitoneally) produced convulsions in all mice and lethal convulsions in 75% of the animals. Buprenorphine pretreatment significantly attenuated lethality, even though cocaine-induced convulsions were equivalent in buprenorphine-treated and vehicle-pretreated mice. This effect appeared to be mediated by the mu-opioid agonist actions of buprenorphine

because pretreatment with low doses of intraperitoneal naltrexone (0.3 to 1.0 mg/kg) antagonized the protective effect of buprenorphine. Another preclinical evaluation using lower intraperitoneal doses of buprenorphine also indicated that buprenorphine pretreatment was associated with an increased LD_{50} for cocaine in mice.[250] Other studies in animals indicated that buprenorphine may enhance some effects of cocaine (e.g., turning in rats), whereas other effects may be attenuated.[251–253]

A clinical laboratory evaluation assessed the safety of buprenorphine alone and in combination with cocaine and morphine.[254] The physiological effects of a single-blind challenge dose of cocaine (30 mg), morphine (10 mg), and saline placebo, all given intravenously, were assessed before and during maintenance of patients on 4 or 8 mg daily of sublingual buprenorphine solution. This dosage of buprenorphine is higher than that used for analgesia but typical of dosages that have been used for opioid addiction treatment. Cardiovascular responses to cocaine and morphine were equivalent under buprenorphine-free and maintenance conditions. The same was observed for respiration and temperature changes in response to cocaine, and morphine was associated with nonstatistically significant lower respiratory rates. These data suggested that daily maintenance on buprenorphine was not associated with adverse effects or toxic interactions with single doses of intravenous cocaine or morphine.

Most of the deaths associated with buprenorphine exposure have been in combination with other drugs, and have been associated with high-dose sublingual tablets (those used for the treatment of opioid dependence) taken by various routes of administration, primarily massive oral or intravenous administration.[226] A majority of the deceased individuals were reported to be addicts.[220,225,255–258] Postmortem buprenorphine plasma concentrations were typically provided in the reports without an estimate of the buprenorphine dose ingested. Although in most cases buprenorphine concentrations in the blood were under 30 ng/mL, in one case a blood buprenorphine concentration of 3300 ng/mL was observed.[258] The most frequently reported concomitant drugs found were benzodiazepines, including clorazepate dipotassium, oxazepam, flunitrazepam, and diazepam; sometimes more than one benzodiazepine was reported. Other drugs found in combination with buprenorphine included morphine and ethanol. Although the precise role of the other drugs in combination with buprenorphine cannot be determined, their ability to produce respiratory depression suggested a pharmacodynamic interaction. While pharmacokinetic interactions cannot be ruled out, a study assessing the possible interaction of buprenorphine with flunitrazepam metabolism argues against a pharmacokinetic interaction.[259] Although both compounds are metabolized by the cytochrome P-450 3A4, the estimated inhibition of buprenorphine N-dealkylation by flunitrazepam *in vivo* was only 0.08%, and the projected buprenorphine inhibition of flunitrazepam metabolism was 0.1–2.5%.

Factors Associated with Buprenorphine Abuse

The first published report of injectable buprenorphine abuse came from New Zealand.[260] Buprenorphine abuse is more frequently observed in individuals already experienced in the use of heroin and other opioids. Buprenorphine is rarely the drug by which opioid abuse is initiated. Where buprenorphine abuse has been reported, buprenorphine is often obtainable at a lower cost, with easier availability, and with a higher and more consistent purity than heroin.[261–265] Because of the extensive first-pass hepatic metabolism, abuse of buprenorphine by the oral route is unlikely. Buprenorphine solutions for parenteral administration would likely be the most desirable based on ease of administration. Buprenorphine tablets could be misused "as is" sublingually, but would require manipulation to effect them suitable for parenteral abuse. Buprenorphine in combination with naloxone apparently has less abuse potential than buprenorphine alone; buprenorphine with naloxone was reportedly less desirable to abusers than buprenorphine alone.[146] Buprenorphine and the buprenorphine/naloxone combination were approved for the treatment of opioid addiction in the United States in October 2002.[14]

The abuse liability of transdermal buprenorphine relative to other forms of buprenorphine

should be considered for 2 populations: 1) patients who use the medication as directed, and 2) substance abusers who may divert and/or misuse the product. When used as directed for analgesia, abuse of transdermal buprenorphine would be limited by the relatively low plasma concentrations achieved, and by the slow rise and fall of these concentrations. A study by Becker and colleagues indicated that transdermal buprenorphine resulted in fewer, less intense and delayed opioid effects, including objective effects (decreases in pupil diameter), subjective effects (general drug effect, drug liking, heroin feeling) and cognitive effects (digit symbol substitution tests), and thus a lower abuse potential than intramuscular buprenorphine.[266] In fact, transdermal buprenorphine produced few significant differences from placebo. The potential that buprenorphine from the transdermal product will be abused by people with addictive disorders was not fully assessed by this study. Nonetheless, abuse of a transdermal product could occur through excessive use of the intact dosage form, through chewing or other methods of altering the dosage form to increase absorption, or through buprenorphine extracted from the system for the purpose of parenteral misuse. However, data from France, where buprenorphine is widely available from general practitioners as sublingual tablets for the treatment of opioid addiction, show a substantially lower death rate associated with buprenorphine compared with methadone.[224] This is consistent with the wider margin of safety in overdose due to the partial agonist activity of buprenorphine.

Summary

Opioid analgesics are the primary therapeutic agents used for moderate to severe pain. In the past, clinicians have often been reluctant to prescribe opioids, especially in high doses. This reluctance was generally based on concern that an "addict" would be created through iatrogenically induced physical dependence. This concern is generally unfounded;[267] rather, pseudoaddiction (an iatrogenic syndrome of abnormal behavior developing as a direct consequence of inadequate pain management) may be of more importance. Contributing factors include prescribing of less than adequate doses of analgesics, increased demand for analgesics by the patient, and deterioration of the doctor-patient relationship.[268]

Chronic pain patients may be more difficult to manage than those in acute pain due to secondary medical and psychiatric disorders related not only to the disease but also to disease treatment. The goal in providing effective therapy should be to eliminate or reduce the pain, to improve the patient's quality of life, and to minimize medication side effects. These goals may be better achieved through the use of longer-acting medications or dosage forms that will provide for more stable analgesic plasma levels, increased patient compliance, and minimal adverse events, and that will also provide better pain control with less risk for physical and psychological dependence. The physiochemical characteristics and pharmacological profile of buprenorphine make it an excellent medication for the treatment of both acute and chronic pain utilizing a variety of different delivery systems, including the transdermal delivery system.

In man, the primary activity of buprenorphine is as a mu-opioid partial agonist and a kappa-opioid antagonist. Buprenorphine is indicated for the treatment of moderate to severe pain. It is not administered orally secondary to extensive first-past metabolism. Typical dosages are 0.2 to 0.4 mg (sublingually) or 0.3 to 0.6 mg (parenterally) every six hours. A 72-hour transdermal product designed to continuously release buprenorphine at either 35, 52.5, or 70 µg/hr is available in Europe. Another transdermal formulation is under development in the United States. Buprenorphine has also been used by other routes of administration (e.g., intra-articular and for sympathetic nerve blocks).

Common side effects following buprenorphine administration may include sedation, nausea and/or vomiting, dizziness, and headache. Respiratory depression may occur and may not be responsive to treatment with naloxone; however, as a mu-opioid partial agonist with a demonstrated ceiling on respiratory depression, buprenorphine may have a better safety profile compared to full mu agonists.

Buprenorphine also has the potential to be abused and should be used cautiously in individuals with a past or current history of substance abuse or dependence. Buprenorphine

produces opioid-like subjective and physiologic effects. The level of effect is limited and dependent on the dose and route of administration. The greatest potential for abuse, however, may be through the diversion of buprenorphine into illicit channels. How significant this diversion may be will be dependent on numerous factors, including general medication availability, the amount of regulatory control over buprenorphine, and the general availability (or lack thereof) of other, more-preferred opioids. Overall, buprenorphine is a highly effective analgesic for the treatment of moderate to severe pain. It has a unique pharmacological and physiochemical profile allowing for relatively safe use, and flexibility with regard to dosage and dosage forms. Nonetheless, buprenorphine has not been as extensively studied in certain populations (e.g., in individuals suffering from pain of malignant origin) as other opioid analgesics and additional research is needed to better define the role for buprenorphine in various patient subpopulations.

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Effects of Intravenous Patient-Controlled Analgesia With Buprenorphine and Morphine Alone and in Combination During the First 12 Postoperative Hours: A Randomized, Double-Blind, Four-Arm Trial in Adults Undergoing Abdominal Surgery

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ABSTRACT

Background: Intense pain in the first 12 hours after major abdominal surgery requires the use of large amounts of analgesics, mainly opioids, which may produce undesirable effects. Buprenorphine (BUP) is not typically used intravenously in this setting, particularly in combination with morphine (MO), due to concerns that BUP might inhibit the analgesic effect of MO.

Objective: This study compared the analgesic effect of BUP and MO separately and in combination for postoperative pain control in patients undergoing abdominal surgery.

Methods: In this double-blind study, adult patients were randomized to receive 1 of 4 regimens for 12 hours: a basal BUP infusion (BUP-i) of 0.4 μg/kg/h + BUP boluses (BUP-b) of 0.15 μg/kg each; a basal MO infusion (MO-i) of 10 μg/kg/h + MO boluses (MO-b) of 5 μg/kg each; a basal BUP-i of 0.4 μg/kg/h + MO-b of 5 μg/kg each; or a basal MO-i of 10 μg/kg/h + BUP-b of 0.15 μg/kg each. Bolus doses were delivered by intravenous patient-controlled anesthesia, with a bolus lockout time of 7 minutes. Diclofenac 75 mg IM q6h was available as rescue pain medication. Every 15 minutes during the first 2 postoperative hours and hourly thereafter, patients used visual analog scales to rate their pain (from 0 = totally free of pain to 10 = unbearable pain), level of sedation (from 1 = totally awake to 10 = heavily sedated), and satisfaction with treatment (from 1 = totally unsatisfied to 10 = fully satisfied). Blood pressure, heart rate, respiration rate, and arterial blood oxygen saturation (SpO_2) were monitored, and adverse effects reported by patients or noted by clinicians were recorded at the same times. Study end points included total opioid consumption (infusion + boluses), demand:delivery ratio, and use of rescue medication.

Results: One hundred twenty patients (63 men, 57 women; age range, 21–80 years; weight range, 40–120 kg) were included in the study. Seventy-four percent had other mild, treated diseases (American Society of Anesthesiologists physical class 2). Pain visual analog scale ratings were comparably high in all groups during the first 2 postoperative hours. Pain intensity ratings at 3 to 12 hours were significantly lower in those who received BUP-i + BUP-b compared with the other treatment groups ($P = 0.018$). The drug requirement during the postoperative period decreased significantly in all groups ($P = 0.01$); however, there was a significant difference between groups in the demand:delivery ratio at 3 to 12 hours (group *

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drug interaction, $P = 0.026$). The numerically lowest demand:delivery ratio was seen with BUP-i + BUP-b. BUP-i was associated with a significantly lower heart rate compared with the other groups ($P = 0.027$); there were no drug-related differences in respiration rate, SpO_2, or sedation. Patients' level of satisfaction with treatment was significantly higher in the group that received BUP-i + BUP-b compared with the other 3 groups ($P < 0.001$). Postoperative nausea and vomiting were mild and occurred at a similar incidence in all groups, as did rescue diclofenac use.

Conclusions: In these patients undergoing abdominal surgery, the BUP-i + BUP-b regimen controlled postoperative pain as well as did MO-i + MO-b or the combinations of BUP and MO. BUP neither inhibited the analgesia provided by MO nor induced undesired sedation or hemodynamic or respiratory effects. (*Clin Ther.* 2009;31:527–541)

Key words: pain, postoperative, morphine, buprenorphine, IV PCA, infusion, bolus.

INTRODUCTION

Intravenous patient-controlled analgesia (IV PCA) enables optimal control of postsurgical pain and is associated with high levels of patient satisfaction, wakefulness, and cooperation.[1] Morphine (MO) is the most commonly used agent in IV PCA protocols. However, the opioid adverse effects associated with MO (eg, sedation, respiratory depression, pruritus, nausea and vomiting) continue to pose a problem.[2]

Buprenorphine (BUP) is a semisynthetic, highly lipophilic opioid derived from thebaine. It partially agonizes the μ-opioid and opioid receptor–like 1 receptors and fully antagonizes the κ- and δ-opioid receptors.[3–7] BUP has higher affinity for—and thus stronger binding to—μ-opioid receptors than for other opioid receptors; however, it has lower intrinsic activity than do full μ-opioid–receptor agonists such as MO, whereas its drug–receptor dissociation rate is comparatively slower.[8,9] BUP is considered 25 to 50 times more potent than MO,[10] and BUP 0.3 to 0.4 mg (administered intramuscularly or intravenously) is considered equianalgesic to MO 10 mg.[11] The most important adverse effects reported with BUP administered intermittently by the intravenous or intramuscular route or by continuous intravenous infusion are respiratory depression, sedation, and hemodynamic instability.[12] Escalating BUP doses have been reported to induce tolerance to BUP and cross-tolerance with MO in rats.[13]

These pharmacologic properties have led to concerns about a possible interaction between BUP and other μ-opioid–receptor agonists or antagonists[14–16] and hence reluctance to use BUP as a postoperative analgesic, even though these concerns have not been supported by substantial prospective clinical data.[17] In clinical studies, concomitant administration of intrathecal MO (4.3 μg/kg) and intravenous BUP (1.3 μg/kg) was associated with a prolonged antinociceptive state, and 46% fewer untoward effects were reported with the combination than with either agent alone.[18,19] These results contradicted earlier claims that coadministration of MO and BUP would inhibit the antinociceptive effects of the individual agents.[20] To date, there appear to be no randomized prospective studies in the literature that have compared the analgesic effect of BUP and MO alone or in combination as an option for IV PCA for postoperative pain control.

The present study compared the analgesic effect of BUP and MO separately and in combination for postoperative pain control. It was hypothesized that because of its higher receptor potency relative to MO, BUP would provide good analgesia (primary goal) with an acceptable adverse-effect profile (secondary goal) when administered in combination with MO via IV PCA at doses lower than those administered previously (MO 5 mg + BUP 0.15 mg [first bolus] and 1.2 mg + 0.04 mg [subsequent boluses], respectively).[20]

PATIENTS AND METHODS

Inclusion and Exclusion Criteria

The study enrolled patients who were scheduled for major abdominal surgery at the Tel Aviv Sourasky Medical Center during 2006. Eligible patients were aged 18 to 80 years and were undergoing gastrectomy, large bowel resection, or partial pancreatectomy. Candidates were approached during the preoperative anesthesia examination and were given a full explanation of the study's aims, the study medications, and the IV PCA device. Consenting patients provided written informed consent. The study protocol and informed-consent form were approved by the institutional review board.

Exclusion criteria included a history of drug or alcohol abuse, psychiatric disturbance, senile dementia, Alzheimer's disease, seizures, suicide risk, use of psy-

chotropic drugs, and hypersensitivity to BUP, MO, NSAIDs, or their excipients. Patients receiving antidepressants, anticonvulsants, or muscle relaxants were excluded, as were those who had taken a monoamine oxidase inhibitor within 2 weeks of surgery. Also excluded were patients with chronic or acute pain of any origin, respiratory failure or insufficiency, uncompensated or congestive heart failure or hepatic failure, and those scheduled for an emergency or palliative procedure. A pregnancy test was performed at screening in all premenopausal women; women who were pregnant or nursing were excluded.

Anesthesia and Surgery Management

Anesthesia and surgery were performed by the same team, although intraoperative care was not controlled. All patients were premedicated with oral diazepam 10 mg the night before and 40 to 75 minutes before surgery. Within 1 to 2 minutes after intravenous administration of a sedative dose of midazolam (1.5–2 mg) and fentanyl (1.5 μg/kg), propofol (1–2 mg/kg) was injected intravenously until the patient lost consciousness. A nondepolarizing muscle relaxant was administered to enable endotracheal intubation. All study patients were mechanically ventilated.

General anesthesia was maintained according to the institution's protocol using nitrous oxide/oxygen 2/1 L/min enriched with isoflurane, with the goal of delivering 1 minimal anesthetic concentration. The nondepolarizing muscle relaxant and fentanyl were infused continually or given by repeated doses to maintain muscle relaxation and analgesia, as well as hemodynamic and ventilatory stability. Standard perioperative monitoring included 5-lead electrocardiography and noninvasive measurement of systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate (HR), respiration rate (RR), end-tidal carbon dioxide concentration (when available), and arterial blood oxygen saturation (SpO_2), measured by fingertip pulse oximetry (AS/3 Compact Patient Monitor, Datex-Ohmeda, Helsinki, Finland). Intraoperative administration of fluids and blood replacement followed common cardiovascular, renal, and laboratory indices.

All intraoperative drugs were stopped toward the end of the procedure, and minimal doses of atropine and neostigmine were administered to reverse muscle relaxation and allow the return of spontaneous respiration. All patients were then transferred to the Post-Anesthesia Care Unit (PACU) for 24 hours of close observation.

Study Design

This was a prospective, randomized, double-blind trial. At the completion of surgery, a computer-generated list was used to allocate patients to receive 1 of 4 protocols (prepared by the hospital pharmacist) for 12 hours: a basal BUP infusion (BUP-i) of 0.4 μg/kg/h + BUP boluses (BUP-b) of 0.15 μg/kg each; a basal MO infusion (MO-i) of 10 μg/kg/h + MO boluses (MO-b) of 5 μg/kg each; a basal BUP-i of 0.4 μg/kg/h + MO-b of 5 μg/kg each; or a basal MO-i of 10 μg/kg/h + BUP-b of 0.15 μg/kg each (**Figure 1**). Bolus doses were delivered by IV PCA.

BUP,* which is approved for postoperative pain control in Europe but not in the United States, was donated by the manufacturer.

The dosages chosen for this study were based on previously reported pain control studies in which low doses of BUP (a 30-mg bolus every 5 minutes) provided satisfactory reduction or elimination of pain along with acceptable tolerability[11,21] compared with high doses (0.4 mg/70-kg bolus).[22,23] The lowest studied dose of BUP administered via IV PCA for the management of acute postoperative (laparotomy) pain was 85 μg (total) in the first hour, followed by 30 μg/h, which was reported to provide adequate pain control for the next 17 hours.[24] In a randomized trial in patients undergoing lumbar spinal fusion who received postoperative IV PCA (30 μg/bolus, with a 5-minute lockout time) without a continuous infusion,[11] the cumulative dose over the 6 consecutive hours of the study was 270 μg. In the present study, a smaller bolus dose of 10 μg/bolus (7-minute lockout time) was chosen, along with a basal infusion of 28 μg/h. The doses were divided into basal (infusion) and demand (bolus) portions on a body-weight basis to minimize the adverse effects of BUP, mainly respiratory depression, while providing adequate analgesia. The selected doses were also consistent with the previously reported pharmacologic relationship between MO and BUP.[6,25] MO was chosen as the comparator because it is the most commonly used agent in postoperative IV PCA.

Study Drug Administration

In the PACU, each patient was connected to an oxygen face mask and a vital signs monitor. At the first complaint of moderate to severe pain at rest

*Trademark: Temgesic Injection® (Reckitt Benckiser Healthcare Ltd., Hull, United Kingdom).

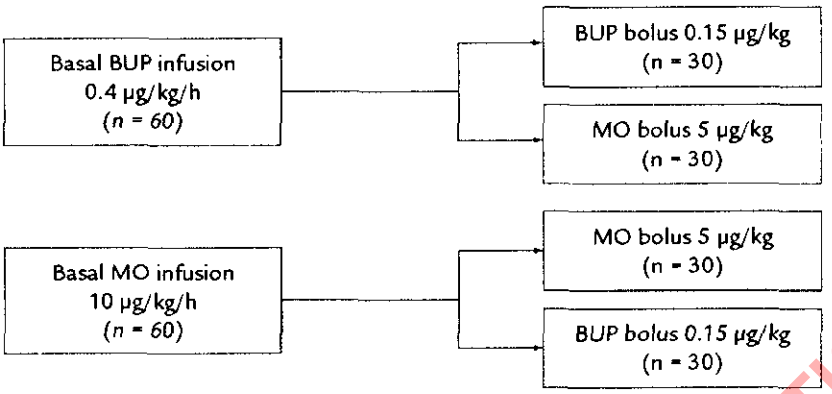

Figure 1. The 4 study protocols. BUP = buprenorphine; MO = morphine.

(5–10 on a visual analog scale [VAS]) and after the PACU attending physician, who was blinded to study-drug allocation, had established that the patient was coherent and cooperative, a PCA system consisting of 2 devices was connected to the patient's intravenous line. The physician started the basal infusion of the assigned drug, and the first bolus was administered 5 minutes later via the second device. Subsequent boluses were administered by the patient. A 7-minute lockout time after administration of each bolus prevented excessive dispensing of drug. The physician could administer 2 additional boluses (applying the specified lockout time) during the first postoperative hour if required for optimal pain control. Rescue diclofenac 75 mg IM could be administered once in the PACU to begin analgesia during the initial opioid titration; thereafter, it could be administered every 6 hours. No hourly dose limit was set on any of the 4 drug protocols. All patients were treated according to the study protocol for 12 hours, after which they received standard pain care in the relevant surgical department.

Patients were discontinued from the study if they required immediate postoperative artificial ventilation lasting over 4 hours, if they were incoherent or experienced continuous sedation (VAS rating ≥5–10), exhibited combative behavior in the PACU, or required postoperative reintervention and/or transfer to the intensive care unit. If a patient was discontinued from the study, another suitable patient was recruited. Patients who were discontinued because of a protocol violation, patient's decision, or ineffectiveness of study drug were not replaced.

Study Assessments

Every 15 minutes during the first 2 postoperative hours and hourly thereafter, patients used a VAS to rate their pain (from 0 = totally free of pain to 10 = unbearable pain), level of sedation (from 1 = totally awake to 10 = heavily sedated), and satisfaction with treatment (from 1 = totally unsatisfied to 10 = fully satisfied) (**Table I**). Blood pressure, HR, RR, and SpO_2 were monitored, and adverse effects reported by patients or noted by clinicians were recorded at the same times.

Statistical Analyses

The data were analyzed at the Statistical Laboratory of the School of Mathematics, Tel Aviv University, using SPSS for Windows version 14.01 (SPSS Inc., Chicago, Illinois).[26]

A prestudy power table in which δ (the mean 6- to 9-hour difference in pain score from a separate pilot study) was set at 1.8, α at 0.05, and power at 0.95 determined a need for a minimum of 15 patients per group. Concomitant analysis of pain VAS ratings and PCA use required a minimum of 25 patients. Demographic data (age, weight), baseline clinical characteristics (HR, RR, SpO_2, SBP, DBP), American Society of Anesthesiologists physical class, duration of surgery, and intraoperative fentanyl use were compared using 1-way analysis of variance (ANOVA). Sex was ana-

Table I. Components of the efficacy and safety evaluations.

Parameters	Mode of Measurement
Efficacy	
Patient-rated pain	VAS from 0 = totally free of pain to 10 = unbearable pain
Patient-rated sedation	VAS from 1 = totally awake to 10 = heavily sedated (patient was awakened if sleepy; if not rousable, no data were recorded at that time point)
Patient-rated satisfaction with treatment	VAS from 1 = totally unsatisfied to 10 = fully satisfied
Total opioid consumption	Infusion + boluses
PCA demand:delivery ratio	Ratio
Rescue medication use	Request for diclofenac 75 mg IM
Safety/tolerability	
Hemodynamic/respiratory parameters	Blood pressure, heart rate, respiration rate, SpO_2 (fingertip pulse oximetry)
Adverse-effect rate	Hourly questioning of patient, medical staff notes

VAS = visual analog scale; PCA = patient-controlled analgesia; SpO_2 = arterial blood oxygen saturation.

lyzed using the Pearson δ test. Hourly activation of the IV PCA device was analyzed by repeated-measures 1-way ANOVA. Patient-rated pain, levels of sedation and satisfaction (VAS), and amounts of analgesics administered hourly were also analyzed using repeated-measures ANOVA; their means were then compared using the *t* test and analyzed using log values because of nonnormal distribution. Total 12-hour drug consumption was analyzed using 1-way ANOVA. Rates of adverse effects were analyzed using the Pearson χ^2 test. The ANOVA tests were always followed by the post hoc Tukey Honest Significant Difference test. Correlations between factors were analyzed using the Pearson correlation (2-tailed). Significance was set at $P \leq 0.05$.

RESULTS

Of the 126 patients originally screened, 6 were excluded. Thus, 120 surgical patients (30 per arm; 100% white) were randomized to treatment, all of whom completed the study (**Figure 2**). There were no significant differences between groups with respect to the distribution of types of major abdominal surgery (data not shown), demographic or clinical characteristics, or intraoperative data (**Table II**). Vital signs and patient-rated pain, sedation, and satisfaction were similar in all groups before connection of the IV PCA device. All patients were coherent before starting the study.

Drug Use

The amount of drug delivered by infusion was weight dependent, so the amount of BUP infused was similar in both BUP-i groups and the amount of MO infused was similar in both MO-i groups. The mean total amounts of opioid (infusion + bolus) delivered in the first 2 hours after surgery in the 2 single-drug protocols were 2-fold those delivered over 3 to 12 hours after surgery ($P < 0.03$). Although the difference was not statistically significant, the amounts of BUP delivered by bolus were 33% lower in patients assigned to the BUP-i + BUP-b protocol compared with the MO-i + BUP-b protocol; the amounts of MO delivered by bolus were also numerically lower in patients assigned to the BUP-i + MO-b protocol compared with the MO-i + MO-b protocol (**Table III**).

The demand:delivery ratios at 3 to 12 hours were significantly different between groups (group * drug interaction, $P = 0.026$) (**Table III**). The BUP-i + BUP-b protocol was associated with a numerically lower ra-

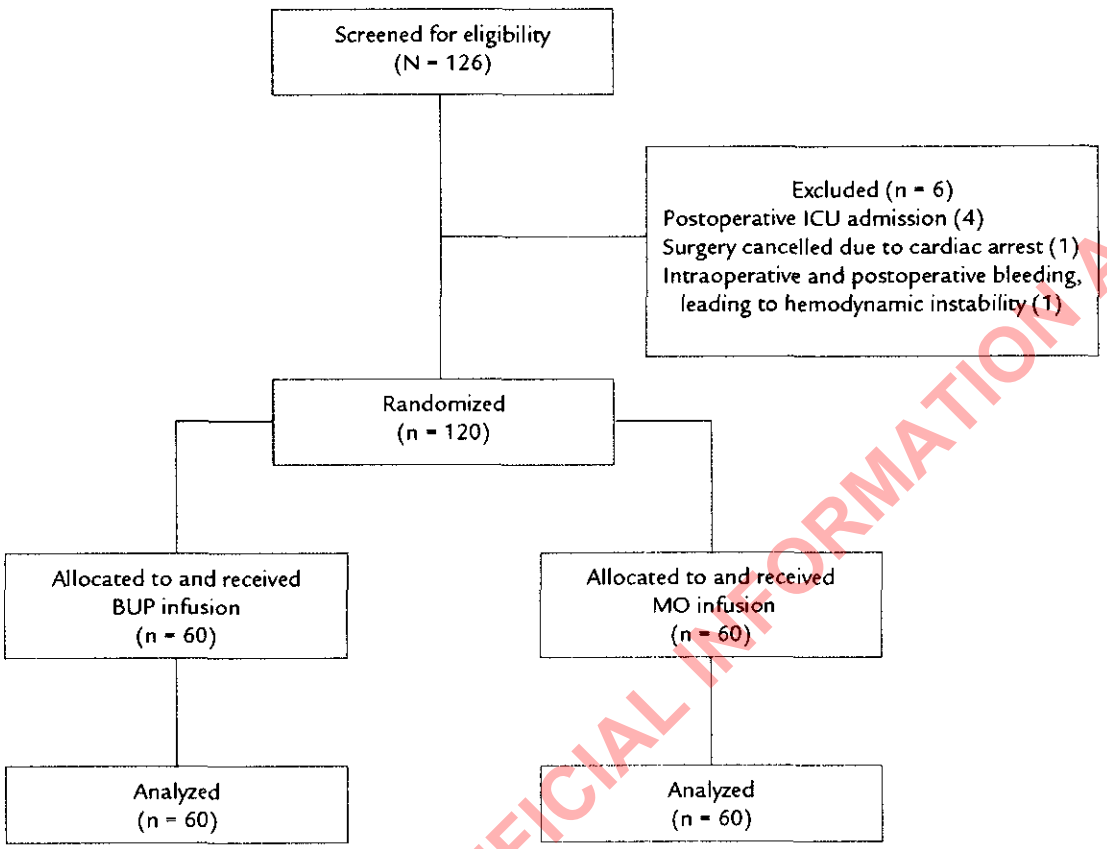

Figure 2. CONSORT diagram. ICU = intensive care unit; BUP = buprenorphine; MO = morphine.

tio than all other protocols. Finally, the equipotency of the total amount of the 2 drugs (infusion + bolus) was 1:30 in the first 2 hours and 1:33 in the next 10 hours. The ratio between the cumulative BUP bolus dose administered in the MO-i + BUP-b group and the cumulative MO bolus dose administered in the BUP-i + MO-b group was 1:30. The overall 4-arm equipotency was 1:32.

Approximately 70% of patients received diclofenac during the first 2 hours in the PACU; thereafter, 3% to 13% of the patients requested a second dose of diclofenac. There was no significant difference in diclofenac use between the 4 groups (Table III).

Pain Evaluation

During the first 2 hours in the PACU, pain VAS scores were similarly high (≥5) in the 4 groups. Pain VAS values demonstrated a group * time interaction at 3 to 12 hours after surgery ($P < 0.001$) (Figure 3). Specifically, pain ratings were significantly lower in patients who received BUP-i compared with those who received MO-i ($P = 0.018$). BUP-b was associated with numerically better pain ratings when combined with BUP-i rather than MO-i (Figure 4). Pain VAS ratings were significantly lower in the group that received BUP-i + BUP-b ($P = 0.04$).

Age was associated with significant differences in pain VAS ratings among all treatment groups. Those aged >65 years rated their pain ~33% lower than did younger patients in each group ($P = 0.006$). The group * time interaction noted earlier also applied to the age subgroups ($P = 0.011$).

Sedation and Satisfaction

Patient-rated sedation improved steadily and similarly among the 4 groups over the course of the study.

Table II. Demographic, anesthesia and surgery, and baseline clinical characteristics of the study population.

Characteristic	BUP-i + BUP-b (n = 30)	MO-i + MO-b (n = 30)	BUP-i + MO-b (n = 30)	MO-i + BUP-b (n = 30)	*P* (ANOVA)
Age, mean (SD), y	61.6 (10.2)	63.1 (15.2)	61.0 (13.2)	64.4 (9.5)	0.70
Weight, mean (SD), kg	73.3 (18.2)	69.8 (12.5)	67.9 (13.5)	70.2 (12.8)	0.54
Age group, no. of patients					0.33
≤65 y	15	16	15	12	
65–80 y	15	14	15	18	
Sex, no. of patients					0.76
Male	18	15	14	16	
Female	12	15	16	14	
ASA physical class, no. of patients					0.76
1	4	4	2	2	
2	22	20	22	25	
3	4	6	6	3	
Type of surgery, no. of patients					0.09
Small/large bowel resection	16	21	16	19	
Gastrectomy	8	6	6	4	
Pancreatectomy	6	3	8	7	
Intraoperative fentanyl, mean (SD), μg/patient	423.3 (169.0)	463.3 (216.5)	446.7 (227.9)	444.2 (226.4)	0.91
Surgery time, mean (SD), min	186.5 (92.4)	208.5 (103.0)	164.2 (69.7)	192.3 (90.0)	0.29
Baseline vital signs, mean (SD)					
Heart rate, beats/min	74.2 (11.9)	73.7 (10.9)	79.4 (10.6)	77.4 (10.9)	0.16
Respiration rate, breaths/min	15.3 (2.7)	14.9 (2.6)	15.4 (2.9)	14.9 (2.2)	0.82
Systolic blood pressure, mm Hg	137.3 (21.2)	140.9 (20.4)	139.7 (28.1)	133.4 (20.5)	0.63
Diastolic blood pressure, mm Hg	77.8 (8.9)	75.4 (12.5)	74.5 (13.7)	74.1 (10.9)	0.64
SpO_2, %	96.7 (2.0)	97.2 (1.6)	97.1 (2.0)	97.1 (2.0)	0.77

BUP-i = buprenorphine infusion; BUP-b = BUP bolus; MO-i = morphine infusion; MO-b = MO bolus; ANOVA = analysis of variance; ASA = American Society of Anesthesiologists; SpO_2 = arterial blood oxygen saturation.

Table III. Use of study drug and rescue medication, level of sedation, hemodynamic and respiratory parameters, and postoperative nausea and vomiting (PONV).

Characteristic	BUP-i + BUP-b	MO-i + MO-b	BUP-i + MO-b	MO-i + BUP-b	*P* (ANOVA)
Opioid amount (infusion + bolus), μg/70 kg*					
First 2 h			–	–	–
Mean (SD)	98 (43)	3065 (1443)			
Range	43–217	889–5354			
3–12 h			–	–	–
Mean (SD)	45 (29)†	1825 (941)†			
Range	23–98	548–4050			
Cumulative 3- to 12-h bolus amount, mean (SD), μg	135 (123)	7445 (5943)	5139 (4718)	178 (159)	0.25
Demand:delivery ratio per group, mean (SD)					
First 2 h	3.29 (2.29)	4.58 (3.58)	5.36 (6.29)	7.28 (8.27)	0.63
3–12 h	2.27 (1.62)‡	2.96 (2.04)†	3.57 (2.80)§	3.72 (3.27)§	0.03
Rescue diclofenac use, no. of events					0.36
First 2 h	23	21	18	22	
3–12 h	1	2	1	4	
Sedation level over 12 h (VAS), mean (SD)	3.07 (1.74)	3.24 (2.00)	3.14 (1.69)	2.96 (1.60)	0.24
Respiration rate over 12 h, mean (SD), breaths/min	16.4 (2.6)	16.4 (2.7)	15.7 (2.2)	16.2 (2.1)	0.30
SpO_2 over 12 h, mean (SD), %	96.8 (2.3)	96.8 (2.4)	96.7 (4.4)	97.2 (2.0)	0.20
PONV, no.					0.36
First 2 h	7	5	10	6	
3–12 h	15	11	13	6	
Antiemetic use, no. of events					0.22
First 2 h	7	4	10	5	
3–12 h	1	3	1	4	

BUP-i = buprenorphine infusion; BUP-b = BUP bolus; MO-i = morphine infusion; MO-b = MO bolus; ANOVA = analysis of variance; VAS = visual analog scale; SpO_2 = arterial blood oxygen saturation.
*To allow comparison, drug amounts were adjusted to 70 kg body weight.
† $P = 0.01$ versus the corresponding ≤2-hour period, *t* test.
‡ $P = 0.026$ versus the corresponding ≤2-hour period, *t* test.
§ $P < 0.001$ versus the corresponding ≤2-hour period, *t* test.

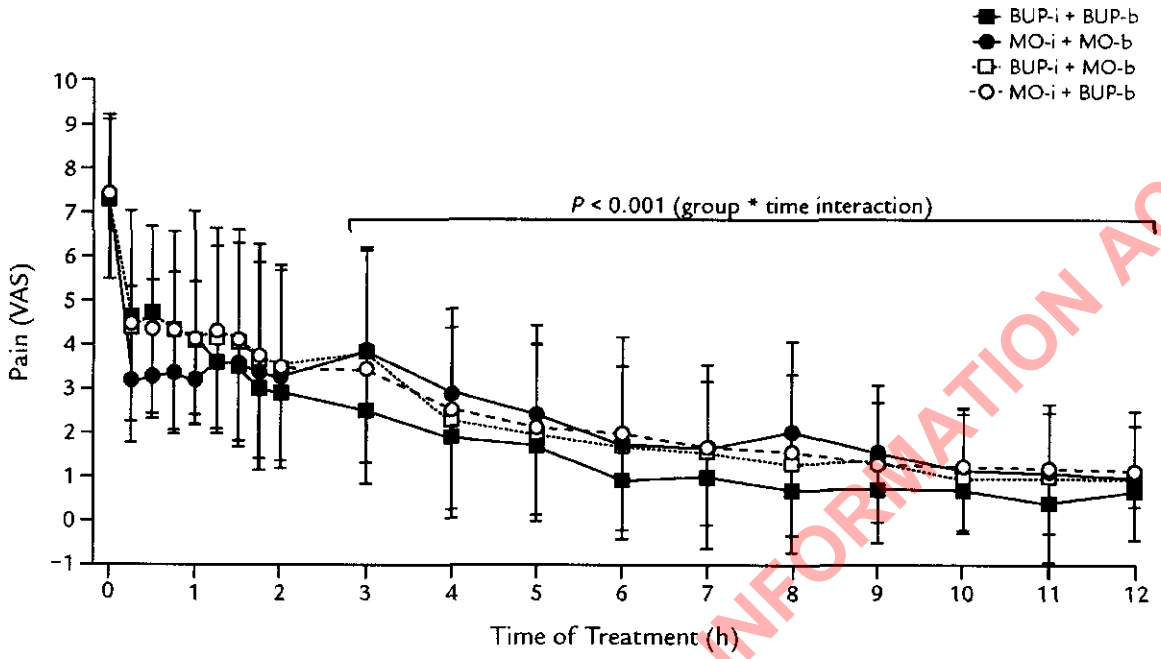

Figure 3. Comparison of the 4 study protocols: mean (SD) patient-rated pain intensity on a visual analog scale (VAS) from 0 = totally free of pain to 10 = unbearable pain. Zero on the x-axis represents the time the patient-controlled analgesia device was connected to the intravenous line by the attending anesthetist. BUP-i = buprenorphine infusion; BUP-b = BUP bolus; MO-i = morphine infusion; MO-b = MO bolus.

There was an overall negative correlation between the mean sedation rate and the mean pain rating (r = –0.182; P = 0.046). Satisfaction with pain control was higher in the group that received BUP-i + BUP-b than in the other 3 groups (group * time interaction, P < 0.001) (Figure 5). There was a negative correlation between the log of the sum of 12-hour drug usage and mean satisfaction levels in all 4 groups (r = –0.21; P = 0.023).

Respiratory Parameters

No differences were found between groups with regard to RR or SpO_2. All groups had a significant increase in RR during the first 2 postoperative hours (P = 0.001) that decreased over time, indicating awakening. There was no occurrence of respiratory depression (<6 breaths/min[27]). SpO_2 during spontaneous ventilation was also comparable in all groups, increasing during the first 2 hours (probably indicating gradual awakening) and decreasing slightly from 6 to 8 hours (time effect, P < 0.001) (data not shown).

Hemodynamic Parameters

All groups had minimal fluctuations in HR during the first 2 hours in the PACU, probably as a result of emergence from anesthesia, that later stabilized (time effect, P < 0.001). However, values were significantly lower in the BUP-i + BUP-b group than in the other 3 groups (HR * drug infusion * bolus interaction, P = 0.027).

SBP was significantly increased in all groups on arrival in the PACU as patients awakened from anesthesia (mean, +15 mm Hg) and subsequently decreased (time effect, P < 0.001). The 2 groups that received BUP-i had a decrease in DBP in the 3- to 12-hour postoperative period (drug infusion * time * DBP interaction, P < 0.001) that was not seen in the groups that received MO-i. During the first 9 hours, there was a significantly greater decrease in DBP in the BUP-i groups than in the MO-i groups (P = 0.001), with subsequent stabilization. No patient had an SBP <80 mm Hg, DBP <40 mm Hg, or HR <40 beats/min at any time during the study.

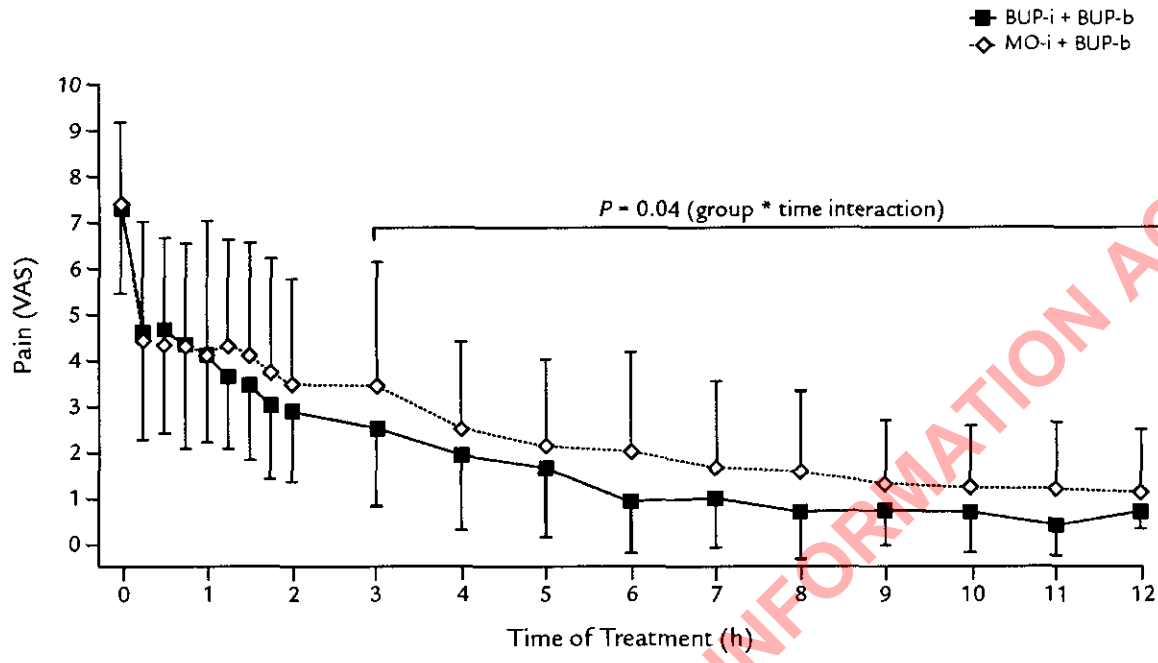

Figure 4. Comparison between buprenorphine infusion (BUP-i) + BUP bolus (BUP-b) and morphine infusion (MO-i) + BUP-b: mean (SD) patient-rated pain intensity on a visual analog scale (VAS) from 0 = totally free of pain to 10 = unbearable pain. Zero on the x-axis indicates the time the patient-controlled analgesia device was connected to the intravenous line by the attending anesthetist.

Adverse Effects

There were no significant differences between groups in the incidence of postoperative nausea and vomiting (PONV) (Table III). Twenty-eight episodes of PONV (38% of all 73 cases) occurred within 2 hours after surgery. These episodes were short-lived and responded to treatment with metoclopramide 10 mg or granisetron 4 mg.

There was 1 case of pruritus in the BUP-i + BUP-b group that occurred 5 hours after initiation of IV PCA. The pruritus was alleviated by promethazine (25 mg IV), which is commonly used for this indication in Israel. No patient experienced dizziness, agitation, or confusion.

DISCUSSION

Based on a search of MEDLINE, this 4-arm, randomized, double-blind, parallel-group study appears to be the first to have compared the clinical effects of BUP and MO, 2 pharmacologically different and reportedly antagonistic opioids,[9,28] given by infusion and boluses (separately and in combination) for analgesia in the first 12 hours after major abdominal surgery. The results indicated that IV PCA with BUP alone or in combination with MO provided equivalent postoperative analgesia to IV PCA with MO alone in patients who had undergone major abdominal surgery. Pain intensity was rated lower in those receiving BUP-i + BUP-b, followed by BUP-i + MO-b, MO-i + BUP-b, and MO-i + MO-b. BUP did not negatively affect patient-rated levels of sedation or satisfaction, or hemodynamic or respiratory parameters. The group that received BUP-i + BUP-b had the lowest HR and DBP of the 4 groups. All groups had similar rates of adverse effects (PONV and pruritus), none of which put any patient at risk or caused drug-related discontinuations. Thus, at the analgesic doses and modes of administration used, BUP continued to be effective and was well tolerated when given both alone and in combination with MO, contradicting past reports of a negative interaction between BUP and other μ-opioid–receptor agonists/antagonists in animals and humans

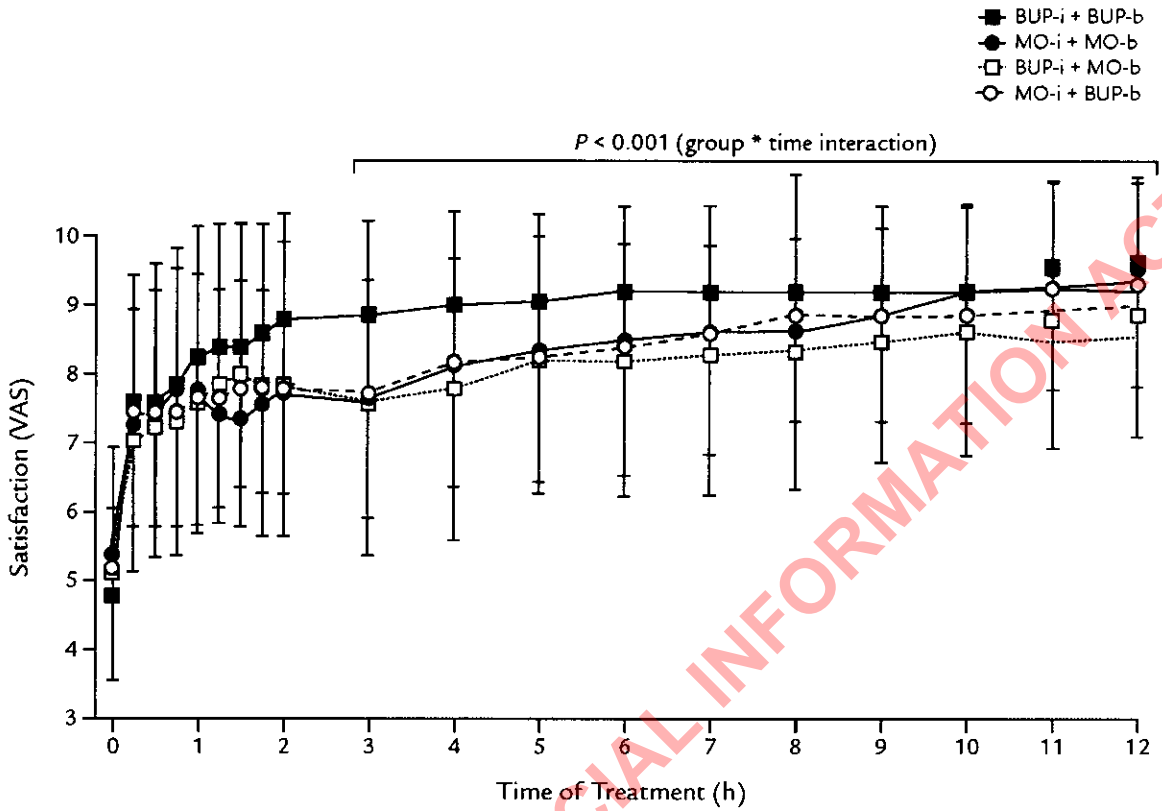

Figure 5. Mean (SD) patient-rated satisfaction on a visual analog scale (VAS) from 1 = totally unsatisfied to 10 = fully satisfied. Zero on the x-axis indicates the time the patient-controlled analgesia device was connected to the intravenous line by the attending anesthetist. BUP-i = buprenorphine infusion; BUP-b = BUP bolus; MO-i = morphine infusion; MO-b = MO bolus.

that might inhibit the antinociceptive effect of the individual drugs.[14–16,20,29]

The primary goal of this study was to determine the antinociceptive efficacy of BUP delivered by IV PCA at the predetermined low infusion and bolus doses. In this respect, it differed from other studies that have used upward/downward titration, administration of high-dose boluses over a limited period, combinations of intramuscular and intravenous administration, and periodic dose limitation.[11,30–33] The doses used in this study, which were 10% to 15% of those reported earlier,[34] were adequate and effective based on the diminished need for bolus doses over time, the demand:delivery ratio, and the decrease in diclofenac use in the 3 to 12 hours after surgery. In addition, levels of satisfaction improved as pain levels decreased, and no patient asked to be withdrawn from the study. The higher amount of drug use in all groups during the first 2 postoperative hours compared with 3 to 12 hours after surgery probably represent recovery from anesthesia coupled with still low levels of blood drug concentrations,[35] as well as supporting the efficacy of the drug protocols.

There is no common opioid dose for either BUP or MO that can be used in an efficacy comparison, apart from the wide range of equipotency data reported previously[7,11]; the protocols used in this study fall within such ranges. The study did not aim to compare drug use per se, but rather to characterize the quality of analgesia obtained using weight-related infusions and boluses of both drugs alone and in combination. The rate of PCA implementation provides an objective assessment of the level of pain and drug efficacy.[4,36] A low overall rate of use (low demand:delivery ratio)

indicated the effectiveness of all 4 protocols in providing analgesia. The numerically lowest demand:delivery ratio was seen in the BUP-i + BUP-b group, which also had the lowest mean pain values in the period from 3 to 12 hours after surgery; compared with MO-i + BUP-b, these results suggest the efficacy of the agonist/antagonist BUP-i protocol within known equianalgesic ratios. Moreover, no antagonism was noted when BUP and MO were used in combination, as indicated by the cumulative bolus doses. Animal experiments have described antagonistic interactions that were hypothesized to be caused by the partial-agonist properties of BUP at the μ-opioid receptor, which, in competition with a full agonist such as MO, would reduce the overall effect of BUP.[14,37,38] The results of the present study are inconsistent with this assumption. Furthermore, the results are consistent with those from a study in rats by Kögel et al,[7] who reported that an antinociceptive effect was achieved even when BUP given at analgesic doses was switched to a full μ-opioid–receptor agonist (MO, oxycodone, hydromorphone, or fentanyl), with no loss of analgesic efficacy and no refractory period between the termination of BUP and the onset of action of the new regimen.

Low oxygenation and decreased minute ventilation are common physiologic occurrences in the early postoperative and postanesthesia period, resulting from incomplete awakening, opioid-induced sedation, or both. Hypoxia and uncontrolled pain may interfere with wound healing after major abdominal surgery. Optimal oxygenation and respiratory status are, therefore, essential. When using opioids, the risk of respiratory depression due to μ-opioid–receptor inhibition of respiratory control centers in the brainstem must be taken into account. BUP appears to be an exception in this respect. Animal studies have suggested a ceiling respiratory effect at increasing BUP doses.[9] In healthy volunteers, BUP was associated with depression of minute ventilation that leveled off at doses ≥3.0 μg/kg (15-fold the dose used in the present study).[39] Administration of BUP 4 μg/kg IM after orthopedic procedures conducted under fentanyl-balanced anesthesia was associated with severe respiratory depression requiring artificial ventilation.[35] In orthopedic patients who were randomized in a 1:33 ratio to receive intramuscular BUP or MO, BUP was associated with a cumulatively longer duration of oxygen desaturation and more episodes of apnea per patient than MO.[40] These effects were associated with the intramuscular mode of administration, which provides the least consistent blood drug concentrations. Finally, postoperative boluses of BUP 80 μg in patients who had undergone thoracotomy provided analgesia but were associated with respiratory depression.[24,34] Interestingly, in 50 women undergoing low-segment cesarean section, BUP at 0.4 to 7.0 mg IV per 24 hours was not associated with respiratory depression.[41]

In the present study, BUP and MO had comparable efficacy in maintaining adequate analgesia without having the effects on ventilation that have been reported in children.[42] Whether this finding was related to the consistency of pharmacologic effect with the infusion compared with bolus-induced peaks, a ceiling effect of BUP on respiratory depression,[43] attainment of optimal pain relief (and therefore better respiratory mechanics), the low dose, or the overall agonist/antagonist properties of BUP cannot be determined based on the study findings. Nevertheless, BUP appears to show promise for use in high-risk patients because of the absence of respiratory depression.

In cardiac patients undergoing surgery, maintenance of a lower HR and DBP has been recommended.[44] In the present study, the BUP-i + BUP-b group had a 10% lower HR compared with the groups that received other combinations of infusion + bolus; the difference was greatest compared with the group that received MO only. DBP was also low in the BUP-i + BUP-b group compared with the other groups. BUP has been reported to be associated with reductions from baseline in BP and HR in animals (10%–15%)[12] and in children (10–12 beats/min).[42] A lower and stable HR could be the effect of better analgesia achieved with BUP compared with MO or of partial μ-opioid–receptor blockade.

In a 3-day study in patients who had undergone cholecystectomy, BUP and MO were given as loading doses followed by boluses administered by IV PCA in a 1:13 ratio, with a 15-minute lockout time.[29] A BUP loading dose (0.1–0.3 mg) followed by 0.1-mg boluses was associated with twice the rate of postoperative nausea on day 1 compared with an induced MO loading dose (2–4 mg) followed by 1-mg boluses (P = NS). Other studies have reported rates of pruritus, dizziness, and sweating with BUP that were 10% to 20% higher than those in the present study.[18,24] BUP administered intravenously or caudally has been associated with high rates (50% and 80%, respectively)

and severity of PONV in children[45] but not in adults.[46] No patients withdrew from the present study, and all adverse effects were mild and tolerable, and responded rapidly to treatment. Use of low but effective BUP doses may partially explain the absence of severe adverse effects.

It is of clinical relevance that sedation decreased and satisfaction improved as pain was progressively controlled with BUP compared with MO alone or in combination. Moreover, no patients exhibited heightened anxiety. BUP has been reported to produce a maximal (ceiling) euphoric effect similar to that of MO 20 mg · 70 kg^{-1}.[47] High sublingual doses of BUP (8 mg) have been associated with a plateau in terms of subjective and physiologic effects,[3,20] unlike the orally administered full μ-opioid–receptor agonist methadone (allowing for a linear dose effect). The steady improvement in the level of sedation over time with BUP in this study was consistent with the findings of Capogna et al.[48] The study findings are also consistent with reports that BUP was associated with less-intense opioid-induced dysphoria, probably because of its partial-agonist activity at μ-opioid receptors.[49] The improvement in satisfaction may have been associated with a BUP-induced positive effect on mood and well-being via its κ-receptor activity.[12,50]

Most published reports concerning the use of BUP for postoperative pain control come from studies in animals or healthy volunteers under overdose-like conditions and are quite old. Thus, no appropriate data appeared to be available with which to compare the results of the present study. In addition, as in other studies,[24,31,33,34,45,48] the results were limited to the first 12 hours after surgery. A full 24 hours of data would have provided information on the first bowel movement[51] and the time to removal of the urinary catheter. Finally, because of the inclusion and exclusion criteria, the results of this study are limited to the population studied.

CONCLUSIONS

In these patients who had undergone major abdominal surgery, BUP-i + BUP-b administered via IV PCA controlled postoperative pain in the first 12 postoperative hours as well as did MO-i + MO-b or the combinations of BUP and MO. BUP neither inhibited the analgesia provided by MO nor induced undesired sedation or hemodynamic or respiratory effects.

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Acute Pain Management Pharmacology for the Patient with Concurrent Renal or Hepatic Disease

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SUMMARY

The clinical utility of most analgesic drugs is altered in the presence of patients with impaired renal or hepatic function not simply because of altered clearance of the parent drug, but also through production and accumulation of toxic or therapeutically active metabolites. Some analgesic agents may also aggravate pre-existing renal and hepatic disease.

A search was performed, taking in published articles and pharmaceutical data to determine available evidence for managing acute pain effectively and safely in these two patient groups. The resulting information consisted mainly of small group pharmacokinetic studies or case reports, which included a large variation in degree of organ dysfunction.

In the presence of renal impairment, those drugs which exhibit the safest pharmacological profile are alfentanil, buprenorphine, fentanyl, ketamine, paracetamol (except with compound analgesics), remifentanil and sufentanil: none of these deliver a high active metabolite load, or suffer from significantly prolonged clearance. Amitriptyline, bupivacaine, clonidine, gabapentin, hydromorphone, levobupivacaine, lignocaine, methadone, mexiletine, morphine, oxycodone and tramadol have been used in the presence of renal failure, but do require specific precautions, usually dose reduction. Aspirin, dextropropoxyphene, non-steroidal anti-inflammatory drugs and pethidine, should not be used in the presence of chronic renal failure due to the risk of significant toxicity.

In the presence of hepatic impairment, most drugs are subject to significantly impaired clearance and increased oral bioavailability, but are poorly studied in the clinical setting. The agent least subject to alteration in this context is remifentanil; however the drugs' potency has other inherent dangers. Other agents must only be used with caution and close patient monitoring. Amitriptyline, carbamazepine and valproate should be avoided as the risk of fulminant hepatic failure is higher in this population, and methadone is contraindicated in the presence of severe liver disease.

Key Words: ACUTE PAIN, ANALGESIA: renal failure, renal function, hepatic failure, hepatic function, review

The clinical utility of most analgesic drugs is altered in the presence of impaired renal or hepatic function: this is not simply because of variations in clearance of the parent drug, but also due to potential production and accumulation of toxic or therapeutically active metabolites. In some cases, analgesic agents may aggravate pre-existing renal and hepatic impairment; consequently modifying their own metabolism.

To assist in the provision of guidelines for the pharmacologic management of acute pain in these situations, a literature review was performed, searching for data on altered dosing requirements, adverse reactions and the mechanisms responsible. Categorization using evidence-based medicine principles was planned, to give appropriate weighting to the consequent findings and recommendations.

With increased understanding of the mechanisms which induce and maintain the pain state, drugs not traditionally used for pain relief have been incorporated into the analgesic armamentarium. These were included in the search criteria, and consist of some antiepileptic and antidepressant medications, mexiletine, alpha-2 agonist drugs and the anaesthetic drug ketamine. They are more commonly used in the treatment of neuropathic pain, although the latter two may also be used for nociceptive pain management.

METHODS

A Medline search was performed using the following key words: acetaminophen, alfentanil, amitriptyline, analgesia, aspirin, bupivacaine, buprenorphine, carbamazepine, clonidine, codeine, dextropropoxyphene, diclofenac, dihydrocodeine, epilim, fentanyl,

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gabapentin, hydromorphone, ketamine, ketorolac, levobupivacaine, lignocaine, meperidine, methadone, mexiletine, morphine, naltrexone, nsaid, oxycodone, paracetamol, pethidine, propacetamol, remifentanil, ropivacaine, sufentanil, tramadol, tricyclic antidepressant, and valproate. The results were then linked in a combined search with each of the following: "renal failure", "renal function", "hepatic failure" and "hepatic function". The resultant abstracts were reviewed for relevance and those which did not address the issues of altered dose requirements or adverse reactions or the mechanisms responsible for these were excluded. Only those articles with an English text body were then obtained.

Published pharmacokinetic data and pharmaceutical company monographs were sought for the drugs listed above.

The following pharmacology texts were consulted:

- **Drug Monitoring Data—Pocket Guide II–2nd Edition.** American Association for Clinical Chemistry, Inc., Washington DC, 1994[43].
- **Therapeutic Guidelines: Analgesic (Victorian Drug Usage Advisory Committee)—3rd Edition.** Therapeutic Guidelines Limited, Victorian Drug Usage Advisory Committee, Melbourne, Vic., Australia, 1997[14].
- **Goodman and Gilman's The Pharmacological Basis of Therapeutics.** Macmillan Publishing Company, New York, 1985.
- **The Australian Medicines Handbook–4th Edition.** Australian Medicines Handbook Pty Ltd, Adelaide, S.A., 2003.
- **MIMS Yearbook 2003–7th Edition.** MediMedia Australia Pty Ltd, Sydney, N.S.W., 2003[7].

Aside from the above texts, around 70 articles were reviewed in depth, and some articles were excluded because they added no new data to larger scale studies or reviews.

FINDINGS

The words "dysfunction", "failure", "impairment" and "insufficiency" appear to be used interchangeably throughout the literature, but will be quantified by degree where possible.

Using evidence-based medicine definitions[1], the best available data consisted of small group non-randomized pharmacokinetic studies, some with a control group of patients displaying normal organ function: this constitutes level III evidence. Some data comprised small group patient case series with drug or effect assessment; constituting level IV evidence. A major portion of the data however, involved single case studies, or expert opinion based upon pharmacological properties of the analgesic agents, which is no longer considered truly evidence based[1]: *It is however, the only guidance available for some pharmacologic agents in this setting. The phrase "use with caution" is encountered frequently in referenced articles without further clarification; in the context of this article the author would suggest that it should at least imply dose titration with observance for and avoidance of toxic or excessive therapeutic effect, and an understanding of the effects of organ dysfunction on drug metabolism.*

The available evidence levels and recommendations are considered separately for each drug class, with discussion of both alterations in therapeutic effect, and potential toxic effects. In all cases where a drug's half-life is prolonged, the resultant delay in achieving a steady state concentration must be considered whilst observing for these effects.

OPIOIDS

Considerable pharmacological variation occurs within this group. The majority of biotransformation is liver-dependant, including that for the short acting agents. Minimal evidence exists to guide the appropriate use of opioids in the presence of hepatic failure. Titration to effect should be more cautious than usual with all opioids in the presence of liver failure[2]. A small number of case reports link opioid usage with acute renal failure, reversible with naloxone[3,4], however this is not borne out in the literature as a common problem, and no explanation for the underlying mechanism was given, excepting animal data linking opioid dosage with an increase in vasopressin levels.

Alfentanil

A controlled pharmacokinetic study assessing patients with end stage renal failure found an increase in the unbound plasma fraction of this drug due to alterations in protein binding, but no change in plasma clearance, which occurs primarily through hepatic metabolism[2,5] (Level III evidence for both references). Under these conditions there may be a decreased dosage requirement, but no change in the required dosing intervals, as the drug does not have significant active metabolites[2].

In a study assessing 9 children with cholestatic liver disease and 10 children with chronic renal failure undergoing organ transplantation, no significant difference was found in alfentanil clearance or half-life[6] (Level III evidence), suggesting the drug is safe to use in these groups.

Buprenorphine

This drug undergoes liver metabolism followed

by primary biliary excretion. Metabolite levels are increased four-fold in the presence of renal failure, but this is unlikely to have clinical consequences. It may be given in standard doses in the presence of renal failure[2] (Level III evidence). No evidence was found to guide treatment in the presence of hepatic dysfunction.

Codeine

Approximately 10% of codeine is metabolised to morphine, which provides the majority of its clinical effect. Most ingested codeine is converted to codeine-6-glucuronide which is then renally excreted. Although many opioids have been associated with central nervous system (CNS) excitation and seizures at higher doses, codeine appears to have a lower therapeutic ratio, and may cause these effects when the standard daily dose is exceeded[7]. It has been reported to cause prolonged sedation in the presence of renal failure, with a beta half-life of up to 27 hours in dialysis dependant patients[2] (Level III evidence). The available evidence does not support clinical use in the presence of renal or hepatic failure.

Dextropropoxyphene

Plasma concentrations of both dextropropoxyphene and nordextropropoxyphene, its major metabolite, are significantly increased with renal failure, and the half-life of the metabolite is prolonged[2]. The potential consequences of this include CNS, respiratory and cardiac depression[2]. It has been associated with a number of deaths, many quite rapid, in cases of both accidental and intentional overdosage[8]. Animal studies found intracardiac conduction delays in the presence of overdosage due to both the parent drug and its metabolite[2]. It is inefficiently cleared during dialysis, and its use is not recommended in the presence of renal failure[2].

It is subject to considerable first pass hepatic metabolism after absorption, and has been associated with impairment of liver function[8]. No studies were located which specifically assessed safe usage in the presence of hepatic failure.

Dihydrocodeine

This probably has similar elimination to codeine, and has been reported to cause prolonged sedation, reversible with naloxone[2]. It has not been so intensively studied however, and should be avoided in the presence of renal failure.

No evidence was found to guide treatment in the presence of hepatic dysfunction.

Fentanyl

Fentanyl is subject to a high hepatic extraction ratio, which may lead to decreased clearance values in the presence of altered hepatic blood flow during uraemia. The pharmacokinetics of fentanyl have been studied in eight patients with end stage renal failure undergoing renal transplantation after a loading dose of 25 μg/kg, and a strong correlation existed between clearance and blood urea nitrogen levels. The most marked changes in clearance occurred when urea levels were greater than twice the normal value[9] (Level IV evidence). Fentanyl has no active metabolites and has been shown in some pharmacokinetic studies to have no significant change in clinical effects, with normal clearance values in the presence of chronic renal failure. It does have a prolonged clearance (half-life up to 25 hours) in the critically ill patient which must be taken into consideration[2]. It does not appear to have been studied extensively in the paediatric population with organ failure, however a single article reported normal pharmacokinetic values in one child with renal failure given high-dose fentanyl anaesthesia, but markedly impaired clearance (1/20 normal) in a child who underwent hepatic manipulation during surgery[10]. Considering the lack of active metabolites, fentanyl is an ideal agent for use in renal failure; with the provision that high levels of uraemia may significantly prolong clearance and require a decrease in dosage. (The available data suggests 1/2 to 1/3 of usual commencement doses may be required in this case.)

Hepatic failure is likely to impair fentanyl clearance and require a dosage reduction, however no data was found to guide this specifically.

Hydromorphone

Hydromorphone is a semi-synthetic derivative of morphine, metabolized in part to hydromorphone-3-glucuronide (H3G), which is present at a steady state concentration approximately 27 times that of the parent drug in normal patients. H3G has been shown to accumulate in the presence of renal failure to a level approximately four times higher. It is postulated as the cause for neuroexcitation and cognitive impairment which has been reported with this drug in the presence of renal failure, and is a reason to consider an alternative agent if these symptoms should occur[11]. One retrospective study compared hydromorphone use in 55 palliative care patients with either normal or impaired renal function, who were switched to this drug from other opioids (mostly morphine) because of adverse reactions. There was no significant difference in opioid conversion factors between groups and

a lower incidence of unwanted side-effects. Whilst the median doses were higher in the normal group, the mean doses were not significantly different between groups. This study suggests that hydromorphone use may be safe in the presence of renal failure, and is associated with a lower incidence of side effects than morphine in this group[12] (Level III evidence).

The drug undergoes a high first pass metabolism[13], and will be subject to increased bioavailability in the presence of hepatic impairment. No evidence was found to guide safe use of the drug in this scenario.

Methadone

The drug has a long half-life and is therefore not suitable for the initial management of acute pain[14]. It has a high oral bioavailability of around 80% of the ingested dose. Renal excretion of the unchanged drug accounts for approximately 20% of the total dose[2], whilst the majority of clearance occurs through the gastrointestinal tract after hepatic transformation to predominantly inactive metabolites[15]. A case report of two patients with renal failure showed serum methadone levels in the range expected with normal renal function, however it is generally recommended that lower starting doses be used when initiating therapy for the patient with renal failure, with subsequent doses titrated to effect[2]. It is contraindicated in the presence of severe liver disease[14].

Morphine

The parent drug has been shown to undergo normal biotransformation in the presence of renal failure[16] (Level III evidence), however the clearance of one of the active primary metabolites morphine-6-glucuronide (M6G) is highly renal dependant, and its consequent accumulation may cause a prolonged clinical effect. The half-life of M6G is prolonged from a normal value of 2.1 hours, up to as much as 27 hours in end stage renal failure. The other major metabolite, Morphine-3-glucuronide (M3G) also accumulates with renal failure[2] (Level III evidence): it is associated with antinociception and irritability, but has not been reported as a frequent cause of side-effects in the patient with renal failure: it may decrease the seizure threshold however, so morphine should probably be avoided where epilepsy and renal failure co-exist.

As M3G and M6G are products of morphine breakdown, it must be remembered that equivalent oral doses of morphine which are higher than parenterally administered morphine, will produce a greater metabolite load[17,18] (Level III evidence in reference 17). This should be considered as an additional risk factor when converting to oral morphine and necessitates a reduction in equivalence dosing by a factor of up to three, or the use of an alternative agent with inactive metabolites.

A wide variation in susceptibility to M6G effects may occur in the patient with renal failure. At least two causes for this have been determined. Firstly, up to 20% of patients may have decreased sensitivity to M6G due to genetic variation in the μ-opioid receptor: these patients could feasibly tolerate standard morphine dosage regimens, despite metabolite accumulation: only minimal clinical evidence of this has been reported[19]. A second cause for variation is known to exist in which active transport (efflux) of M6G across the blood brain barrier may be modulated via p-glycoprotein, which has been described as sensitive to modulation (decreased efflux) by verapamil and amitriptyline. (Other drugs may also cause this effect)[19,20]. Both these variations can not be predicted clinically at present.

The time to onset of M6G effects may be quite prolonged as it is slow in traversing the blood brain barrier. In a controlled trial comparing eight normal patients with six end stage renal failure patients, peak morphine cerebrospinal fluid (CSF) morphine levels were similar between groups, but CSF M6G levels peaked at 12 hours in normal patients, and continued to rise to a 24 hour peak (at which time measurements were ceased) in those with end stage renal failure. The peak level was approximately 15 times that of the normal group, with the consequent risk of delayed sedation[17] (Level III evidence). Delayed sedation causing unconsciousness despite absence of elevated morphine levels has been reported following high loading doses in patients with renal failure. In one (adult) case the metabolite load resulted in prolonged sedation with initial onset time 26 hours after M6G blood levels approached their peak. At the onset of unconsciousness, plasma morphine levels were below the limit of quantification[21]. A similar case scenario has been reported in a child with renal failure using morphine patient-controlled analgesia, although M6G levels were not documented in this case[22].

Whilst morphine and its metabolites are usefully removed during haemofiltration (47-100%) and haemodialysis (24-84%)[2], they are not significantly cleared by continuous ambulatory peritoneal dialysis, which has similar clearance values to end stage renal failure[20,23] (Level III evidence in both references).

On the basis of widespread clinical use and avail-

able evidence, morphine appears to be a safe agent to use in the presence of renal failure, provided it is carefully titrated to effect, and provided it is not continued where large doses are likely to be required with acute pain. In the situation where high initial doses are required, there is a significant risk that high metabolite levels will lead to delayed sedation as the pain abates. In this scenario, ongoing analgesia should be altered to a shorter acting drug or one without active metabolites such as fentanyl or oxycodone until analgesic requirements decrease to a lower, steady state. If parenteral morphine doses are converted for oral administration in the presence of renal failure, then the likelihood of a significant increase in metabolite load due to first pass metabolism must be considered, and doses appropriately lowered.

Morphine use in hepatic failure does not appear to have been usefully studied. Reported hazards include precipitation of hepatic encephalopathy, increased oral bioavailability of morphine due to its normal high first pass metabolism when given via this route[24], and impaired clearance.

Oxycodone

Oxycodone is eliminated mainly through hepatic metabolism to noroxycodone and oxymorphone, and some effect has been attributed to metabolite activity. One controlled study compared 10 normal patients with 10 uraemic patients who underwent cadaver renal transplants, after a single loading dose of oxycodone. None of the transplanted patients had immediate graft function, and in all cases the oxycodone half-life was significantly prolonged. The median half-life increased by a factor of 1.7, although individual variation within the transplant group was significant, with values up to 10 times normal. Oxycodone has a lower hepatic clearance than morphine, and it was considered that some of the variation in the latter group may be accounted for by alterations in hepatic blood flow with uraemia, or the use of calcium channel blockers which are known to reduce hepatic blood flow and enzyme activity[25] (Level III evidence). With this in mind, oxycodone should be cautiously titrated to effect in the presence of renal failure.

Pethidine

Pethidine (known also as meperidine) is primarily cleared by hepatic demethylation to norpethidine, its sole active metabolite[2]. Norpethidine has a usual half life of 14 to 21 hours[2], but this is prolonged in the presence of renal failure[2,26,27] to around 35 hours[2], The accumulation of this metabolite has been associated with seizures and death[2]. In patients with normal renal function, toxicity will occur in approximately 19 per cent of cases where doses exceed around 10 mg/kg/day or therapy exceeds three days duration[27] (Level III evidence). The toxic dose will obviously be much lower in the presence of renal failure, and safe doses have not been determined. A single dose in the presence of renal failure is unlikely to produce clinically significant toxicity[2], however its use is not recommended in the presence of renal failure[2,26,27], and with the existence of better alternatives its use should now be contraindicated in this situation. Its use during dialysis does not appear to have been studied. Pethidine has not been studied in the presence of hepatic failure, but there is no basis on which to recommend its use above other agents without toxic metabolites.

Remifentanil

This drug undergoes blood esterase hydrolysis to a minimally active metabolite. It has been shown in pharmacokinetic and clinical effect studies in patients with renal failure[2,28,29] (Level III evidence in references 28 and 29), hepatic cirrhosis, mild hepatic encephalopathy[30], and during the anhepatic phase of liver transplantation[31] (Level III evidence) to have no significant change in clinical effects compared with published normal subject data, and slight, statistically significant changes in serum levels. One study titrating to haemodynamic response under general anaesthesia required a mean reduction to 2/3 of the control group infusion rate in the presence of renal failure[29] (Level III evidence). It represents the ideal opioid for use in both renal and hepatic failure when used within an appropriate clinical setting, which must include regular assessment of sedation levels and respiratory function, with a reliable infusion device, and a skilled clinician with training in the safe use of this potent opioid. It is not appropriate for use outside of a high dependency clinical setting.

Sufentanil

This drug has no active metabolites, and is not generally expected to require dose adjustment in the presence of renal failure[14]. Clearance and half-life were more variable than normal in adolescents with chronic renal failure, despite a lack of statistical difference[32] (Level III evidence), and there has been a case report of unexpected prolonged sedation in a patient with renal failure, so it should be used with caution[2]. In patients with uncomplicated cirrhosis under anaesthesia, loading doses of 3 μg/kg were not associated with significant differences in plasma

clearance or elimination half-life over 10 hours of measurement[33] (Level III evidence).

Tramadol

Tramadol is primarily metabolized in the liver to substances including the only pharmacologically active metabolite; *O*-desmethyltramadol (M1), which contributes toward its analgesic effect. Both the parent drug and its metabolites undergo primarily renal excretion, and hence are subject to accumulation in the presence of renal failure[34]. It has not been implicated in the production of renal impairment in man, and one animal study assessing renal blood flow in rats found no alteration in those with normal kidneys, nor those with experimentally induced nephritis, despite an increase in systemic blood pressure[35] (Level III evidence).

The product manufacturers' literature recommends that dosage intervals should be increased to every 12 hours where creatinine clearance is less than 30 ml/min (24 hours for slow release formulation), and that the drug should be avoided where creatinine clearance is less than 10 ml/min[34]. This recommendation for twelve hourly dosing is impractical for treating acute pain as it ignores the need for a loading dose. No evidence was found to guide appropriate loading in this circumstance, however if used in the absence of such guidelines' it would be prudent to titrate the drug cautiously and cease dosing if agitation, hyperreflexia, myoclonus or other signs of serotonergic syndrome occur.

In the presence of severe hepatic insufficiency where its use is contemplated, only the 50 mg immediate release formulation should be used, with cautious titration to clinical effect. Dosage intervals will need to be extended, and the patient should be observed for signs of serotonergic syndrome; if these occur the drug should be ceased, and the syndrome appropriately managed as per product guidelines[34].

ALPHA-2 AGONISTS

Clonidine

Clonidine has been utilised as an anti-hypertensive agent in patients with renal failure at doses of up to 600 μg orally or transdermally daily. No deterioration in renal function occurred, and no unusual side-effects were documented. The half-life was increased from a normal value of 12 hours up to 40 hours with severe renal failure[36]. The drug is normally less than 50% metabolized by the liver, with the remainder excreted unchanged in urine[37]. It should be given at a reduced dose in the presence of renal failure.

Dexmedetomidine

As a new agent, dexmedetomidine has not been widely studied in the context of acute pain management, although it is approved for the provision of combined analgesia and sedation within the intensive care setting. It undergoes extensive hepatic metabolism to an inactive metabolite and may prove suitable for use in the presence of renal failure.

No evidence was found to guide the use of either drug in the presence of hepatic dysfunction.

TRICYCLIC ANTIDEPRESSANTS

This drug class undergoes primarily hepatic metabolism. Amitriptyline is most commonly used, and undergoes conversion in the liver to nortriptyline, the active agent. The doses used to assist with management of neuropathic pain are generally less than those used to treat depression, however the articles which assessed use in renal failure all considered the latter, higher doses. There is little indication for dose reduction in renal failure[38,39] (Level III evidence in both references), however, it has been suggested that metabolite accumulation may increase the likelihood of unwanted side- effects[38].

Both amitriptyline (2-10% incidence of elevated liver function tests) and nortriptyline have been associated with acute fulminant hepatic failure, but the mechanism remains uncertain[40]. They both require ongoing monitoring to exclude abnormalities in liver function during introduction, in which case the drug should be discontinued.

LOCAL ANAESTHETICS

The amide type local anaesthetics which include bupivacaine, levobupivacaine, lignocaine and ropivacaine, undergo primarily liver metabolism to inactive metabolites prior to excretion. The local anaesthetic procaine has an ester linkage which also allows hydrolysis by plasma cholinesterase. Toxic levels of local anaesthetics are calculated on the basis of steady state concentrations during short intravenous infusion[41], however the systemic absorption rate associated with various routes of administering these drugs is quite variable[42]. In general all local anaesthetics will be subject to decreased clearance with hepatic failure, and may be associated with a higher risk of side-effects in the presence of renal failure due to altered protein binding and volume of distribution.

One study looked at eleven patients given bilateral intercostal nerve blocks following hepatic transplant, to assess the effects of bupivacaine 2 mg/kg in this group. A total of twelve blocks were performed, and six of these gave rise to toxic threshold levels of 2 to

TABLE 1
Opioid pharmacology with renal or hepatic dysfunction: Summarised findings

Opioid agent	Potential effects due to metabolite. Accumulation in the presence of renal dysfunction.	Recommendations for use in the presence of renal dysfunction.	Reported use in the presence of hepatic dysfunction.
Alfentanil	Nil significant metabolites[2].	Dose reduction required[2,5].	Unchanged clearance in children with cholestatic disease[6].
Buprenorphine	Nil significant metabolites[2].	Standard doses may be used[2].	Nil.
Codeine	Neuro-excitation may occur at standard doses[7]. Morphine metabolite accumulation increases sedation risk.	Not recommended on basis of available evidence[2].	Nil.
Dextropropoxyphene	Cardiac and hepatic toxicity[2,8].	Not recommended on basis of available evidence[2].	Nil.
Dihydrocodeine	Unknown, probably similar to codeine[2].	Not recommended due to insufficient evidence of safety[2].	Nil.
Fentanyl	Nil significant metabolites[2].	May require dose reduction[2,9].	Case report of greatly impaired clearance after hepatic manipulation[10].
Hydromorphone	Neuro-excitation and delayed sedation possible[11].	Dose reduction required[12].	Nil. Higher bioavailability likely[13].
Methadone	Nil significant metabolites[15].	Not recommended for initial treatment due to long half-life[14].	Cautious use with mild degrees of liver dysfunction reported[2].
Morphine	Delayed sedation from M6G with renal failure, especially when using high initial doses[2]. Neuro-excitation from M3G[2]. Higher metabolite load with oral dosing[17,18].	Dose reduction required. Choose an alternative agent if high doses likely to be used.	Precipitation of hepatic encephalopathy reported[24], also increased oral bioavailability.
Oxycodone	Increased opioid effects due to less active metabolites, which have impaired excretion[25].	Dose reduction required with uraemia[25].	Nil.
Pethidine	Neuro-excitation and seizures due to norpethidine accumulation[2,26,27].	Not recommended (single dose probably safe)[2].	Nil.
Remifentanil	Nil significant metabolites[2,28].	May require slight dose reduction[29].	Case report of safe use. Suggested need for dose reduction[30].
Sufentanil	Nil significant metabolites[14].	Dose reduction may be required[2,32].	3 μg/kg loading reported safe with uncomplicated cirrhosis[33].
Tramadol	Increased tramadol-like effects from *O*-desmethyltramadol (M1)[34].	Dose reduction required. Avoid where creatinine clearance <10 ml/min[34].	Nil. Manufacturer's literature suggests safety with mild degrees of dysfunction using reduced doses.

4 μg/ml bupivacaine, but no detectable clinical effects. In those patients whose results were displayed in graphic form, the elimination half life was six hours: approximately double the normal value[41] (Level IV evidence). In the absence of further studies to assess safety with other causes of hepatic failure, these results indicate the need to avoid using analgesic techniques which require large doses of bupivacaine to obtain spread of the drug, as plasma clearance following redistribution from the effect site will not have occurred in time for further dosing. The maximum daily dose should be at least halved. Using the figures supplied by the *Australian Medicines Handbook*, this would indicate a maximum adult dose of 200 mg/day.

Lignocaine has previously been shown to have impaired clearance in patients with hepatic disease[43], after hepatectomy, and with viral hepatitis[41]. No quantitative dosage alterations were determined, however it would be prudent to assume that adrenaline will have less of a protective effect for larger single doses due to the prolonged half-life, and that the lower dose range should be used cautiously in patients with hepatic impairment, observing regularly

for signs of toxicity during infusion or injection. Lignocaine also gives rise to some active metabolites which will be less rapidly cleared in the presence of renal failure, and may increase the risk of toxicity with prolonged infusions[44].

One study assessed the use of 0.5% levobupivacaine for axillary block in eight patients with end stage renal disease, and compared clinical outcomes and pharmacokinetic values with eleven patients who had normal renal function. Following a dose of 50 to 60 ml of the solution, there was no significant difference between groups for clearance of the drug or clinical outcome[45] (Level III evidence). As bupivacaine has a greater cardiac toxicity than both ropivacaine and levobupivacaine, but similar metabolism and duration of action[46,47], these latter two are probably more suitable for use in the presence of renal or hepatic failure if larger doses are required. All local anaesthetic agents should however be used cautiously where either problem exists. Those regional anaesthesia techniques which use lower drug doses such as spinal anaesthesia would theoretically be safer, but no comparative study was located using the search strategies outlined.

Mexiletine

This drug undergoes extensive hepatic metabolism, but is also excreted by up to 15% unchanged in the urine. It has been used in the acute setting for treatment of refractory neuropathic pain in patients who have responded to intravenous lignocaine, with which it has structural similarities. It has a significant antiarrhythmic effect, and hepatic impairment will increase the risk of toxicity[48]. It is not recommended in this situation unless other treatment modalities have been exhausted, and the potential risks taken into account. Plasma concentrations should then be monitored to allow dose titration[49].

It has been shown to have normal clearance in patients with renal failure where the creatinine clearance exceeds 10 ml/min[50] (Level IV evidence), and unchanged plasma levels in dialysis dependant patients given 600 mg/day[49] (Level III evidence). In the absence of large controlled trials, the lowest effective dose should be used.

KETAMINE

Ketamine use in acute pain management involves the use of low infused doses (between 0.06 and 0.24 mg/kg/h) to minimize the incidence of hallucinations and dysphoria[51], and to prevent unintentional loss of consciousness. Bolus dosing of 1 to 1.5 mg/kg intravenously has been recommended[52] prior to painful procedures, but this dose range is capable of inducing general anaesthesia in some patients and is only appropriate in the fasted patient under safe conditions for providing general anaesthesia. A pharmacokinetic study of four patient groups receiving ketamine 1.1 to 1.3 mg/kg/h for long-term analgesia and sedation within an intensive care unit did not show a significant increase in ketamine levels in patients with cardiogenic shock or acute renal failure (Level III evidence), (a 20% increase in this group did not reach statistical significance). The renal failure group had significantly higher dehydronorketamine metabolite levels, however this was only by a factor of five, and it has but one hundredth the potency of ketamine. Less than 10% of the delivered dose of ketamine was removed during haemodialysis or haemofiltration. Animal studies found the drug to undergo mostly hepatic elimination, and did not show evidence of renal blood flow alteration[53]. The search parameters did not uncover any studies using the lower range analgesic doses, but the above values for higher infusion rates indicate that a dose adjustment is unnecessary in the presence of renal failure.

No data was found to guide the appropriate use of low dose ketamine in the presence of hepatic failure.

ANTI-EPILEPTICS

These may be considered during the acute setting as an adjunct in the treatment of neuropathic pain. Those used are carbamazepine, valproate, and gabapentin. Combination therapy using more than one of these agents is not recommended for acute pain management, as pharmacokinetic interactions may occur in an unpredictable fashion[54], and the risk of fatal hepatotoxicity from valproate is increased in this situation[55]. Gabapentin is probably the safest agent in the presence of either renal failure or hepatic failure.

Carbamazepine

This drug has been reported to cause acute hepatic failure rarely (around 1/30,000 cases) in children, and elevation of hepatic enzymes (approximately 6% of patients treated)[56]. It is also an inducer of hepatic enzymes. The drug undergoes primarily hepatic metabolism, with less than 1% excreted renally, and is contraindicated in severe hepatic impairment[54]. It has also been reported as causing reversible acute renal failure, although this is rare[57,58]. Its use in the acute setting should be associated with regular monitoring of hepatic and renal function to allow discontinuation if these should deteriorate.

Valproate

Fatal hepatic failure may occur due to valproate treatment: pathological data suggests that some cases are the result of chronic liver damage and cirrhosis[59]. This rare complication has an incidence of between 1/10,000-49,000 in adults[59,60], but may be significantly increased with the combination of antiepileptic medications, due to diversion of metabolism toward toxic pathways. The initial presentation may include anorexia, abdominal discomfort, nausea and vomiting, prior to depressed consciousness in association with biochemical markers of hepatic injury[61]. The complication is more common in children, and was reported in association with 21 childhood deaths from hepatic failure in the United Kingdom prior to the year 2000[62]. Abnormalities of liver function occur in up to 44% of patients[60]: and may include elevated transaminases and impaired coagulation[63]. There is some evidence that this complication is associated with impaired beta-oxidation of the drug. Aspirin also interferes with beta-oxidation and should not be used concurrently. Valproate should be avoided in patients with known liver disease[61]. If used in the presence of renal failure, decreased albumin levels may lead to an increase in unbound serum levels, and doses should be lowered[64]. Plasma levels of the drug may be monitored to assess the potential for toxicity.

Gabapentin

Gabapentin undergoes primarily renal excretion in unchanged form, and has an approximate elimination half life of 132 hours in dialysis dependant patients. The half life during haemodialysis is around four hours, with a recommendation to replace losses by 200-300 mg for every four hours of this[65] (Level IV evidence). It otherwise requires dose reduction with renal failure according to creatinine clearance, in line with published guidelines[54].

This drug was not found to be associated with hepatic failure under the search conditions indicated, and is probably the safest choice in this class in the presence of hepatic failure. It must be remembered that this is a relatively new drug, and some unexpected adverse effects may not yet have been elucidated.

NON STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) AND COX-2 SPECIFIC INHIBITORS

This class are traditionally associated with the risk of precipitating acute renal failure due to inhibition of prostaglandin production, and consequent renal afferent arterial vasoconstriction with the potential to reduce glomerular filtration rate. In most cases this is reversible, and is associated more frequently with dehydration, hypotension, pre-existing renal failure, liver cirrhosis and excessive dosage[66,67]. There is only limited evidence suggesting a causal association with chronic renal failure[68]. Some studies have found no significant effect in patients with normal renal function, but there appears to be a small risk of idiosyncratic reaction, even in this group[67]. The onset of acute renal failure due to this class of drug is usually associated with oliguria and increased serum urea, creatinine and potassium levels[67], which necessitates cessation of the agent responsible.

There is no strong evidence that any one NSAID is safer in terms of renal side-effects when equipotent doses are used. The newer COX-2 specific inhibitors, despite having lesser gastrointestinal and haematological effects, are pharmacodynamically similar in their effects on the renal vascular bed, and have similar renal side-effects[69-71]. The use of NSAIDs, aspirin or COX-2 specific inhibitors for analgesia should be avoided in the presence of chronic renal failure, due to the likely impairment of potassium handling, and the increased risk of acute renal failure or bleeding[71,72]. If no alternative exists, then dosages must be kept to a minimum, hypotension and hypovolaemia prevented, and renal function monitored to allow cessation should deterioration occur: The first few days of treatment are associated with the highest risk, and creatinine clearance is a more sensitive measure of impairment than serum creatinine level[68].

Elevated liver function tests have been reported in up to 15% of patients taking NSAIDs, and should lead to cessation of the drug if they occur[71]. Patients using the drugs parecoxib, rofecoxib or celecoxib with intercurrent moderate hepatic impairment were studied, and experienced elevated steady state drug levels, leading to a recommendation for decreased dosage in this subgroup[69-71]. No study assessed use in severe degrees of hepatic insufficiency. In all cases of hepatic insufficiency where NSAIDS are considered, regular monitoring of liver function should occur to allow cessation in the event of deterioration.

Ketorolac

Ketorolac is subject to extensive hepatic metabolism prior to renal excretion. The potential for renal toxicity has been extensively studied following a significant association with acute renal failure on its introduction. The recommended dose ranges have since been decreased, and it is not recommended for use beyond five days. One study retrospectively reviewed 198 healthy patients following donor nephrectomy, of whom 83 received ketorolac, with a mean total dose of 200 mg. The preoperatively calcu-

lated creatinine clearance was equal to the group who did not receive ketorolac, but the postoperative values showed a slight decrease in clearance on the second postoperative day. There was no subgroup of patients who showed an association with renal function and the amount of ketorolac given, and there was no difference in creatinine clearance between normal and treated groups after three months from the time of surgery[66] (Level III evidence). The relevance of this study is questionable as these patients may be assumed to have significant renal reserve on the basis of their suitability for kidney donation.

In the presence of mild renal impairment (creatinine clearance 20 to 50 ml/min), the half-life is approximately doubled: some authors suggest usage in this group, with dosage reduction to less than 60 mg/day. It should be avoided in patients with a greater degree of renal failure. In the presence of liver cirrhosis, clearance is slightly prolonged and the risk of renal dysfunction is also higher[67], so dosage reduction is also necessary.

PARACETAMOL

Paracetamol (known also as acetaminophen) has been implicated in analgesic nephropathy: however the problem is statistically likely only in the case of prolonged use of compound analgesics containing at least two antipyretic agents along with caffeine or codeine. The resultant nephropathy has been linked to the synergistic effect of inhibition of prostaglandin synthesis and glutathione depletion in this situation[68]. In a study on nine patients with chronic stable renal failure using 40 mg/kg/day for three days, it did not alter renal glomerular or tubular function, however sulphate and glucuronide metabolites accumulated[73] (Level III evidence). Paracetamol is associated with less risk of acute renal failure than NSAIDS[72] or COX-2 inhibitors[74], and is the simple analgesic of first choice in the patient with renal dysfunction. It may accumulate in uraemic patients due to effects on hepatic blood flow, but this was not addressed in any of the studies found: in this situation it would be wise to limit doses to the above figure of 40 mg/kg/day, and monitor hepatic function frequently during initiation of therapy.

Hepatic toxicity is a known consequence of paracetamol overdose, due to the formation of a reactive intermediate which binds to hepatocytes and causes tissue necrosis: this is protected against by endogenous glutathione, unless tissue stores become depleted. Liver enzyme inducers such as alcohol or barbiturates may increase the risk for toxic metabolite formation, and in the presence of hepatic cirrhosis, the prolongation of paracetamol clearance which occurs renders the patient more susceptible to toxic effects. In the presence of cirrhosis, drug dosage should be reduced[75], although in the presence of moderate to severe liver failure, it should be avoided altogether.

RECOMMENDATIONS

The wide difference in degree of renal and hepatic impairment which exists, coupled with the proportionally small population group affected, has determined that most drugs are not studied extensively in this group prior to introduction. Small group pharmacokinetic studies and case reports cannot conclusively guide drug use for all degrees of organ failure. It remains up to the clinician in these cases to consider fully the risk/benefit equation for any drug introduced, in conjunction with other factors such as potential adverse reactions and known pharmacodynamic or pharmacokinetic interactions.

In consideration of the available data on patients with renal failure, the following statements may be made:

- Those drugs which exhibit the safest pharmacological profile are alfentanil, buprenorphine, fentanyl, ketamine, paracetamol (except with compound analgesics), remifentanil and sufentanil: none of these delivers a high active metabolite load, or suffer from significantly prolonged clearance. A slight dosage reduction may be required.
- Amitriptyline, bupivacaine, clonidine, gabapentin, hydromorphone, levobupivacaine, lignocaine, methadone, mexiletine, morphine, oxycodone, and tramadol have been used in the presence of renal failure, but do require specific precautions, most frequently a significant dosage reduction. Levobupivacaine is probably safer than bupivacaine because of a higher therapeutic ratio and similar clearance mechanisms. Ropivacaine has not been studied in patients with significant renal disease[46].
- Aspirin, dextropropoxyphene, non-steroidal anti-inflammatory drugs and pethidine should not be used in the presence of chronic renal failure, due to the risk of significant toxicity.

In the presence of hepatic impairment, most drugs are subject to significantly impaired clearance and increased oral bioavailability, but are poorly studied in the clinical setting. The available data indicates the following:

- The agent least subject to alteration in metabolism is remifentanil; however the drug's potency limits its use to the acute care/high dependency setting.
- Sufentanil clearance is unlikely to be impaired with uncomplicated mild cirrhosis.

- Tramadol may be given at lower doses, as per product guidelines, with lesser degrees of hepatic impairment.
- Methadone is contraindicated in the presence of severe liver disease due to the potential for greatly prolonged clearance.
- Local anaesthetic clearance may be impaired to quite significant degrees, and all types must be administered cautiously in decreased doses. The two newer agents; ropivacaine and levobupivacaine, may be safer than bupivacaine due to a higher therapeutic index, but have not been studied in this context[46,47].
- Amitriptyline, carbamazepine and valproate use should be avoided as the risk of fulminant hepatic failure is higher in this population.
- NSAIDs are subject to decreased clearance and an increased risk of causing renal failure. If used, the dose must be decreased in accordance with product guidelines.
- Paracetamol may unpredictably accumulate and lead to hepatic necrosis. It has been used in the presence of mild cirrhosis, and should be associated with regular monitoring of hepatic function in this situation. It should be avoided in greater degrees of hepatic impairment.
- No evidence was found using the search protocol to guide treatment using other agents.

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